High rates of durable response are achieved with imatinib after treatment with interferon α plus cytarabine: results from the International Randomized Study of Interferon and STI571 (IRIS) trial

François Guilhot,[1] Brian Druker,[2] Richard A. Larson,[3] Insa Gathmann,[4] Charlene So,[5] Roger Waltzman,[5] and Stephen G. O'Brien[3]

[1]CIC 802 INSERM, CHU de Poitiers, Poitiers, France; [2]Oregon Health and Science University Cancer Institute, Portland, OR, USA; [3]University of Chicago, Chicago, IL, USA; [4]Novartis Pharma AG, Basel, Switzerland; [5]Novartis Pharmaceuticals, East Hanover, NJ, USA, and [6]University of Newcastle, Newcastle, UK.

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Correspondence: François Guilhot, Department of Oncology-Hematology and Cell Therapy, CIC 802 INSERM, CHU de Poitiers, 86021, France. E-mail: f.guilhot@chu-poitiers.fr

ABSTRACT

Background

Imatinib is the standard of care for newly diagnosed chronic-phase chronic myeloid leukemia. The largest randomized clinical trial of imatinib was the multinational IRIS trial in which 1106 patients were randomized to receive either imatinib 400 mg/day or a standard regimen of interferon-α plus cytarabine.

Design and Methods

Patients were allowed to cross over to the opposite treatment for intolerance, lack of response, disease progression, and, following release of the initial efficacy data, reluctance to remain on therapy with interferon-α plus cytarabine. The safety and efficacy of imatinib in patients who crossed over from interferon-α plus cytarabine to imatinib is reported here.

Results

Of 553 patients originally assigned to interferon-α plus cytarabine, 65% crossed over to imatinib, of whom 67% continue to receive treatment. After a median of 54 months of imatinib treatment on study, 93% achieved complete hematologic remission, 86% achieved major cytogenetic remission, and 81% achieved a complete cytogenetic remission as the best observed response. Estimated rates of freedom from progression to accelerated or blast phase and overall survival were 91% and 89%, respectively, at 48 months after starting imatinib.

Conclusions

This is the largest analysis to date describing the efficacy of imatinib in patients who have received prior therapies for chronic myeloid leukemia and it demonstrates excellent responses to this treatment. *(ClinicalTrials.gov identifier: NCT00006343)*

Key words: durable response, imatinib, interferon-α, cytarabine.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by an aberrant chromosomal translocation that results in the so-called Philadelphia chromosome.[1] This translocation fuses two genes, resulting in the constitutively active intracellular protein-tyrosine kinase BCR-ABL. Imatinib mesylate (STI571, Glivec®/Gleevec®, Novartis Pharmaceuticals, East Hanover, NJ, USA) is an inhibitor of the BCR-ABL tyrosine kinase. In patients with newly diagnosed CML in chronic phase (CP) response rates to this drug were superior to those to treatment with a standard regimen of interferon α (IFN-α) plus cytarabine (Ara-C) in the phase 3 International Randomized Study of Interferon and STI571 (IRIS).[2-4]

Historically, the activity of IFN-α in the treatment of CML was attributed to various effects on the immune system such as modulation of immunoglobulin production, inhibition of T-cell cytotoxicity, monocyte/macrophage function and natural killer cell activity.[5] IFN-α has the potential to control progression of CML-CP and was the first non-myelotoxic drug shown to cause a marked reduction in the percentage of Philadelphia chromosome-positive (Ph^+) cells in the bone marrow. Combination therapy with cytarabine and IFN-α in CML-CP patients was shown to increase the rate of major cytogenetic responses and prolong survival compared to IFN-α alone.[6] Continued research into the treatment of patients with CML has shown that achievement of a sustained complete cytogenetic response correlates with prolonged survival.[4,7] Treatment with IFN-α yields complete cytogenetic response rates ranging from 10% to 25%, particularly in patients with low-risk Sokal scores.[8]

The advent and success of imatinib therapy in CML have dramatically changed the CML therapeutic algorithm. Randomized trial data from IRIS confirmed that imatinib was superior to IFN-α as first-line therapy.[4] However, it is clinically relevant to note that intolerance, lack of response to IFN-α, or loss of response to IFN-α did not preclude a subsequent response to imatinib.[4] The aim of this analysis was to assess the long-term outcome of patients who received IFN-α and then crossed over to imatinib within the IRIS trial.

The IRIS trial enrolled 1106 adult patients with newly diagnosed CML-CP and permitted crossover between treatment arms provided that intolerance to initial treatment or lack of efficacy could be demonstrated.[3] Intolerance to IFN-α was defined as a recurrent grade 3 non-hematologic toxicity, recurring despite appropriate dose reductions and optimal symptomatic management or a non-hematologic toxicity that was life-threatening such that retreatment with IFN-α would be deemed medically inappropriate. A subsequent trial amendment also permitted crossover to imatinib for reluctance to continue on IFN-α + Ara-C after the initial efficacy data were released. Based on a median follow-up period of nearly 5 years for this group of patients in the IRIS trial, this report provides a summary of the efficacy and safety of imatinib therapy in these patients who demonstrated failure, intolerance, or reluctance to continue on IFN-α + Ara-C.

Design and Methods

The IRIS phase 3 trial enrolled 553 patients with newly diagnosed Ph^+ CML-CP into each treatment arm between June 2000 and January 2001. Patients received either imatinib 400 mg once daily or IFN-α (target dose, 5 million units per square meter of body surface area per day [U/m^2/day]) in conjunction with subcutaneous low-dose Ara-C 20 mg/m^2/day (maximum daily dose, 40 mg) for 10 days every month after having reached their maximum tolerated dose of IFN-α. Crossover to the other treatment arm of imatinib was allowed only if there were no response at pre-specified time points, intolerance to therapy, or progression consisting of a loss of response or an increase in the white blood cell count.[3] The Study Management Committee reviewed all crossover cases and specifically approved the cases of intolerance to IFN-α + Ara-C and increase in white blood cell count. In January 2002, after all patients had completed at least 1 year of treatment, the protocol was amended to permit crossover based on reluctance to continue therapy with IFN-α + Ara-C due to the improved outcome observed in the imatinib arm or lack of response at 12 months.

End-points

The primary study end-point of IRIS was event-free survival (referred to as progression-free survival in prior publications).[3,4] Events were the first occurrence of any of the following during treatment: death from any cause, progression to accelerated phase or blast crisis (AP/BC), or loss of a complete hematologic response or major cytogenetic response. Event-free survival was shown to be statistically superior for patients on the imatinib arm at the first interim analysis at 18 months, which prompted the data to be released and published.[3] For the current analysis, event-free survival was measured from the start of imatinib therapy (after crossover) until the occurrence of any of the same events described above. A cytogenetic response was determined by evaluating at least 20 metaphase marrow cells per sample and was categorized as complete (0% Ph^+ metaphases) or partial (1-35% Ph^+ metaphases). Major cytogenetic response includes partial and complete cytogenetic responses. After discontinuation of the imatinib study treatment, patients were followed only for subsequent transplant information and survival. Overall survival was defined for this report as the time from starting imatinib therapy (after crossover) until death (from any cause) and was censored at the last date of contact for patients alive (or lost to follow-up or who withdrew consent).

Statistical methods

January 31st, 2007 was the cut-off date used for this analysis, and the study remains ongoing. The 95% confidence intervals for best observed response rates were calculated using Pearson-Clopper limits. Event-free survival, progression to AP/BC, and overall survival were

analyzed by the Kaplan-Meier method. All safety data are based on a January 2006 data cut-off as collection of adverse events was not required thereafter.

Results

Of 553 patients originally randomized to the IFN-α + Ara-C treatment, 359 (65%) crossed over to imatinib, 181 (33%) patients discontinued study treatment, and 13 (2%) patients remained on IFN-α + Ara-C. As of January 2007, 239 (67%) patients who crossed over continued to receive imatinib on study protocol. The reasons for discontinuation of treatment with IFN-α + Ara-C and crossover to imatinib are summarized in Table 1. Most patients crossed over because of intolerance of IFN-α + Ara-C (n = 144), lack of response by indicated landmarks (n=97), or progression on IFN-α + Ara-C (n = 77). An additional 41 (7%) patients cited reluctance to continue on IFN-α + Ara-C as the primary reason for crossover.

The median time from diagnosis of CML-CP to initiation of imatinib treatment was 13 months (range, 2-61 months). Prior to crossover, the median duration of treatment with IFN-α + Ara-C was 9 months (range, 0.5-54 months). Patients who crossed over to imatinib because of intolerance were treated with IFN-α + Ara-C for a median of 4 months (range, 0.5-48 months). Those with a lack of response to IFN-α + Ara-C crossed over to imatinib after a median of 13 months, and patients who were reluctant to continue on IFN-α + Ara-C crossed over to imatinib after a median of 18 months of therapy. Of the patients who crossed over to imatinib, 13% did so within the first 3 months of treatment, 22% between 3 and 6 months, 14% between 6 and 9 months, 8% between 9 and 12 months, 33% between 12 to 24 months, and 10% after 24 months of first-line treatment with IFN-α + Ara-C. At the January 31st, 2007 data cut-off, 13 (2%) of the 553 original patients randomized to IFN-α + Ara-C were still receiving IFN-α study treatment.

Patients who crossed over to receive imatinib had received imatinib for a median of 54 months (mean, 47 months; range, 0.2-74 months) at the data cut-off for these analyses. The median follow-up was 51 months in the patients who were reluctant to continue IFN-α, 61 months in those with intolerance, 54 months for those with lack of response, and 49 months for patients who progressed on IFN-α + Ara-C. Sixty-six percent of patients had an imatinib dose adjustment (45% transient interruptions) with an average dose of 395 mg/day in the 359 patients who crossed over to this treatment. As of January 31st, 2007, 120 of 359 (33%) patients who crossed over to imatinib had discontinued imatinib therapy (Table 1). "Unsatisfactory therapeutic effect" was the most common reason for study discontinuation, cited by 15% of patients who crossed over to second-line imatinib. Loss of complete hematologic response was noted in 1%, loss of major cytogenetic response in 1%, and progression to AP/BC in 8%. Other reasons for discontinuation included: adverse events (5%), bone marrow transplantation (2.8%), protocol violation (2.8%), withdrawal of consent (5.3%), death (1%), loss from follow-up (< 1%), and other reasons (< 1%).

Of the 359 patients treated with imatinib after IFN-α + Ara-C, 93% achieved a best response of complete hematologic response, 86% achieved a best response of major cytogenetic response, and 81% achieved a best response of complete cytogenetic response (Table 2). The complete cytogenetic response rate was 95% in patients who were reluctant to continue IFN-α + Ara-C therapy, 83% in those intolerant of IFN-α + Ara-C, 78% in those who did not respond to IFN-α + Ara-C, and 71% in those who progressed on initial IFN-α + Ara-C

Table 1. Status of IRIS patients randomized to IFN-α + Ara-C, reason for crossover, and status after crossover as of January 31st, 2007.

Status of patients randomized to IFN-α + Ara-C (n= 553)	n (%)
Remaining on first-line IFN-α	13 (2)
Discontinued first-line IFN-α and study	181 (33)
Crossed over to imatinib on study	359 (65)
Intolerance of treatment	144 (26)
Lack of response	97 (18)
No CHR at 6 months	41 (7)
No CHR at 12 months	3 (<1)
No MCyR at 12 months	49 (9)
No MCyR at 24 months	4 (<1)
Reluctance to continue on IFN-α + Ara-C	41 (7)
Progression	77 (14)
Increase in WBC count	25 (5)
Loss of CHR	29 (5)
Loss of MCyR	23 (4)

Status of patients who received imatinib after crossover from IFN-α + Ara-C (n=359)	n (%)
Remaining on imatinib	239 (67)
Discontinued imatinib on study	120 (33)
Adverse events	18 (5)
Death	4 (1)
Unsatisfactory therapeutic effect	54 (15)
Stem cell transplantation	10 (3)
Protocol violation	10 (3)
Withdrawal of consent	19 (5)
Lost to follow-up	2 (<1)
Other	3 (<1)

CHR: complete hematologic response; MCyR: major cytogenetic response; WBC: white blood cell.

Table 2. Best observed rates of response in patients who crossed over to imatinib (n=359).

Response	n (%) [95% CI]
Complete hematologic response	335 (93%) [90.2, 95.7]
Major cytogenetic response	307 (86%) [81.4, 89.0]
Complete cytogenetic response	289 (81%) [76.0, 84.5]

(Figure 1). Among the 359 patients who crossed over to imatinib, the best observed complete cytogenetic response rates at 1, 2, and 3 years after initiation of imatinib were 60%, 74%, and 77%, respectively. In the current follow-up, only 8% of the 289 patients who achieved a complete cytogenetic response had an event thereafter during treatment (3% progressed to AP/BC).

Thirty-nine patients who achieved a complete cytogenetic response on IFN-α + Ara-C treatment crossed over to second-line imatinib. The estimated event-free survival rate of these patients at 48 months was 93%, with only one patient progressing to AP/BC. The event-free survival rate at 48 months was 88% for the 49 patients who had achieved a partial cytogenetic response on IFN-α + Ara-C before crossing over to imatinib therapy. The event-free survival rate for the 271 patients randomized in the IFN-α + Ara-C arm who failed to achieve a major cytogenetic response was 84%. Although not statistically significant, a trend was observed between increasing event-free survival rate and the magnitude of cytogenetic response in patients treated with IFN-α + Ara-C prior to crossover (i.e., patients who achieved a complete cytogenetic response had a better event-free survival rate than those who failed to achieve a major cytogenetic response).

After 18 months of imatinib therapy following IFN-α + Ara-C, the event-free survival rate was 92%, and the estimated overall survival rate was 97%; these were similar to the 18-month data for the cohort of patients who received imatinib as first-line therapy. The estimated rate of freedom from progression to AP/BC at 48 months following crossover to imatinib was 91%, and the rates were 97%, 93%, 92%, and 82% in patients who were reluctant to continue IFN-α + Ara-C, were intolerant of IFN-α + Ara-C, or who crossed over to imatinib because of lack of response or progression, respectively (Figure 2). Considering all events, including loss of complete hematologic response, loss of major cytogenetic response, and death during treatment, the estimated event-free survival at 48 months after initiation of imatinib following crossover was 86%, and specifically, 94%, 88%, 86%, and 75% in patients who had been reluctant to continue IFN-α + Ara-C, were intolerant of IFN-α + Ara-C, or crossed over because of lack of response or progression, respectively (Figure 2).

Based on an intent-to-treat analysis, the overall survival (since randomization into the IRIS study) of the entire group initially randomized to IFN-α + Ara-C, regardless of whether they crossed over to imatinib, was lower than that observed in patients initially randomized to imatinib (84% *vs.* 88% at 6 years, respectively;

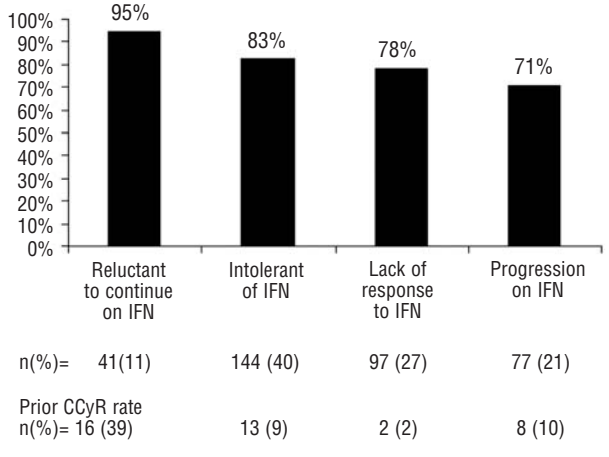

Figure 1. Complete cytogenetic responses among patients randomized to IFN-α + Ara-C in the IRIS trial who crossed over to imatinib according to the reason for change. Progression (as reason for crossover) was defined as an increase in white blood cell count, loss of complete hematologic response, or loss of major cytogenetic response (CCyR: complete cytogenetic response).

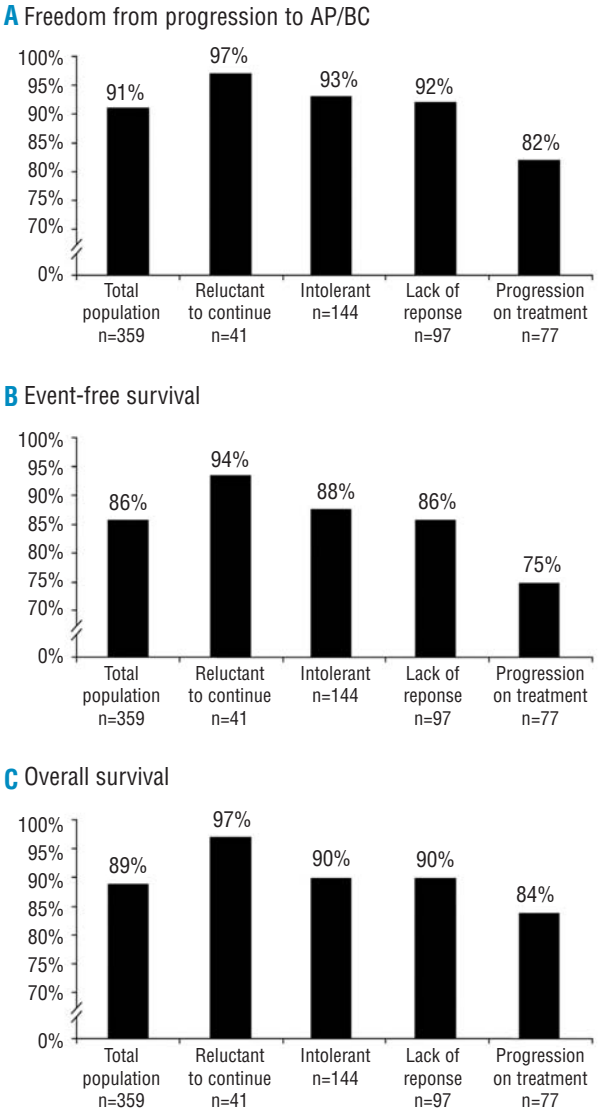

Figure 2. Estimated outcome rates at 48 months following initiation of imatinib in patients who crossed over from IFN-α + Ara-C. Progression (as reason for crossover) was defined as an increase in white blood cell count, loss of complete hematologic response, or loss of major cytogenetic response.

p=0.075) (Figure 3).[4] The estimated overall survival rate at 48 months after crossing over to imatinib was 89%. Specifically, the overall survival rates at 48 months were 97% in patients who were reluctant to continue IFN-α + Ara-C, 90% in patients who did not tolerate IFN-α + Ara-C, and 90% and 84% in patients who crossed over because of lack of response or progression, respectively.

Outcome of patients who crossed over from imatinib to interferon-α plus cytarabine

Fourteen patients crossed over from imatinib to IFN-α + Ara-C after a median of 13 months on imatinib: four because of intolerance, nine because of progression, and one because of lack of response. After a median of 6 months of treatment with IFN-α + Ara-C, all had discontinued second-line therapy: three because of adverse events, nine because of an unsatisfactory therapeutic effect, one because of bone marrow transplantation, and one because of a protocol violation. Only one patient who crossed over from imatinib to IFN-α + Ara-C subsequently achieved a complete cytogenetic response. Three patients who achieved a complete cytogenetic response on first-line imatinib therapy did not have a documented complete cytogenetic response while on second-line IFN-α + Ara-C.

Safety

Imatinib treatment after IFN-α + Ara-C was well tolerated, with a safety profile similar to that observed in patients who were randomized to initial treatment with imatinib (Table 3). The most frequently reported non-hematologic grade 3 or 4 toxicities in patients treated with imatinib following IFN-α + Ara-C were elevations in the levels of liver enzymes (5%), abdominal pain, musculoskeletal pain, hemorrhage (3% each), fluid retention, diarrhea, fatigue, joint pain, rash, and myalgia (2% each). The following newly occurring or worsening grade 3 or 4 hematologic toxicities were noted: neutropenia (26%), thrombocytopenia (11%), and anemia (5%). These were slightly higher than the 17%, 9%, and 4% incidences, respectively, observed in patients treated with imatinib as first-line therapy.

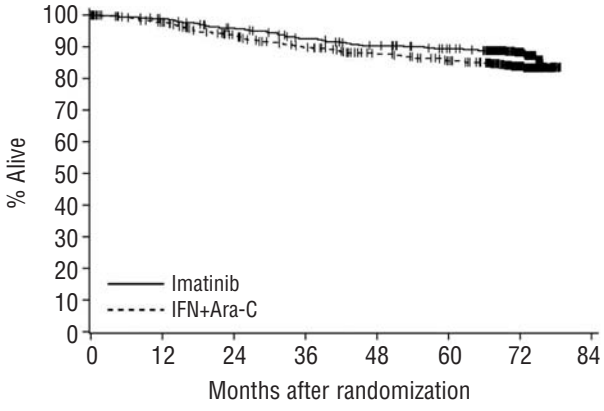

Figure 3. Overall survival for all patients in the intent-to-treat population. Data are presented for patients initially randomized to the imatinib (solid line) or IFN-α + Ara-C (dashed line) treatment arms. At 6 years, overall survival rates were 88% for patients randomized to imatinib versus 84% for patients randomized to IFN-α+ Ara-C (p=0.075).

Discussion

Prior to the advent of imatinib, IFN-α was a standard initial therapy for CML-CP. This analysis assessed the population of patients in the IRIS study that crossed over to imatinib, a median of 9 months after starting IFN-α + Ara-C. Initially, IRIS subjects were allowed to cross over to imatinib due to intolerance, lack of response, or disease progression while receiving IFN-α + Ara-C. The efficacy of imatinib, documented in clinical trials, resulted in a protocol amendment, which allowed patients who were reluctant to continue therapy with IFN-α + Ara-C to cross over to imatinib within the study, regardless of response. Although the complete cytogenetic response rate for the total population of patients who crossed over to imatinib therapy was 81%, this rate was highest among the subgroup of

Table 3. Adverse events reported in 15% or more of patients receiving second-line imatinib (versus first-line imatinib) at January 31st, 2006 cut-off.

Adverse Event	First line imatinib n=551 (%)		Second line imatinib n=359 (%)	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Non-hematologic				
Fluid retention	61.7	2.5	59.6	1.7
Superficial edema	59.9	1.5	58.2	0.8
Other fluid retention events	6.9	1.3	5.3	0.8
Muscle cramps	49.2	2.2	46.2	1.4
Diarrhea	45.4	3.3	40.7	2.2
Nausea	49.5	1.3	37.6	0.3
Musculoskeletal pain	47.0	5.4	37.0	3.3
Rash and related terms	40.1	2.9	32.3	1.7
Abdominal pain	36.5	4.2	29.5	3.1
Fatigue	38.8	1.8	28.4	2.2
Joint pain	31.4	2.5	25.6	2.2
Headache	37.0	0.5	24.2	1.4
Nasopharyngitis	30.5	–	23.1	–
Hemorrhages	28.9	1.8	21.2	3.1
Vomiting	22.5	2.0	17.8	0.3
Myalgia	24.1	1.5	17.5	1.7
Cough	20.0	0.2	15.0	0.3
Hematologic*				
Anemia	49.5	4.4	41.5	5.0
Neutropenia	65.7	16.7	63.2	26.2
Thrombocytopenia	58.8	8.9	44.0	11.1
Biochemical*				
Elevated serum alanine or aspartate aminotransferase	59.2	5.3	46.5	4.7

**Newly occurring or worsening laboratory toxicity based on Common Toxicity Criteria grades for laboratory values.*

patients who were reluctant to continue therapy, and who, presumably, were already having some degree of response to IFN-α + Ara-C. Of even greater importance, the overall survival rate was higher among the patients who were reluctant to continue IFN-α + Ara-C than among those who were intolerant of, did not respond to, or who progressed on initial IFN-α + Ara-C therapy. However, based on an intent-to-treat analysis, the overall survival rate of the group initially randomized to IFN-α + Ara-C, regardless of whether they crossed over to imatinib, was lower than that observed in patients initially randomized to imatinib.[4] Following 18 months of therapy with imatinib after crossing over from IFN-α + Ara-C, the event-free survival rate (92%) and estimated overall survival rate (97%) were consistent with those observed in a previous phase 2 trial of imatinib in patients with CML-CP after failure of prior IFN-α therapy.[10] In that trial, similar results were reported with an estimated 89% of patients free from progression to AP/BC, and an estimated 95% alive after 18 months. However, the median time from diagnosis and the median duration of prior IFN-α therapy for these patients were longer at 34 and 14 months, respectively, than in the IRIS trial.

A recent 7-year update of response rates and duration of responses observed in patients enrolled in the IRIS trial and randomized to front-line imatinib therapy reported a 93% estimated rate of freedom from progression to AP/BC, 81% event-free survival, and 86% overall survival.[11] One possible explanation for the comparable responses may be that patients who crossed over to imatinib quite quickly after starting IFN-α + Ara-C because of intolerance and, particularly, those who were reluctant to continue IFN-α + Ara-C, both constitute a subpopulation of patients with treatment-responsive CML. However, patients who crossed over to treatment with imatinib had improved responses and survival compared to patients who remained on IFN-α + Ara-C. At 6 years, estimated event-free survival rates in an intent-to-treat analysis were 83% for those initially randomized to imatinib and 63% for those patients initially randomized to IFN-α + Ara-C; rates of freedom from progression to AP/BC were 93% for patients in the imatinib arm and 86% for those in the IFN-α + Ara-C arm ($p<0.001$).

The long-term benefits of imatinib therapy were assessed by Roy *et al.* in a retrospective comparison of 42-month follow-up data from 551 patients with newly diagnosed patients with CML-CP treated with front-line imatinib in the IRIS trial and 325 similar patients who received IFN-α + Ara C in the multicenter French CML91 trial.[12]

Estimated complete cytogenetic response rate, survival free of progression to AP/BC, and overall survival rate were significantly higher with imatinib than with IFN-α + Ara C ($p<0.001$, $p=0.004$, and $p<0.001$, respectively). The comparative analysis of long-term outcomes between the IRIS and CML91 studies described above and the 5-year follow-up results of the IRIS trial both demonstrate that imatinib is the most effective front-line therapy for patients with CML-CP. The most appropriate role for IFN-α now remains to be defined. The goal of eradicating CML completely has prompted researchers to explore the possibility of discontinuing the use of imatinib selectively in patients with a documented complete molecular response or with undetectable transcript levels for at least 2 years.[13] Of 12 such patients with CML who discontinued imatinib after previous treatment with IFN-α, six continued to have undetectable CML by molecular assays after a median follow-up of 18 months (range, 9-24 months) but the other six relapsed within 6 months. A sustained complete molecular response following discontinuation of imatinib was not associated with duration of previous IFN-α therapy. The potential role of IFN-α in current CML treatment has also been reported by Essers *et al.*, who demonstrated that IFN-α treatment stimulates dormant hematopoietic stem cells thereby making them susceptible to other chemotherapeutic agents.[14]

The data discussed in this study focus on cytogenetic responses. A previous analysis of patients who crossed over to imatinib in IRIS demonstrated that molecular responses were comparable between patients receiving imatinib as first- or second-line treatment, with an estimated 85% and 82% of patients, respectively, achieving both complete cytogenetic response and major molecular response by 5 years on therapy.[15] Our observations are complemented by those in two recent studies of patients with CML-CP in complete or near complete cytogenetic response following therapy with IFN-α whose responses at the molecular level improved when they switched from IFN-α treatment to imatinib.[16,17] A progressive and consistent decline in minimal residual disease or maintenance of major molecular response, as measured by quantitative polymerase chain reaction, was documented in nearly every patient treated.

In summary, IRIS patients who received first-line treatment with IFN-α + Ara-C had considerable clinical benefit after crossing over to imatinib within the study. After 5 years, the outcomes of these patients were very similar to those of patients who received first-line treatment with imatinib. The usefulness of IFN-α therapy in the imatinib era of treatment of CML-CP requires further investigation.

Authorship and Disclosures

FG was the principal investigator and takes primary responsibility for the paper. FG, BD, and CS designed the research. FG, BD, RL, and SO performed the research. FG, IG, RL, and CS analyzed and interpreted the data. FG and RW wrote the paper. All authors reviewed the manuscript.

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