ORIGINAL ARTICLE

Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

Brian J. Druker, M.D., François Guilhot, M.D., Stephen G. O'Brien, M.D., Ph.D., Insa Gathmann, M.Sc., Hagop Kantarjian, M.D., Norbert Gattermann, M.D., Michael W.N. Deininger, M.D., Ph.D., Richard T. Silver, M.D., John M. Goldman, D.M., Richard M. Stone, M.D., Francisco Cervantes, M.D., Andreas Hochhaus, M.D., Bayard L. Powell, M.D., Janice L. Gabrilove, M.D., Philippe Rousselot, M.D., Josy Reiffers, M.D., Jan J. Cornelissen, M.D., Ph.D., Timothy Hughes, M.D., Hermine Agis, M.D., Thomas Fischer, M.D., Gregor Verhoef, M.D., John Shepherd, M.D., Giuseppe Saglio, M.D., Alois Gratwohl, M.D., Johan L. Nielsen, M.D., Jerald P. Radich, M.D., Bengt Simonsson, M.D., Kerry Taylor, M.D., Michele Baccarani, M.D., Charlene So, Pharm.D., Laurie Letvak, M.D., and Richard A. Larson, M.D., for the IRIS Investigators*

ABSTRACT

BACKGROUND

The cause of chronic myeloid leukemia (CML) is a constitutively active BCR-ABL tyrosine kinase. Imatinib inhibits this kinase, and in a short-term study was superior to interferon alfa plus cytarabine for newly diagnosed CML in the chronic phase. For 5 years, we followed patients with CML who received imatinib as initial therapy.

METHODS

We randomly assigned 553 patients to receive imatinib and 553 to receive interferon alfa plus cytarabine and then evaluated them for overall and event-free survival; progression to accelerated-phase CML or blast crisis; hematologic, cytogenetic, and molecular responses; and adverse events.

RESULTS

The median follow-up was 60 months. Kaplan–Meier estimates of cumulative best rates of complete cytogenetic response among patients receiving imatinib were 69% by 12 months and 87% by 60 months. An estimated 7% of patients progressed to accelerated-phase CML or blast crisis, and the estimated overall survival of patients who received imatinib as initial therapy was 89% at 60 months. Patients who had a complete cytogenetic response or in whom levels of *BCR-ABL* transcripts had fallen by at least 3 log had a significantly lower risk of disease progression than did patients without a complete cytogenetic response ($P<0.001$). Grade 3 or 4 adverse events diminished over time, and there was no clinically significant change in the profile of adverse events.

CONCLUSIONS

After 5 years of follow-up, continuous treatment of chronic-phase CML with imatinib as initial therapy was found to induce durable responses in a high proportion of patients. (ClinicalTrials.gov number, NCT00006343.)

Address reprint requests to Dr. Druker at the Oregon Health and Science University Cancer Institute, L592, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, or at drukerb@ohsu.edu.

*Authors' affiliations and investigators in the International Randomized Study of Interferon and STI571 (IRIS) are listed in the Appendix.

N Engl J Med 2006;355:2408-17.

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the expansion of a clone of hematopoietic cells that carries the Philadelphia chromosome (Ph).[1] The Ph chromosome results from a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11).[2] The molecular consequence of this translocation is a novel fusion gene, *BCR-ABL*, which encodes a constitutively active protein, tyrosine kinase.[3-5] Imatinib (Gleevec, Novartis; formerly called STI571) is a relatively specific inhibitor of the BCR-ABL tyrosine kinase and has efficacy in CML.[6-11]

Before the availability of imatinib, interferon alfa plus cytarabine was considered standard therapy for patients with CML who were not planning to undergo allogeneic hematopoietic stem-cell transplantation.[12,13] A randomized trial that compared imatinib with interferon alfa plus cytarabine in the chronic phase of CML demonstrated the significant superiority of imatinib in all standard indicators of the disease within a median follow-up of 19 months.[14] The trial was designed as a crossover study, and given the superior results with imatinib, a large proportion of patients in the interferon group switched to imatinib. In addition, at the time of Food and Drug Administration approval of imatinib, many patients who were assigned to receive interferon alfa plus cytarabine left the study. Consequently, the trial has evolved into a long-term study of the result of treating newly diagnosed patients in the chronic phase of CML with imatinib. We now report 60 months of follow-up data and focus on patients who received imatinib as a primary treatment.

Methods

Study Design

The design of the study has been described previously.[14] The International Randomized Study of Interferon and STI571 (IRIS) was a multicenter, international, open-label, phase III randomized study. Eligible patients had to be between 18 and 70 years of age, must have been diagnosed with Ph-positive CML in chronic phase within 6 months before study entry, and must not have received treatment for CML, except for hydroxyurea or anagrelide.

Patients were recruited from June 2000 through January 2001 and were randomly assigned to receive imatinib at a dose of 400 mg orally per day or subcutaneous interferon alfa at a daily target dose of 5 million U per square meter of body-surface area, plus 10-day cycles of cytarabine at a daily dose of 20 mg per square meter every month. Patients receiving imatinib who did not have a complete hematologic response within 3 months or whose bone marrow contained more than 65% Ph-positive cells at 12 months could have a stepwise increase in the dose of imatinib to 400 mg orally twice daily as long as there were no dose-limiting adverse events. Patients were allowed to cross over to the other treatment group if they did not achieve either a complete hematologic response after 6 months of therapy or a major cytogenetic response after 12 months or if they had a relapse or an increase in white-cell count or could not tolerate treatment. All crossover requests were made anonymously and considered weekly by the study management committee (see the Appendix).

End Points

The primary end point was event-free survival, which was referred to in previous presentations and articles as the time to progression, or progression-free survival. Events were defined by the first occurrence of any of the following: death from any cause during treatment, progression to the accelerated phase or blast crisis of CML, or loss of a complete hematologic or major cytogenetic response. Secondary end points were the rate of complete hematologic response (defined as a leukocyte count $<10\times10^9$ per liter, a platelet count of $<450\times10^9$ per liter, <5% myelocytes plus metamyelocytes, no blasts or promyelocytes, no extramedullary involvement, and no signs of the accelerated phase or blast crisis of CML); a cytogenetic response in marrow cells, categorized as complete (no Ph-positive metaphases), partial (1 to 35% Ph-positive metaphases), or major (complete plus partial responses) on the basis of G-banding in at least 20 cells in metaphase per sample; progression to the accelerated phase or blast crisis; overall survival; safety; and tolerability. Signs of a molecular response were sought every 3 months after a complete cytogenetic response was obtained with the use of real-time quantitative polymerase chain reaction to measure the ratio of *BCR-ABL* transcripts to *BCR* transcripts. Results were expressed as "log reductions" below a standardized baseline derived from

a median ratio of *BCR-ABL* to *BCR* obtained from 30 untreated patients with chronic-phase CML.[15]

ETHICS AND STUDY MANAGEMENT

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed by the ethics committee or institutional review board at each participating center. All patients gave written informed consent, according to institutional regulations. The academic investigators and representatives of the sponsor, Novartis, designed the study. Data-management and statistical-support staff at a contract research organization collected the data, which were analyzed and interpreted by a biostatistician from Novartis in close collaboration with the investigators. The study management committee and all academic investigators had access to the raw data. The study management committee, composed of four academic investigators, served as the writing committee. Along with the Novartis biostatistician, they vouch for the accuracy and completeness of the data.

Table 1. Enrollment, Outcomes, and Reasons for Crossover and Discontinuation.*

Variable	Imatinib (N=553)	Interferon Alfa plus Cytarabine (N=553)
	no. of patients (%)	
Assignment of patients		
Continued first-line treatment	382 (69)	16 (3)
Discontinued first-line treatment	157 (28)	178 (32)
Crossed over to other treatment	14 (3)	359 (65)
Discontinued second-line treatment	14 (3)	108 (20)
Reason for crossover		
Other than progression		
Intolerance of treatment†	4 (<1)	144 (26)
No complete hematologic response at 6 mo	0	41 (7)
No major cytogenetic response at 12 mo	1 (<1)	49 (9)
Other	0	48 (9)
Progression only		
Increase in white-cell count†	2 (<1)	25 (5)
Loss of complete hematologic response	5 (<1)	29 (5)
Loss of major cytogenetic response	2 (<1)	23 (4)
Reason for discontinuation‡		
Adverse event	23 (4)	35 (6)
Death	10 (2)	2 (<1)
Unsatisfactory therapeutic effect	59 (11)	29 (5)
Stem-cell transplantation	16 (3)	7 (1)
Protocol violation	15 (3)	17 (3)
Loss to follow-up	5 (<1)	6 (1)
Withdrawal of consent	25 (5)	76 (14)
Other	4 (<1)	6 (1)

* The first patient entered the study on June 16, 2000, and enrollment ended January 30, 2001.
† The crossover of patients with this condition to the other treatment group needed previous approval by the study management committee.
‡ A total of 157 patients who received imatinib and 178 patients who received interferon alfa plus cytarabine discontinued therapy.

STATISTICAL ANALYSIS

The study is ongoing, but January 31, 2006, was the cutoff date for this analysis. This date marked 5 to 5.5 years after patients started to receive imatinib treatment. We followed all 553 patients who were assigned to receive imatinib for an analysis of safety and efficacy until they stopped taking imatinib, and we have continued to follow all patients until death, loss to follow-up, or withdrawal of consent. Survival data were also collected on patients who underwent bone marrow transplantation after imatinib treatment. We performed analyses of survival and event-free survival, using the Kaplan–Meier method according to the intention-to-treat principle and using all data available, regardless of whether crossover occurred. Differences between subgroups of patients receiving imatinib were calculated by the log-rank test. Cumulative rates of complete hematologic and cytogenetic responses were estimated according to the Kaplan–Meier method, in which data from patients receiving imatinib who did not have an adequate response, who had switched to interferon alfa plus cytarabine, or who had discontinued treatment for reasons other than progression of CML were censored at the last follow-up visit. For the estimation of cumulative response rates, we censored data from patients with progressive CML at maximum follow-up. We used the life-table method to determine yearly event probabilities. The safety of imatinib was analyzed for 551 patients who received at least one dose of the study drug during the trial. For the 553 patients assigned to receive interferon alfa plus cytarabine, disposition and overall survival were summarized.

Table 2. Proportion of Patients Receiving First-Line Imatinib Therapy with Grade 3 or Grade 4 Adverse Events.

Hematologic or Hepatic Condition	Grade 3 or Grade 4 Adverse Events			
	Total Events (N=551)	Years 1 and 2 (N=551)	Years 3 and 4 (N=456)	After Year 4 (N=409)
	percent			
Neutropenia	17	14	3*	1*
Thrombocytopenia	9	8	1*	<1*
Anemia	4	3	1†	<1‡
Elevated liver enzymes	5	5	<1*	0*
Other drug-related adverse event	17	14	4*	2*

* P<0.001 for the comparison of events in years 3 and 4 and after 4 years with those in years 1 and 2.
† The difference between events in years 3 and 4 and those in years 1 and 2 did not reach statistical significance.
‡ P<0.01 for the comparison of events after 4 years with those in years 1 and 2.

RESULTS

PATIENTS

Five years after the last of 1106 patients had started treatment, and with a median of 60 months of follow-up, 382 of 553 patients (69%) in the imatinib group and 16 of 553 patients (3%) in the group given interferon alfa plus cytarabine continued with their initially assigned treatment (Table 1). Of the patients given interferon plus cytarabine, 359 (65%) had crossed over to imatinib, whereas 14 patients (3%) in the imatinib group had switched to the alternative treatment. The most common reason for crossover among patients given interferon plus cytarabine was intolerance of treatment (26%). Of these patients, 90 (16%) switched because they did not achieve a complete hematologic or major cytogenetic response by the designated target dates, as did 77 patients (14%) with disease progression. An additional 178 patients (32%) given interferon alfa plus cytarabine discontinued therapy. The reasons most commonly reported were withdrawal of consent (14%) and adverse events (6%). In the imatinib group, 23 patients (4%) discontinued therapy owing to an adverse event, and 25 patients (5%) withdrew consent (Table 1).

Since few patients were still receiving interferon alfa plus cytarabine at 60 months, the remainder of this report focuses on the long-term follow-up of patients who received imatinib as the initial therapy for CML. They had been treated with imatinib for a mean (±SD) of 50±19 months (median, 60 months). Among the 382 patients who continued receiving imatinib, the mean daily dose during this reporting period was 382±50 mg. In 82% of these patients, the last reported daily dose was 400 mg; 6% were receiving 600 mg, 4% were receiving 800 mg, and 8% were receiving less than 400 mg.

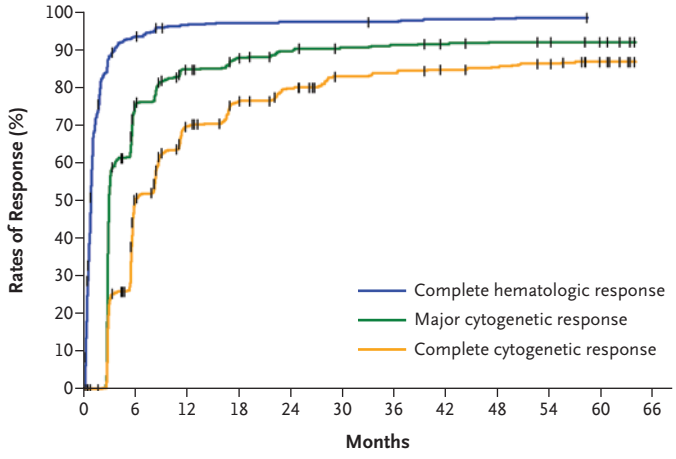


Figure 1. Kaplan–Meier Estimates of the Cumulative Best Response to Initial Imatinib Therapy.

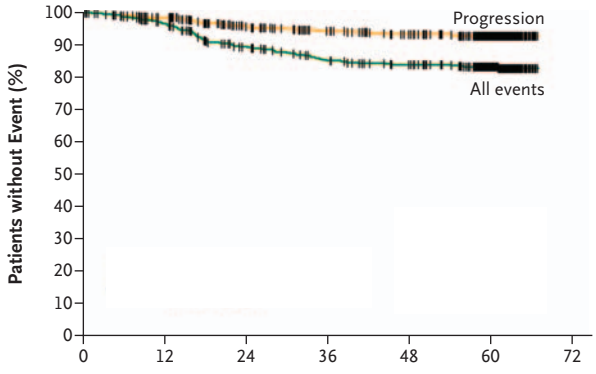
At 12 months after the initiation of imatinib, the estimated rates of having a response were as follows: complete hematologic response, 96%; major cytogenetic response, 85%; and complete cytogenetic response, 69%. At 60 months, the respective rates were 98%, 92%, and 87%. Data for patients who discontinued imatinib for reasons other than progression and who did not have an adequate response were censored at the last follow-up visit. Data for patients who did not have an adequate response and who stopped imatinib because of progression were censored at maximum follow-up.

ADVERSE EVENTS

After a median follow-up of 60 months, the adverse events reported were similar to those reported previously.[14] The most commonly reported adverse events were edema (including peripheral and periorbital edema) (60%), muscle cramps (49%), diarrhea (45%), nausea (50%), musculoskeletal pain (47%), rash and other skin problems (40%), abdominal pain (37%), fatigue (39%), joint pain (31%), and headache (37%). Grade 3 or 4 adverse events consisted of neutropenia (17%), thrombocytopenia (9%), anemia (4%), elevated liver enzymes (5%), and other drug-related adverse events (17%). Congestive heart failure was reported as being drug-related in one patient (<1%). Newly occurring or worsening grade 3 or 4 hematologic or biochemical adverse events were infrequent after both 2 and 4 years of therapy (Table 2).

EFFICACY

Figure 1 shows the estimated cumulative rates of complete hematologic remission: 96% at 12 months and 98% at 60 months. The best observed rate of complete hematologic response was 97%.



No. of Events					
Progression	8	22	29	33	35
All events	18	55	76	82	85
No. at Risk					
Progression	513	461	431	409	280
All events	505	447	414	395	274

Figure 2. Kaplan–Meier Estimates of the Rates of Event-free Survival and Progression to the Accelerated Phase or Blast Crisis of CML for Patients Receiving Imatinib.

At 60 months, the estimated rate of event-free survival was 83%. At that time, 93% of the patients had not progressed to the accelerated phase or blast crisis. The following were considered events: death from any cause during treatment, progression to the accelerated phase or blast crisis, loss of a complete hematologic response, loss of a major cytogenetic response, or an increasing white-cell count. The number of patients with events and the number of patients available for analysis are shown.

At 12 months, the estimated rate of major cytogenic response was 85% and that of complete cytogenetic response was 69%. At 60 months, the estimated rates were 92% and 87%, respectively. With a median follow-up of 60 months, the best observed rate of major cytogenetic response was 89%, and the best rate of complete cytogenetic response was 82%. Of the 382 patients who still received imatinib at 60 months, 368 (96%) had a complete cytogenetic response.

There were significant differences in the rates of cytogenetic response, according to a scoring system devised by Sokal and colleagues,[16] which divides patients with CML into low-risk, intermediate-risk, and high-risk groups. In patients who were deemed to be at low risk on the Sokal scoring system, the rate of complete cytogenetic response was 89%; the rate among patients at intermediate risk was 82%; and for those at high risk, the rate was 69% (P<0.001).

Among 124 patients who had a complete cytogenetic response and whose blood samples taken at 1 and 4 years were available, *BCR-ABL* transcripts in the blood samples were measured. After 1 year, levels of *BCR-ABL* transcripts had fallen by at least 3 log in 66 of 124 patients (53%); after 4 years, levels had fallen in 99 of 124 patients (80%) (P<0.001). The proportion of patients with a reduction of at least 4 log in transcript levels increased from 22 to 41% between 1 and 4 years (P<0.001). The median log reduction of *BCR-ABL* transcripts was 3.08 at 1 year and 3.78 at 4 years (P<0.001).

LONG-TERM OUTCOMES

At 60 months, the estimated rate of event-free survival was 83% (95% confidence interval [CI], 79 to 87), and an estimated 93% of patients (95% CI, 90 to 96) had not progressed to the accelerated phase or blast crisis (Fig. 2). Of the 553 patients receiving imatinib, 35 (6%) progressed to the accelerated phase or blast crisis, 14 (3%) had a hematologic relapse, 28 (5%) had a loss of major cytogenetic response, and 9 (2%) died from a cause unrelated to CML. The estimated annual rate of treatment failure after the start of imatinib therapy was 3.3% in the first year, 7.5% in the second year, 4.8% in the third year, 1.5% in the fourth year, and 0.9% in the fifth year. The corresponding annual rates of progression to the accelerated phase or blast crisis were 1.5%, 2.8%, 1.6%, 0.9%, and 0.6%, respectively. In the 454 patients who had

a complete cytogenetic response, the annual rates of treatment failure were 5.5% in the first year, 2.3% in the second year, 1.1% in the third year, and 0.4% in the fourth year after a response was achieved. The corresponding annual rates of progression to the accelerated phase or blast crisis were 2.1%, 0.8%, 0.3%, and 0%, respectively, in these patients.

EFFECT OF RESPONSE ON OUTCOME

Cytogenetic and molecular responses had significant associations with event-free survival and deterrence against progression to the accelerated phase or blast crisis (Fig. 3). A landmark analysis of the 350 patients who had had a complete cytogenetic response at 12 months after the initiation of imatinib treatment revealed that at 60 months, 97% of the patients (95% CI, 94 to 99) had not progressed to the accelerated phase or blast crisis. For the 86 patients with a partial cytogenetic response, the estimate was 93% (95% CI, 87 to 99); for the 73 patients who did not have a major cytogenetic response within 12 months, the estimate was 81% (95% CI, 70 to 92) (overall, $P<0.001$; $P<0.001$ for the comparison between patients with a complete response and those without a complete response, and $P=0.20$ for the comparison between patients with a complete response and those with a partial response) (Fig. 3A).

At 60 months, the estimated risk of disease progression was significantly higher for the high-risk group of patients, according to the Sokal scoring system ($P=0.002$); the estimated rates for patients in the high-risk, intermediate-risk, and low-risk groups were 17%, 8%, and 3%, respectively. However, the Sokal score was not associated with disease progression in patients who had a complete cytogenetic response (95%, 95%, and 99% in the high-risk, intermediate-risk, and low-risk groups, respectively) ($P=0.20$ overall; $P=0.92$ for the comparison between the intermediate-risk group and the high-risk group, and $P=0.16$ for the comparison between the low-risk group and the high-risk group).

The molecular responses at 12 and 18 months were also associated with long-term outcomes. At 60 months, the patients who had a complete cytogenetic response and a reduction of at least 3 log in levels of *BCR-ABL* transcripts in bone marrow cells after 18 months of treatment had an estimated rate of survival without progression of CML of 100%. In the group with a reduction of less

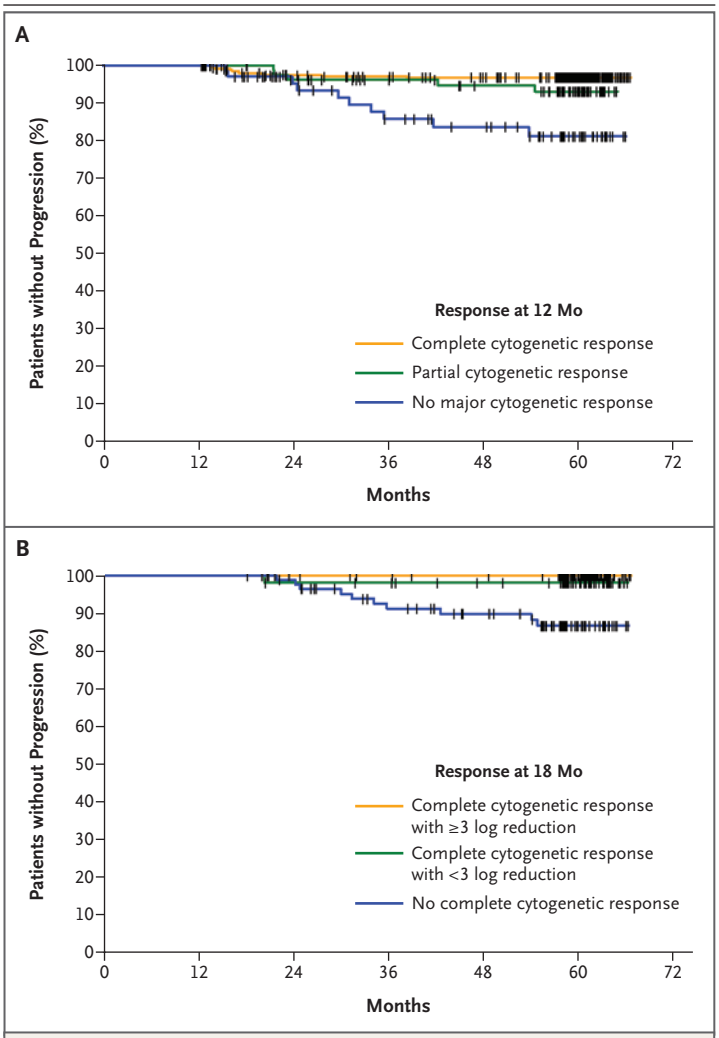


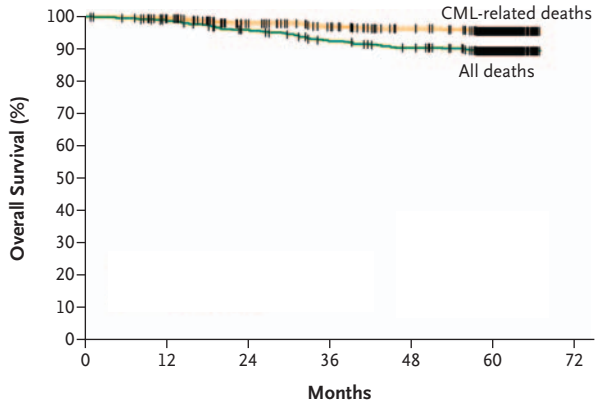
Figure 3. Rate of Progression to the Accelerated Phase or Blast Crisis on the Basis of Cytogenetic Response after 12 Months or Molecular Response after 18 Months of Imatinib Therapy.

Panel A shows that at 60 months, of the 350 patients with a complete cytogenetic response after 12 months of imatinib therapy, an estimated 97% had not progressed to the accelerated phase or blast crisis. The corresponding rates for 86 patients with a partial cytogenetic response and for 73 patients who did not have a major cytogenetic response were 93% and 81%, respectively ($P<0.001$; $P=0.20$ for the comparison between patients with a complete cytogenetic response and those with a partial response). At 12 months, 44 patients had discontinued imatinib and thus were not included in this analysis. Panel B shows that at 60 months, of the 139 patients with a complete cytogenetic response and a reduction in levels of *BCR-ABL* transcripts of at least 3 log, 100% were free from progression to the accelerated phase or blast crisis. The corresponding rate for 54 patients with a complete cytogenetic response and a reduction in levels of *BCR-ABL* transcripts of less than 3 log was 98%; the rate for 88 patients without a complete cytogenetic response was 87% ($P<0.001$; $P=0.11$ for the comparison between patients with a major molecular response and those without a major molecular response). At 18 months, 86 patients had discontinued imatinib and 186 patients had achieved a complete cytogenetic response but did not have a PCR result available.

than 3 log in levels of *BCR-ABL* transcripts, the estimated rate was 98% (P=0.11). However, in the absence of a complete cytogenetic response, the rate was 87% (P<0.001) (Fig. 3B). No patient who had a complete cytogenetic response and reduction of at least 3 log in levels of *BCR-ABL* transcripts at 12 months had progressed to the accelerated phase or blast crisis at 60 months.

OVERALL SURVIVAL

By the cutoff date for this analysis, 57 patients (10%) who received imatinib had died; 5 of these patients had switched to interferon alfa plus cytarabine. The estimated overall survival rate at 60 months was 89% (95% CI, 86 to 92) (Fig. 4). Allogeneic hematopoietic stem-cell transplantation was carried out in 44 patients who discontinued imatinib: 11 had progressed to the accelerated phase or blast crisis, 15 had had a hematologic or cytogenetic relapse, and 18 had stopped therapy for other reasons (including safety and withdrawal of consent). Of the 44 patients who underwent transplantation, 14 (32%) died. At 60 months, with data censored at the time of transplantation, the estimated overall survival rate was 92% (95% CI, 89 to 95). After data were censored for patients who had died from causes unrelated to CML or transplantation, the overall estimated survival rate was 95% (95% CI, 93 to 98) at 60 months (Fig. 4).



No. of Deaths					
Related to CML	3	11	16	19	23
All deaths	6	22	41	52	57
No. at Risk					
Related to CML	536	498	474	450	322
All deaths	542	518	492	475	333

Figure 4. Overall Survival among Patients Treated with Imatinib Based on an Intention-to-Treat Analysis.

The estimated overall survival rate at 60 months was 89%. After the censoring of data for patients who died from causes unrelated to CML or transplantation, the estimated overall survival was 95% at 60 months. At the time of analysis, 57 patients had died. The number of patients with events and the number of patients available for analysis are shown.

DISCUSSION

The initial analysis of this study, performed at a median follow-up of 19 months, showed a high rate of response and an acceptable rate of side effects of imatinib as initial therapy for newly diagnosed chronic-phase CML.[14] The present analysis, with a median follow-up of 60 months, showed an estimated relapse rate of 17% at 60 months, and an estimated 7% of all patients progressed to the accelerated phase or blast crisis. The 5-year estimated overall survival rate for patients who received imatinib as initial therapy (89%) is higher than that reported in any previously published prospective study of the treatment of CML.[17]

This trial allowed patients to cross over to the alternate treatment, and most patients in the interferon group either switched to imatinib or discontinued interferon. On the basis of an intention-to-treat analysis, there was no significant difference in overall survival between the group of patients who began their treatment with interferon and those who began their treatment with imatinib (data not shown). Previous randomized studies of interferon alfa plus cytarabine, performed before the availability of imatinib, showed a 5-year overall survival of 68 to 70%.[12,13] With the use of historical comparisons, a survival advantage for initial therapy with imatinib over interferon alfa can be demonstrated.[18]

In a landmark analysis, 97% of patients with a complete cytogenetic response within 12 months after starting imatinib did not progress to the accelerated phase or blast crisis by 60 months. Notably, patients who were deemed to be at high risk on the basis of Sokal scores had a lower rate of complete cytogenetic response (69%) than did patients who were at low risk or intermediate risk (89% and 82%, respectively). However, the risk of relapse in patients who had a cytogenetic response was not associated with the Sokal score. With interferon treatment, by contrast, the Sokal score was important even among patients with a complete cytogenetic response.[19]

Remarkably, no patient who had a complete cytogenetic response and a reduction in levels of *BCR-ABL* transcripts of at least 3 log at 12 or 18 months after starting imatinib had progression

of CML by 60 months. Only 2% of patients who had a complete cytogenetic response and a reduction in levels of *BCR-ABL* transcripts of less than 3 log at 18 months had progressed to the accelerated phase or blast crisis at 60 months.

It is currently recommended that imatinib therapy be continued indefinitely. Anecdotal reports suggest that the discontinuation of imatinib, even in patients with undectectable levels of *BCR-ABL* transcripts, results in relapse.[20-24] Although it is not known why imatinib is not able to eradicate the malignant clone, potential mechanisms include drug efflux[25] and amplification or mutation of the *BCR-ABL* gene.[26] It is also possible that imatinib cannot completely inhibit BCR-ABL kinase activity; low levels of activity would allow cells to survive but not proliferate. As an alternative, the malignant clone could persist through mechanisms that are independent of the BCR-ABL kinase.[27]

Initial studies of two new inhibitors of the BCR-ABL kinase that are more potent than imatinib — dasatinib and nilotinib — showed high response rates in patients who had had a relapse during imatinib therapy.[28,29] Despite their potency, these inhibitors cannot eradicate all CML cells in vitro.[30] As was the case in patients in our study, it is assumed that in patients receiving these drugs a durable response can be achieved even without disease eradication if there is a reduction in levels of *BCR-ABL* transcripts of at least 3 log.

Notably, the rate of disease progression in patients in our study is apparently trending downward, although the trend has not reached statistical significance. If it persists, such a trend would be consistent with the findings that mutations in the *BCR-ABL* gene are the major cause of relapse in patients treated with imatinib.[31] If we presume that mutations precede imatinib therapy (as the data suggest),[32,33] the emergence of resistance to the drug would depend on the size of the mutant clone at the start of therapy and its doubling time. Since most mutated and unmutated *BCR-ABL* clones have similar doubling times,[34] a patient with a mutant clone should be at highest risk for relapse during the first several years of therapy. This prediction is in line with the apparent downward trend in the risk of disease progression observed in our study.

Dr. Druker's institution is the site of clinical trials sponsored by Novartis, but neither he nor his laboratory reports receiving funds from Novartis. Dr. Guilhot reports receiving consulting and lecture fees from Novartis; Dr. O'Brien, consulting fees from Novartis and Bristol-Myers Squibb and lecture fees from Novartis; Ms. Gathmann, being an employee of and having equity ownership in Novartis; Dr. Kantarjian, consulting fees from Novartis, Bristol-Myers Squibb, and MGI Pharma; Dr. Gattermann, consulting and lecture fees from Novartis and Pharmion; Dr. Deininger, consulting and lecture fees from Novartis and Bristol-Myers Squibb; Dr. Silver, consulting fees from Novartis; Dr. Goldman, lecture fees from Novartis; Dr. Stone, consulting and lecture fees and grant support from Novartis and Bristol-Myers Squibb; Dr. Cervantes, consulting fees from Novartis and lecture fees from Novartis and Bristol-Myers Squibb; Dr. Hochhaus, consulting and lecture fees from Novartis and Bristol-Myers Squibb; Dr. Powell, lecture fees from Pharmion; Dr. Gabrilove, consulting fees from Novartis; Dr. Rousselot, lecture fees from Novartis Oncology; Dr. Cornelissen, consulting fees from Novartis Oncology; Dr. Hughes, consulting and lecture fees from Novartis; Dr. Fischer, consulting fees from LymphoSign and Novartis and lecture fees from Novartis; Dr. Saglio, consulting and lecture fees from Novartis; Dr. Gratwohl, consulting fees from Novartis, Pfizer, and Amgen and lecture fees from Novartis; Dr. Radich, consulting fees from Novartis and Bristol-Myers Squibb and lecture fees from Novartis; Dr. Simonsson, consulting fees from Novartis and Bristol-Myers Squibb; Dr. Taylor, consulting fees from Amgen, Novartis, Bristol-Myers Squibb, and Celgene and lecture fees from Novartis; Dr. Baccarani, consulting fees from Novartis, Bristol-Myers Squibb, Merck, and Pfizer and lecture fees from Novartis, Bristol-Myers Squibb, Schering, and Pfizer; Dr. So, being an employee of Novartis and having equity ownership in Novartis and Pfizer; Dr. Letvak, being an employee of and having equity ownership in Novartis; and Dr. Larson, consulting and lecture fees from Novartis. No other potential conflict of interest relevant to this article was reported.

We thank the coinvestigators; the members of the medical, nursing, and research staff at the trial centers; the clinical trial monitors and the data managers and programmers at Novartis for their contributions; and Tillman Krahnke and Manisha Mone for their invaluable collaboration.

APPENDIX

From the Oregon Health and Science University Cancer Institute, Portland (B.J.D.); Centre Hospitalier Universitaire, Poitiers, France (F.G.); University of Newcastle, Newcastle, United Kingdom (S.G.O.); Novartis, Basel, Switzerland (I.G.); M.D. Anderson Cancer Center, Houston (H.K.); Heinrich Heine University, Dusseldorf, Germany (N.G.); Universität Leipzig, Leipzig, Germany (M.W.N.D.); Weill–Cornell Medical Center, New York (R.T.S.); National Heart, Lung, and Blood Institute, Bethesda, MD (J.M.G.); Dana–Farber Cancer Institute, Boston (R.M.S.); Hospital Clinic I Provincial, Barcelona (F.C.); University of Heidelberg, Mannheim, Germany (A.H.); Wake Forest University Baptist Medical Center, Winston-Salem, NC (B.L.P.); Mount Sinai School of Medicine, New York (J.L.G.); Hôpital Saint Louis, Paris (P.R.); Centre Hospitalier Universitaire de Bordeaux, Pessac, France (J.R.); Erasmus Medical Center, Rotterdam, the Netherlands (J.J.C.); Royal Adelaide Hospital, Adelaide, Australia (T.H.); Universitätsklinik für Innere Medizin I, Vienna (H.A.); Johannes Gutenberg Universität, Mainz, Germany (T.F.); University Hospital Gasthuisberg, Leuven, Belgium (G.V.); Vancouver Hospital, Vancouver, BC, Canada (J.S.); Azienda Ospedaliera S. Luigi Gonzaga, Orbassano, Italy (G.S.); University Hospital Basel, Switzerland (A.G.); Aarhus Amtssygehus, Aarhus, Denmark (J.L.N.); Fred Hutchinson Cancer Research Center, Seattle (J.P.R.); Akademiska Sjukhuset, Uppsala, Sweden (B.S.); Mater Hospital, Brisbane, Australia (K.T.); Policlinico S. Orsola–Malpighi, Bologna, Italy (M.B.); Novartis, Florham Park, NJ (C.S., L.L.); and University of Chicago, Chicago (R.A.L.).

The following investigators participated in IRIS: **Australia** — *Royal Brisbane Hospital, Herston:* S. Durrant; *Monash Medical Centre, Melbourne:* A. Schwarer; *Sir Charles Gairdner Hospital, Perth:* D. Joske; *Australian Leukemia and Lymphoma Group, Melbourne:* J. Seymour; *Royal Melbourne Hospital, Parkville:* A. Grigg; *St. Vincent's Hospital, Darlinghurst:* D. Ma; *Royal North Shore Hospital, St. Leonards:* C. Arthur; *Westmead Hospital, Westmead:* K. Bradstock; *Royal Prince Alfred Hospital, Sydney:* D. Joshua. **Belgium** — *A.Z. Sint-Jan, Brugge:* A. Louwagie; *Institut Jules Bordet, Brussels:* P. Martiat; *Cliniques Universitaires, Yvoir:* A. Bosly. **Canada** — *McGill University, Montreal:* C. Shustik; *Princess Margaret Hospital, Toronto:* J. Lipton; *Queen Elizabeth II Health Sciences Centre, Halifax, NS:* D. Forrest; *McMaster University Medical Centre, West Hamilton, ON:* I. Walker; *Université de Montréal, Montreal:* D.-C. Roy; *CancerCare Manitoba, Winnipeg:* M. Rubinger; *Ottawa Hospital Regional Cancer Centre, Ottawa:* I. Bence-Bruckler; *University of Calgary and Tom Baker Cancer Centre, Calgary, AB:* D. Stewart; *London Regional Cancer Centre, London, ON:* M. Kovacs; *Cross Cancer Center, Edmonton, AB:* A.R. Turner. **Denmark** — *Kobenhavns Amts Sygehus i Gentofte, Hellerup:* H. Birgens; *Danish University of Pharmaceutical Sciences and University of Southern Denmark, Copenhagen:* O. Bjerrum. **France** — *Hôpital Claude Huriez, Lille:* T. Facon; *Hôtel Dieu Hospital, Nantes:* J.-L. Harousseau; *Henri Mondor Hospital, Creteil:* M. Tulliez; *Centre Hospitalier Universitaire (CHU) Brabois, Vandoeuvre-les-Nancy:* A. Guerci; *Institut Paoli-Calmettes, Marseille:* D. Blaise; *Hopital Civil, Strasbourg:* F. Maloisel; *CHU la Milétrie, Poitiers:* M. Michallet. **Germany** — *University of Regensburg, Regensburg:* R. Andreesen; *Krankenhaus Muenchen Schwabing, Munich:* C. Nerl; *Universitätsklinikum Rostock, Rostock:* M. Freund; *Heinrich Heine University, Düsseldorf:* N. Gattermann; *Carl-Gustav Carus Universität, Dresden:* G. Ehninger; *Leipzig University Hospital, Leipzig:* M. Deininger; *Medizinische Klinik III, Frankfurt:* O. Ottmann; *Clinical Center Rechts der Isar, Munich:* C. Peschel; *University of Heidelberg, Heidelberg:* S. Fruehauf; *Philipps-Universität Marburg, Baldingerstraße, Marburg:* A. Neubauer; *Humboldt Universität, Berlin:* P. Le Coutre; *Robert Bosch Hospital, Stuttgart:* W. Aulitzky. **Italy** — *University Hospital, Udine:* R. Fanin; *San Orsola Hospital, Bologna:* G. Rosti; *Università La Sapienza, Rome:* F. Mandelli; *Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia:* M. Lazzarino; *Niguarda Ca' Granda Hospital, Milan:* E. Morra; *Azienda Ospedaliera e Cliniche Universitarie San Martino, Largo R Benzi, Genoa:* A. Carella; *University of Pisa, Pisa:* M. Petrini; *Azienda Ospedaliera Bianchi-Malacrino-Morelli, Reggio Calabria:* F. Nobile; *University of Bari, Policlinico, Bari:* V. Liso; *Cardarelli Hospital, Naples:* F. Ferrara; *University of Parma, Parma:* V. Rizzoli; *Ospedale Civile, Pescara:* G. Fioritoni; *Institute of Hematology and Medical Oncology Seragnoli, Bologna:* G. Martinelli. **the Netherlands** — *Vrije Universiteit Academic Medical Center, Amsterdam:* G. Ossenkoppele. **New Zealand** — *University of Auckland, Auckland:* P. Browett. **Norway** — *Medisinsk Avdeling, Rikshospitalet, Oslo:* T. Gedde-Dahl; *Ullevål Sykehus, Oslo:* J.-M. Tangen; *Hvidovre Hospital, Betalende:* I. Dahl. **Spain** — *Hospital Clinic, Villarroel, Barcelona:* J. Odriozola; *University of Barcelona, Barcelona:* J.C. Hernández Boluda; *Hospital Universitario de la Princesa, Madrid:* J.L. Steegman; *Hospital Universitario de Salamanca, Salamanca:* C. Cañizo; *San Carlos Clinical Hospital, Madrid:* J. Diaz; *Institut Català d'Oncología, Barcelona:* A. Granena; *Hospital Lluis Alcanyis, Cta Xativa-Silla:* M.N. Fernández. **Sweden** — *Karolinska Hospital, Stockholm:* L. Stenke; *Huddinge Sjukhus, Huddinge:* C. Paul; *Medicinkliniken Universitetssjukhuset, Örebro:* M. Bjoreman; *Regionsjukhuset, Linköping:* C. Malm; *Sahlgrenska Hospital, Göteborg:* H. Wadenvik; *Endokrinsekt/Medklin Universitetssjukhuset, Lund:* P.-G. Nilsson; *Universitetssjukhuset Malmo University Hospital, Malmo:* I. Turesson. **Switzerland** — *Kantonsspital, St. Gallen:* U. Hess; *University of Bern, Bern:* M. Solenthaler. **United Kingdom** — *University of Nottingham and Nottingham City Hospital, Nottingham:* N. Russell; *Kings College, London:* G. Mufti; *St. George's Hospital, Medical School, London:* J. Cavenagh; *Royal Liverpool University Hospital, Liverpool:* R.E. Clark; *Cambridge Institute for Medical Research, Cambridge:* A.R. Green; *Glasgow Royal Infirmary, Glasgow:* T.L. Holyoake; *Manchester Royal Infirmary, Manchester:* G.S. Lucas; *Leeds General Infirmary, Leeds:* G. Smith; *Queen Elizabeth Hospital, Edgbaston, Birmingham:* D.W. Milligan; *Derriford Hospital, Plymouth:* S.J. Rule; *University Hospital of Wales, Cardiff:* A.K. Burnett; **United States** — *Walt Disney Memorial Cancer Institute, Orlando, FL:* R. Moroose; *Roswell Park Cancer Center, Buffalo, NY:* M. Wetzler; *Gibbs Cancer Center, Spartanburg, SC:* J. Bearden; *Ohio State University School of Medicine, Columbus:* S. Cataland; *University of New Mexico Health Sciences Center, Albuquerque:* I. Rabinowitz; *University of Maryland Cancer Center, Baltimore:* B. Meisenberg; *Montgomery Cancer Center, Montgomery, AL:* K. Thompson; *State University of New York Upstate Medical Center, Syracuse:* S. Graziano; *University of Alabama at Birmingham, Birmingham:* P. Emanuel; *Hematology and Oncology, Inc., Dayton, OH:* H. Gross; *Billings Oncology Associates, Billings, MT:* P. Cobb; *City of Hope National Medical Center, Duarte, CA:* R. Bhatia; *Cancer Center of Kansas, Wichita:* S. Dakhil; *Alta Bates Comprehensive Cancer Center, Berkeley, CA:* D. Irwin; *Cancer Research Center of Hawaii, Honolulu:* B. Issell; *University of Nebraska Medical Center, Omaha:* S. Pavletic; *Columbus Community Clinical Oncology Program, Columbus, OH:* P. Kuebler; *Michigan State University Hematology/Oncology, Lansing:* E. Layhe; *Brown University School of Medicine, Providence, RI:* P. Butera; *Loyola University Medical Center, Shreveport, LA:* J. Glass; *Duke University Medical Center, Durham, NC:* J. Moore; *University of Vermont, Burlington:* B. Grant; *University of Tennessee, Memphis:* H. Niell; *University of Louisville Hospital, Louisville, KY:* R. Herzig; *Sarah Cannon Cancer Center, Nashville:* H. Burris; *University of Minnesota, Minneapolis:* B. Peterson; *Cleveland Clinic Foundation, Cleveland:* M. Kalaycio; *Fred Hutchinson Cancer Research Center, Seattle:* D. Stirewalt; *University of Utah, Salt Lake City:* W. Samlowski; *Memorial Sloan-Kettering Cancer Center, New York:* E. Berman; *University of North Carolina School of Medicine, Charlotte:* S. Limentani; *Atlanta Cancer Center, Atlanta:* T. Seay; *University of North Carolina School of Medicine, Chapel Hill:* T. Shea; *Indiana Blood and Marrow Institute, Beech Grove:* L. Akard; *San Juan Regional Cancer Center, Farmington, NM:* G. Smith; *University of Massachusetts Memorial Medical Center, Worcester:* P. Becker; *Washington University School of Medicine, St. Louis:* S. Devine; *Veterans Affairs Medical Center, Milwaukee:* R. Hart; *Louisiana State University Medical Center, New Orleans:* R. Veith; *Decatur Memorial Hospital, Decatur, IL:* J. Wade; *Rocky Mountain Cancer Centers, Denver:* M. Brunvand; *Oncology-Hematology Group of South Florida, Miami:* L. Kalman; *Memphis Cancer Center, Memphis, TN:* D. Strickland; *Henry Ford Hospital, Detroit:* M. Shurafa; *University of California, San Diego, Medical Center, La Jolla:* A. Bashey; *Western Pennsylvania Cancer Institute, Pittsburgh:* R. Shadduck; *Tulane Cancer Center, New Orleans:* H. Safah; *Southbay Oncology Hematology Partners, Campbell, CA:* M. Rubenstein; *University of Texas Southwest Medical Center, Dallas:* R. Collins; *Cancer Care Associates, Tulsa, OK:* A. Keller; *Robert H. Lurie Comprehensive Cancer Center, Chicago:* M. Tallman; *Northern New Jersey Cancer Center, Hackensack:* A. Pecora; *University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh:* M. Agha; *Texas Oncology, Dallas:* H. Holmes; and *New Mexico Oncology Hematology Consultants, Albuquerque:* R. Guidice. **Study Management Committee:** *Oregon Health and Science University Cancer Institute Research and Patient Care, Portland:* B.J. Druker; *University Hospital, Poitier, France:* F. Guilhot; *University of Chicago, Chicago:* R.A. Larson; *University of Newcastle upon Tyne, Newcastle upon Tyne, UK:* S.G. O'Brien. **Independent Data Monitoring Board:** *Rambam Medical Center, Haifa, Israel:* J. Rowe; *Wayne State University, Barbara Ann Karmanos Cancer Institute, Detroit:* C.A. Schiffer; *International Drug Development Institute, Brussels:* M. Buyse. **Protocol Working Group:** *Policlinico San Orsola–Malpighi, Bologna, Italy:* M. Baccarani; *Hospital Clinic, Barcelona:* F. Cervantes; *Erasmus Medical Center, Rotterdam, the Netherlands:* J. Cornelissen; *Johannes Gutenberg Universität, Mainz, Germany:* T. Fischer; *Universität Heidelberg, Mannheim, Germany:* A. Hochhaus; *Hanson Institute Centre for Cancer, Adelaide, Australia:* T. Hughes; *Medical University of Vienna, Vienna:* K. Lechner; *Aarhus Amtssygehus, Aarhus, Denmark:* J.L. Nielsen; *CHU de Bordeaux, Pessac, France:* J. Reiffers; *Hôpital Saint Louis, Paris:* P. Rousselot; *San Luigi Gonzaga Hospital, Turin, Italy:* G. Saglio; *Vancouver Hospital, Vancouver, BC, Canada:* J. Shepherd; *Akademiska Sjukhuset, Uppsala, Sweden:* B. Simonsson; *University Hospital, Basel, Switzerland:* A. Gratwohl; *Imperial College, London:* J.M. Goldman; *University of Michigan Health System, Ann Arbor:* M. Talpaz; *Mater Misericordiae Public Hospital, Brisbane, Australia:* K. Taylor; and *University Hospital Gasthuisberg, Leuven, Belgium:* G. Verhoef.

REFERENCES

1. Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. Science 1960;132:1497.
2. Rowley JD. A new consistent abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
3. Heisterkamp N, Stam K, Groffen J, de Klein A, Grosveld G. Structural organization of the bcr gene and its role in the Ph′ translocation. Nature 1985;315:758-61.
4. Konopka JB, Watanabe SM, Witte ON. An alteration of the human c-abl protein in K562 leukemia cells unmasks associated tyrosine kinase activity. Cell 1984;37:1035-42.
5. Shtivelman E, Lifshitz B, Gale RP, Canaani E. Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. Nature 1985;315:550-4.
6. 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.
7. Druker BJ, Sawyers CL, Kantarjian H, et al. 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. N Engl J Med 2001;344:1038-42. [Erratum, N Engl J Med 2001;345:232.]
8. 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.
9. 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.]
10. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myeloid leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99:3530-9.
11. 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.
12. 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.
13. 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.
14. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
15. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-32.
16. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
17. 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.
18. Roy L, Guilhot J, Krahnke T, et al. Survival advantage from imatinib compared with the combination interferon-alpha plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials. Blood 2006;108:1478-84.
19. Bonifazi F, de Vivo A, Rosti G, et al. Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. Blood 2001;98:3074-81.
20. Rousselot P, Huguet F, Rea D, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than two years. Blood (in press).
21. Breccia M, Diverio D, Pane F, et al. Discontinuation of imatinib therapy after achievement of complete molecular response in a Ph+ CML patient treated while in long lasting complete cytogenetic remission (CCR) induced by interferon. Leuk Res 2006;30:1577-9.
22. Mauro MJ, Druker BJ, Maziarz RT. Divergent clinical outcome in two CML patients who discontinued imatinib therapy after achieving a molecular remission. Leuk Res 2004;28:Suppl 1:S71-S73.
23. Merante S, Orlandi E, Bernasconi P, Calatroni S, Boni M, Lazzarino M. Outcome of four patients with chronic myeloid leukemia after imatinib mesylate discontinuation. Haematologica 2005;90:979-81.
24. Cortes J, O'Brien S, Kantarjian H. Discontinuation of imatinib therapy after achieving a molecular response. Blood 2004;104:2204-5.
25. Thomas J, Wang L, Clark RE, Pirmohamed M. Active transport of imatinib into and out of cells: implications for drug resistance. Blood 2004;104:3739-45.
26. Chu S, Xu H, Shah NP, et al. Detection of BCR-ABL kinase mutations in CD34+ cells from chronic myelogenous leukemia patients in complete cytogenetic remission on imatinib mesylate treatment. Blood 2005;105:2093-8.
27. Graham SM, Jorgensen HG, Allan E, et al. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. Blood 2002;99:319-25.
28. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. N Engl J Med 2006;354:2531-41.
29. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome–positive ALL. N Engl J Med 2006;354:2542-51.
30. Copland M, Hamilton A, Elrick LJ, et al. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood 2006;107:4532-9.
31. Shah NP, Sawyers CL. Mechanisms of resistance to STI571 in Philadelphia chromosome-associated leukemias. Oncogene 2003;22:7389-95.
32. Willis SG, Lange T, Demehri S, et al. High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naive patients: correlation with clonal cytogenetic evolution but not response to therapy. Blood 2005;106:2128-37.
33. Roche-Lestienne C, Preudhomme C. Mutations in the ABL kinase domain pre-exist the onset of imatinib treatment. Semin Hematol 2003;40:Suppl 2:80-2.
34. Griswold IJ, MacPartlin M, Bumm T, et al. Kinase domain mutants of Bcr-Abl exhibit altered transformation potency, kinase activity, and substrate utilization, irrespective of sensitivity to imatinib. Mol Cell Biol 2006;26:6082-93.