Survival advantage from imatinib compared with the combination interferon-α plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials

Lydia Roy, Joëlle Guilhot, Tillmann Krahnke, Agnès Guerci-Bresler, Brian J. Druker, Richard A. Larson, Steve O'Brien, Charlene So, Giorgio Massimini, and François Guilhot

In the multinational IRIS study comparing imatinib with interferon plus cytarabine (IFN/Ara-C) in patients with newly diagnosed chronic-phase chronic myelogenous leukemia (CP CML), imatinib demonstrated significantly higher rates of complete cytogenetic responses (CCyRs) and improved progression-free survival (PFS). However, because of a high early crossover rate to imatinib, survival benefit was not assessable. Here, we report the result of a study comparing long-term outcome of patients included in 2 prospective randomized trials: 551 patients assigned to imatinib in the IRIS trial from 2000 to 2001 and 325 patients who received the combination IFN/Ara-C in the CML91 trial between 1991 and 1996 before imatinib was available. With a follow-up of 42 months for both groups of patients, estimated CCyR, survival free of transformation, and overall survival were significantly higher with imatinib compared with IFN/Ara-C ($P < .001$, $P = .004$, and $P < .001$, respectively). Improved overall survival was also confirmed within different Sokal prognostic risk groups. Of interest, among all patients who achieved major cytogenetic response or CCyR at 12 months, the survival rate was similar irrespective of their treatment. In conclusion, within the limitation of this historical comparison, there is a survival advantage from first-line therapy with imatinib over IFN/Ara-C. (Blood. 2006; 108:1478-1484)

Introduction

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder characterized by a reciprocal t(9;22)(q34;q11) chromosomal translocation, which creates the Philadelphia chromosome (Ph). The latter harbors the *BCR-ABL* fusion gene, encoding a 210-kDa chimeric oncoprotein, with deregulated constitutive tyrosine kinase activity, responsible for leukemogenesis.[1]

For almost 20 years, allogeneic stem cell transplantation for younger patients or interferon-alpha (IFN-α)–based regimens were the only effective therapies resulting in a substantial survival improvement in chronic-phase CML.[2,3] IFN-α was the first drug shown to cause a marked and sustained reduction in Ph-positive marrow cells in some patients. Those patients treated with IFN-α who achieved a major or complete cytogenetic response (MCyR or CCyR, respectively) had a significant improvement in survival.[4,5] However, prolonged administration of high-dose IFN-α was often not well tolerated, and the CCyR rate was only about 10% in most cases. Because of preliminary results suggesting that cytogenetic responses were improved with low-dose cytarabine (Ara-C) in chronic-phase CML,[6] combination phase 1/2 trials of IFN-α plus Ara-C were designed. Then, 2 large phase 3 randomized trials were independently conducted. The multicentric French CML91 trial[7,8] (721 patients) first demonstrated the superiority of the combination over IFN-α alone, in terms of complete hematologic response (CHR), cytogenetic response (MCyR: 35% vs 31%; CCyR: 13% vs 9% at 12 months), and also overall survival (estimated 3-year survival: 85.7% vs 79.1%). Similar conclusions favoring IFN plus Ara-C were next reported for the multicentric Italian trial[9] (538 patients) with improvement of cytogenetic responses rates (MCyR: 28% vs 18%; CCyR 14% vs 8% at 24 months). However, overall survival benefit was not confirmed by the Italian trial. Based on these results, the combination of IFN-α plus Ara-C was considered as the standard for patients in chronic-phase CML.

At the end of the 1990s, imatinib mesylate (STI571, Gleevec; Novartis Pharmaceuticals), a rationally designed, potent selective competitive inhibitor of the Bcr-Abl protein tyrosine kinase,[10] was initially used for CML patients in late chronic-phase who were resistant or intolerant to therapy with IFN-α. Promising results were rapidly observed with high rates of CHR, but also MCyR (up

From the Department of Oncology-Hematology and Cell Therapy, EA 3805 and Clinical Research Centre, Centre Hospitalier Universitaire (CHU) La Milétrie, Poitiers, France; Novartis Pharma, Basel, Switzerland; the Department of Hematology, CHU Brabois, Vandoeuvre les Nancy, France; Oregon Health Science University Cancer Institute, Portland, OR; the University of Chicago, Chicago, IL; and the University of Newcastle, Newcastle, United Kingdom.

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Presented in part at the 2005 annual meeting of the American Society of Hematology, Atlanta, GA, December 12, 2005.[14]

Reprints: François Guilhot, Department of Oncology-Hematology and Cell Therapy, CHU La Milétrie, 2 Rue de la Milétrie, 86021 POITIERS CEDEX, France; e-mail: f.guilhot@chu-poitiers.fr.

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to 65%) including 48% with CCyR, even after IFN-α failure.[11,12] It was therefore hypothesized that the drug would be at least as effective in early chronic-phase CML. A large multinational trial (also referred to as the IRIS study: International Randomized Study of IFN-α plus Ara-C vs STI571) randomized 1106 newly diagnosed patients with CML in chronic phase to receive either imatinib (400 mg orally daily) or the standard combination IFN-α (5 MU/m^2 daily) plus Ara-C (20 mg/m^2 subcutaneously daily for 10 days every month).[13] Superiority of imatinib was confirmed for early response end points—namely, higher estimated rates of MCyR (87% vs 35%) and CCyR (76% vs 14.5%) at 18 months and low rates of disease progression to accelerated phase or blast crisis (3.3% vs 8.5%) after 18 months—as well as for better tolerance. Thus, imatinib was quickly approved for the frontline treatment for patients with newly diagnosed CML in chronic phase. However, as the design of the IRIS trial allowed crossover between both arms in case of intolerance or lack of efficacy, many patients crossed over from IFN/Ara-C to imatinib, and survival rates (97% vs 95%) were not significantly different. Indeed, 64% of patients assigned to the IFN-α plus Ara-C arm switched to imatinib after a median duration of treatment of 9 months. Thus, overall survival analysis based on intention to treat was assessable but could not show a difference.

The best alternative approach to estimate the survival benefit of imatinib would be a comparison between a group of patients receiving imatinib and a similar homogeneous group of patients included in an earlier prospective trial assessing the combination IFN-α plus Ara-C as first-line therapy who did not have access to imatinib. Thus, we performed a retrospective analysis comparing the outcome of patients first treated with imatinib in the IRIS trial, and patients assigned to IFN-α and Ara-C in the CML91 trial. The results of this study were presented in part at the 2005 meeting of the American Society of Hematology and are now reported in full in this paper.[14] The results demonstrate a higher overall survival with imatinib and confirm previous conclusions for CCyR and progression-free survival as well.

Patients and methods

Patients and treatments

All patients included in both the CML91 and the IRIS trials were adults older than 18 years of age with Philadelphia chromosome–positive CML in chronic phase, diagnosed within the preceding 6 months, based on the date of the first cytogenetic analysis. They had been treated previously with only hydroxyurea before inclusion in the CML91 study, whereas hydroxyurea and/or anagrelide were allowed in the IRIS study. The details of both trials have been previously published.

Between March 1991 and April 1996, 721 patients were enrolled and analyzed in the French CML91 trial, half being randomly assigned to the IFN-α plus Ara-C group (n = 361). Thirty-six were not treated, and the 325 patients who actually received the combination of IFN-α plus Ara-C were selected for further analysis in the present study. These patients received IFN-α starting at 5 MIU/m^2 subcutaneously daily with hydroxyurea 50 mg/kg per day orally as needed until a stable complete hematologic response (CHR) was achieved. Monthly courses of Ara-C at a dose of 20 mg/m^2 per day for 10 days were added to the IFN-α therapy within 3 months. In the multinational IRIS study, 553 patients were randomized to each treatment group between June 2000 and January 2001. The current comparison analyzed only the 551 patients initially assigned to the imatinib arm, who actually received imatinib at the initial dose of 400 mg daily. Hydroxyurea was allowed during the initial 6 months of therapy to keep white blood cell (WBC) count lower than 20×10^9/L. For patients who failed to achieve either a CHR at 3 months or at least a minor cytogenetic response at 12 months, the imatinib dosage was increased to 400 mg twice a day in the absence of dose-limiting toxicities.

Using Sokal's formula,[15,16] a prognostic score was calculated for each patient before inclusion in the CML91 trial. Based on the Sokal score and the availability of an HLA-matched family donor, bone marrow transplantation was required for all patients younger than 35 years of age regardless of their Sokal score and also for high-risk patients from 35 to 50 years of age. In the IRIS study, both Sokal and Hasford[17] scores were calculated whenever complete data were available. However, they were not used for patient management in the trial.

End points and response criteria

End points in the CML91 study were rates of hematologic response at 6 months, cytogenetic response at 12 months, and overall survival. In the IRIS trial, the primary end point was progression, which was defined by any of the following events, whichever came first: death from any cause during treatment, accelerated-phase or blast-phase CML, loss of complete hematologic response, loss of major cytogenetic response, or an increased WBC count. Secondary end points were the rates of complete hematologic and cytogenetic responses. Based on these designs, MCyR and CCyR rates, progression-free survival, and overall survival were selected for end points in the current study.

In both trials, the definitions for cytogenetic responses were quite similar. Partial response was defined by the decrease of Ph-positive marrow metaphase cells to 1% to 34% in CML91 or 1% to 35% in IRIS; complete response required the absence of Ph-positive cells on karyotype analysis; major response was defined as the sum of complete and partial cytogenetic responses. In the IRIS trial, the cytogenetic analyses were performed every 3 months for the first 12 months and every 6 months thereafter. In the CML91 study, cytogenetics at 3 months was optional; however, they were performed at 6, 9, and 12 months for the first 12 months, and every 4 months thereafter.

As several criteria for progression defined in the IRIS study (eg, loss of hematologic or cytogenetic response, confirmed increase in WBC) were not used at the time of the CML91 study, only accelerated phase, blastic phase, or death (due to any cause during treatment), whichever occurred first, were selected for the purpose of this comparison. The term "survival free of transformation" (ie, accelerated phase, blast crisis patients, and death) will be used in this analysis. The definitions of accelerated phase and blastic crisis differed slightly between the 2 trials. The percentage of peripheral blasts was slightly lower in the CML91 study for the diagnosis of accelerated and blastic phases (15% and 30% for IRIS vs 10% and 20% for CML91, respectively). The differences were considered as minor.

For a unified approach, the cut-off date for analysis was set at 42 months after start of study treatment. This time corresponded to the last update for the IRIS study when the current comparison was planned.

Statistics

The study groups' base-line characteristics were compared by the Wilcoxon test in the case of continuous variables and by the chi square or the Fisher exact test, when appropriate, in the case of binary variables and categoric variables.

When analysis was carried out by Sokal score, 3 categories were used for CML91 patients (low/intermediate/high risk) and 4 categories (low/intermediate/high risk/missing) for IRIS patients. In any multivariate analysis, patients with missing Sokal score from the IRIS trial were excluded, but they were included in all pooled analyses.

Time to cytogenetic response (complete response only vs other, as well as major response vs other) until 42 months, and response rates at 12 and 36 months were estimated by the Kaplan-Meier method. Time to MCyR and CCyR was summarized (median and range) for patients who responded. Cytogenetic response rates were stratified by Sokal score. The cumulative number of patients included in the landmark analysis was compared by Fisher exact test.

Overall survival and survival free of transformation were presented and compared overall, by cytogenetic response at 12 months (landmark analysis) and Sokal score using Kaplan-Meier methods. Concerning

survival free of transformation, only the combined end point of death or accelerated or blastic phase was analyzed. In order to take into account the differences between definition of phases, analyses were conducted first using the respective definition of each study and then, censoring at the date of assessment for the 2 patients of the CML91 study who would not have been considered in transformation using the IRIS definition. Overall survival was analyzed based on intention-to-treat principle first (considering all deaths), and then censoring at the time of the stem cell transplantation. Other analyses were conducted per protocol, patients without occurrence of events being censored at time of discontinuation of study treatment. When censoring was applied, patients were censored no later than 42 months after start of study treatment to account for the different follow-up duration of the 2 trials. Comparisons between groups were performed using log-rank tests for survival, survival free of transformation, and time to cytogenetic response. At selected time points (1, 2, and 3 years), Kaplan Meier estimates and relative risk (RR) were presented jointly with their 95% confidence interval (95% CI). Cox-models were used for multivariate analysis.[18]

All tests were 2-sided at a significance level of 5%. The analysis used SAS version 8 (SAS Institute, Cary, NC). Data were exchanged between the 2 collaborative groups. All analyses were performed on raw data, and statistical tests were cross-checked by both collaborative groups.

Results

Patients' characteristics and discontinuation of treatment

The pretreatment characteristics of both groups of patients selected for this study are reported and compared in Table 1. Median age was similar in the 2 groups, as well as spleen size, WBC count, eosinophils, hemoglobin, and platelet levels at diagnosis. However, the 2 groups differed significantly for sex distribution ($P = .039$), percentages of basophils ($P = .001$) and peripheral blasts ($P < .001$), and for Sokal risk group distribution ($P < .001$). Of note, a substantial number of patients from the IRIS group (n = 168, 30%) had an unknown Sokal risk, whereas it was determined for 100% of patients from the CML91 study. When patients with unknown Sokal score were excluded from the analysis, the Sokal risk distribution remained significantly different ($P = .007$) between both groups with more intermediate cases in the CML91 study. The median follow-up for surviving patients is 42 months in both studies.

Table 1. Patients and baseline characteristics of the IRIS study group (551 patients) and the CML91 group (325 patients)

Variable	IRIS study Patients in study	CML91 study Patients in study	*P*
No. of patients	551	325	—
Sex, no. (%)			.039
Male	341 (62)	178 (55)	—
Female	210 (38)	147 (45)	—
Age at diagnosis, y, median (range)	50 (18-70)	50 (18-71)	—
Splenomegaly			
No. assessable patients	442	325	—
Median cm under costal margin (range)	0 (0-27)	0 (0-21)	—
No. of patients with splenomegaly (%)	192 (43)	150 (46)	—
Median spleen size larger than 0 cm (range)	7 (1-27)	7 (1-21)	—
WBC at diagnosis			—
No. assessable patients	532	322	—
WBC count, $\times 10^9$/L (range)	96.4 (3.5-537)	74.8 (4.2-665)	—
Peripheral blood blasts cells at diagnosis			—
No. assessable patients	469	325	—
Blasts (%) total	0.4 (0-38)*	0 (0-9)	< .001
No. of patients with more than 0 blasts (%)	236 (69)	105 (31)	< .001
Median blasts more than 0, % (range)	2 (0.01-38)	2 (1-9)	.018
Basophils at diagnosis, median % (range)	3 (0-27)*	4 (0-18)	.001
No. assessable patients	474	322	—
Eosinophils at diagnosis, median % (range)	2 (0-37)	2 (0-9)	—
No. assessable patients	474	321	—
Hemoglobin at diagnosis, g/L (range)	123 (43-219)	125 (66-170)	—
No. assessable patients	518	322	—
Platelets at diagnosis, $\times 10^9$/L (range)	372 (53-3070)	389 (81-2385)	—
No. assessable patients	521	325	—
Sokal risk group, no. (% all patients/% assessable patients)			
Low	201 (36/52)	163 (50)	< .001
Intermediate	111 (20/29)	124 (38)	.007
High	71 (13/19)	38 (12)	—
Not known	168 (30/0)	0 (0)	—
No. assessable patients	383	325	—
Duration of randomized treatment, mo, median (range)	41.8 (0.16-42.0)	30.7 (0.30-42.0)	—
Median follow-up			
No. assessable patients	551	325	—
All patients, mo (range)	42.0 (0.59-42.0)	42.0 (5.32-42.0)	—
Surviving patients, mo, range (no. patients)	0.59-42.0 (504)	34.66-42.0 (292)	—

Continuous variables are presented with median and range. Binary and categoric variables are presented with frequency and percentage. Unless otherwise indicated, the number of patients assessable was 551 in the IRIS study and 325 in the CML91 study.

— indicates not applicable/not assessed.

*Despite high percentage of blasts or basophils at time of diagnosis, these patients were kept in the analysis as they fit the inclusion criteria at randomization.

A total of 130 patients (24%) in the imatinib group and 202 patients (62%) in the IFN-α plus Ara-C group discontinued the treatment ($P < .001$). Time to discontinuation was 41.8 months (range, 0.16-42 months) for the imatinib group and 31 months (range, 0.29-42 months) for the IFN-α plus Ara-C group. The most common reason was lack of efficacy or intolerance, which occurred more frequently with the IFN-α plus Ara-C treatment (Table 2). No patients from the CML91 study received imatinib. A few patients (14 of 551) in the IRIS trial assigned to the imatinib arm crossed over to IFN-α plus Ara-C combination. At the time of analysis, 38 patients (7%) had proceeded to bone marrow transplantation in the IRIS study, and 33 patients (10%) in the CML91 trial. Nine patients died during treatment (8 receiving imatinib; 1, the IFN plus Ara-C combination).

Cytogenetic responses

At the time of analysis, CCyR was observed in 81% (IRIS) and 32% (CML91) of patients. Among patients who achieved a CCyR in both groups, loss of response was subsequently observed in 44 (11%) of 399 patients with imatinib and 40 (38%) of 105 with IFN-α plus Ara-C ($P < .001$).

Of note, 15% of the patients treated with first-line imatinib in the IRIS study had never achieved MCyR. Among them, 7% were still under study treatment, and 8% had gone off treatment. In the CML91 group, there were 49% with such unsatisfactory cytogenetic response (26% on treatment and 23% off treatment, respectively). At the time of the CML91 trial, the higher proportion of patients still receiving IFNα plus Ara-C despite the absence of response is explained by the lack of other valuable therapeutic options before the imatinib era.

Estimated rates of MCyR and CCyR are shown in Figure 1A-B and summarized in Table 3. In both groups, most of the patients achieved their best cytogenetic response within 24 months. However, the results were highly significantly better with imatinib compared with IFN-α plus Ara-C. The occurrence of MCyR estimated for the IRIS and CML91 groups was 85% and 39% at 12 months (RR = 4.95; 95% CI, 4.03 to 6.09; $P < .001$) and 93% and 62% at 36 months (RR = 3.91; 95% CI, 3.26 to 4.68; $P < .001$), respectively. For CCyR, estimated rates were 70% and 14% at 12 months (RR = 8.92; 95% CI, 6.43 to 12.37; $P < .001$), and 87% and 42% at 36 months (RR: 4.69; 95% CI, 3.77 to 5.83; $P < .001$) for imatinib and the IFN-α plus Ara-C combination, respectively. For patients who achieved CCyR, the median time to achieve the response was 6 months (range, 2-40 months) with imatinib, whereas it was 13 months (range, 3-41 months) with IFN-α plus Ara-C.

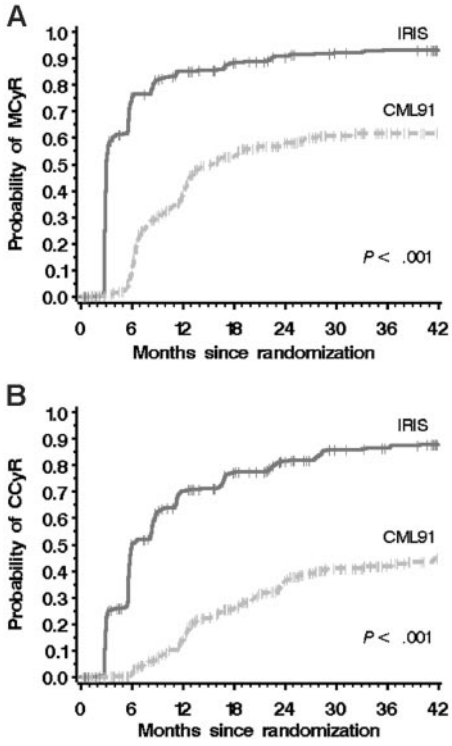

Figure 1. Cytogenetic responses in IRIS and CML trials. Kaplan-Meier estimates of rates of major (A) and complete (B) cytogenetic responses.

Disease progression and overall survival

Survival free of transformation was better for the imatinib arm ($P = .004$) (Figure 2A), within the IRIS and CML91 trials (ie, 57 of 551 and 45 of 325 patients who transformed, respectively). However, 2 patients in the CML91 study would not have been classified as in transformation using the IRIS definition. When these patients are censored at the date of assessment, the difference remains significant in favor of the imatinib arm ($P = .01$). After 12 months, the estimated rates were 98% (95% CI: 97 to 99) for the imatinib group and 96% (95% CI: 94 to 98) in the IFN-α plus Ara-C group. This difference was not significant at that time. However, at 36 months, estimated rates of freedom from transformation were 90% (95% CI: 87 to 93) and 82% (95% CI: 77 to 87) in the imatinib and IFN-α plus Ara-C groups, respectively, and the

Table 2. Failure and reasons for treatment discontinuation

Variable	IRIS study, no. (%)	CML91 study, no. (%)
No. assessable	551	325
No. crossovers	14	0
No. discontinuations	130 (24)	202 (62)
Unsatisfactory therapeutic effect	46 (8)	116 (36)
Adverse event(s)	20 (4)	51 (16)
Death	8 (1)	1 (1)
Toxicity and insufficient response	0	32 (10)
No longer requires study drug		
BMT	16 (3)	0 (0)
Complete response	NA	2 (1)
Lost to follow-up	(4) (1)	0 (0)
Other exit from protocol	36 (7)	0 (0)
BMT	38 (7)	33 (10)
Allogeneic	NA	4
Autograft	NA	29
Death	47 (9)	63 (19)
CML (acceleration and blast crisis)	21 (45)	45 (71)
BMT	5 (11)	10 (16)
Toxicity of treatment	0 (0)	1 (2)
Unrelated to CML disease or treatment	20 (43)	7 (11)
Unknown	1 (2)	0 (0)

BMT indicates bone marrow transplantation; NA, not assessable.

Table 3. Estimated rates of cytogenetic responses

	IRIS study, % (95% CI)	CML91 study, % (95% CI)
Major response		
At 12 mo	85 (82-88)	39 (33-45)
At 36 mo	93 (91-96)	61 (55-68)
Complete response		
At 12 mo	70 (66-74)	14 (10-18)
At 36 mo	87 (83-90)	42 (35-48)

$P < .001$ by log-rank test by 42 months.

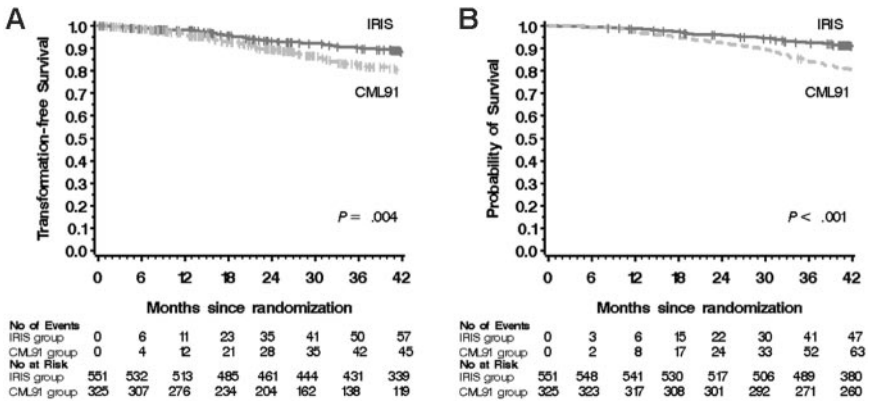

Figure 2. Outcome of patients in IRIS and CML 91 trials. Kaplan-Meier estimates of transformation (death, accelerated phase, or blast crisis)–free survival (A) and overall survival (B).

difference was significant with a relative risk at 0.55 (95% CI: 0.37 to 0.83; $P = .005$).

After 42 months of follow-up, a total of 47 patients of the imatinib group (8.5%) and 63 patients of the IFN-α plus Ara-C group (19.4%) had died. Accelerated- and blastic-phase CMLs were the major cause of death with IFN-α plus Ara-C. The patients in the imatinib group survived significantly longer than those in the IFN-α plus Ara-C group (Figure 2B) ($P < .001$). At 3 years, the estimated survival rates were 92% (95% CI: 90-95) in the imatinib group and 84% (95% CI: 80-88) in the IFN-α plus Ara-C group. The relative risk of death was 0.46 (95% CI: 0.30-0.69; $P < .001$) at 3 years. Of interest, this relative risk of death remained similar over time (0.44 at 1 year, 0.54 at 2 years, and 0.46 at 3 years). The difference in survival rate remained statistically significant when data on patients who received a bone marrow transplant were censored at the date of transplantation ($P < .001$).

Relationship between cytogenetic response and survival

Overall survival rates were analyzed according to cytogenetic response (MCyR and CCyR) by the landmark method (Figure 3A-B). In both treatment groups, a significant survival advantage was observed for patients who achieved MCyR at 12 months ($P < .001$ in both groups). Using the same method for CCyR at 12 months, a similar significant benefit was observed in the imatinib arm ($P < .001$). Of note, this survival advantage conferred by CCyR was only a trend for patients included in the CML91 ($P = .064$), but the number of these patients was low.

Among all patients of the present study who achieved MCyR within 1 year and were still on treatment at 1 year (n = 437 for IRIS and n = 125 for CML91; $P < .001$), the survival was similar in both groups; at 36 months estimates were 96% in both groups, irrespective of the treatment. For patients who achieved CCyR at 12 months, survival rates at 36 months were 96% (95% CI: 94-98) and 92% (95% CI: 85-99) for imatinib and IFN-α plus Ara-C groups, respectively (difference not significant). However, the number of patients who achieved complete response at 12 months was significantly higher with imatinib compared with IFN-α plus Ara-C (64% for IRIS vs 16% for CML91; $P < .001$).

Prognostic factors

Within all Sokal risk groups, imatinib was superior to the combination of IFN-α plus Ara-C in terms of MCyR, CCyR, survival free of transformation, and overall survival (Figure 4: data shown only for CCyR [A] and overall survival [B]). According to Sokal subgroup categories, the probabilities to achieve CCyR at 12 months for patients included in the imatinib arm were 78%, 68%, and 51% in low-risk, intermediate-risk, and high-risk groups, respectively. Corresponding results were 16%, 14%, and 3% in low-risk, intermediate-risk, and high-risk groups, respectively, for the IFN-α plus Ara-C group ($P < .001$) (Figure 4A). Similar results were observed for estimated rates of MCyR at 12 months: probabilities were 90%, 84%, and 68% in the imatinib group, and 43%, 37%, and 29% in the IFN-α plus Ara-C group for low-risk, intermediate-risk, and high-risk Sokal categories, respectively ($P < .001$).

Overall survival was significantly better in the IRIS group compared with the IFN plus Ara-C group for each category of Sokal risk ($P = .006$, .015, and .010 for low risk, intermediate risk, and high risk, respectively). Moreover, within the imatinib group, Sokal risk calculation remained a prognostic marker for the achievement of CCyR ($P = .001$ in the IRIS group and $P = .030$ in the CML91) and for survival benefit ($P = .035$ in the IRIS group and $P = .004$ in the CML91 group) (Figure 4A-B).

In the univariate analysis, 4 disease-related variables influenced survival significantly: spleen size ($P < .001$), eosinophils ($P = .015$), hemoglobin level ($P = .008$), and WBC count ($P = .002$). After stepwise backward Cox proportional-hazards analysis, only the spleen size remained significant ($P < .001$). After adjustment for disease-related variables and the Sokal risk category, overall survival remained significantly higher in the IRIS

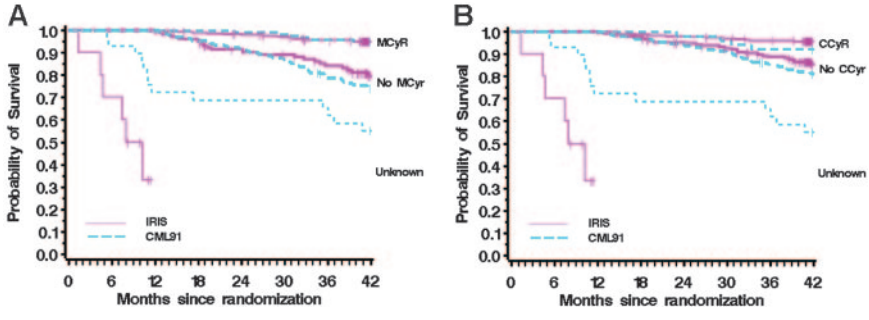

Figure 3. Relationship between cytogenetic responses and outcome. Landmark analysis of survival at 12 months according to major cytogenetic response (A) and complete cytogenetic response (B) in the imatinib group and IFN-alpha plus Ara-C group.

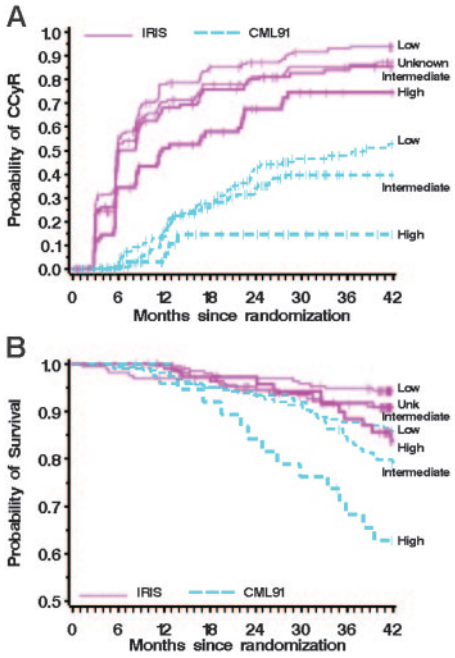

Figure 4. Effects of risk categories on cytogenetic responses and outcomes. Kaplan-Meier estimates of rates of complete cytogenetic responses (A) and overall survival (B), according to the Sokal risk group.

group ($P < .001$; relative risk of death, 0.37; 95 percent confidence interval, 0.24 to 0.59).

Discussion

The prospective, phase-3, randomized, multicenter IRIS trial was designed to compare imatinib at standard dose with then-current gold standard, IFN-α plus Ara-C. The trial demonstrated significant superiority for rates of CHR, MCyR, and CCyR as well as for progression-free survival for imatinib.[13] Imatinib was also better for compliance, toxicity, and quality of life.[19] In addition, the molecular response with imatinib was also significantly better.[20] Because the efficacy of imatinib in chronic-phase CML patients who had previously failed IFN-α therapy had been demonstrated,[12] it was ethically essential to allow patients to cross over from IFN-α plus Ara-C to imatinib in the IRIS trial in case of lack of response or intolerance of treatment. In addition, after the release of the preliminary results that demonstrated the statistical superiority of imatinib, patients in the IFN-α plus Ara-C group who failed to achieve MCyR by 12 months were also allowed to cross over to imatinib. Thus, on an intention-to-treat analysis, the estimated rates of survival were not significantly different, and a direct comparison of long-term survival for the 2 treatment alternatives was not possible.

Nevertheless, a strict comparison of the long-term outcome of patients treated with IFN-α plus Ara-C with that of patients treated with imatinib was of considerable interest. In the present analysis, we compared the outcome of 2 very similar groups of newly diagnosed CP CML patients who had been included in 2 large prospective randomized trials. We selected patients who actually received their assigned experimental treatment: either the IFN-α plus Ara-C combination in the CML91 trial (n = 325) or imatinib as first-line therapy in the IRIS trial (n = 551). We selected a cut-off date of 42 months for the common follow-up, corresponding to the last update available for the IRIS study at the time of this analysis. Our comparison provides confirmatory evidence that imatinib is superior to the combination of IFN-α plus Ara-C in terms of cytogenetic responses, survival free of transformation and, more importantly, overall survival.

Previous historical comparisons have been conducted that concluded that there was a survival benefit of imatinib over IFN-α in patients with CP CML (in both late and early phases). Kantarjian et al[21] analyzed results with imatinib therapy in patients with newly diagnosed CML in CP and compared their outcome with patients who received several different IFN-α regimens. A group of 187 patients in early CML in CP within 1 year from diagnosis treated with 3 different protocols of imatinib were compared with a historic group of 650 patients enrolled from 1982 through 1997 and treated with different IFN-α regimens. A survival advantage for imatinib was noted compared with various IFN-α regimens. A second comparison focused on patients with late chronic phase and on patients treated with imatinib after IFN-α failure.[22] In both analyses, imatinib therapy was an independent favorable prognostic factor for survival. Three-month and 6-month landmark analyses showed that patients in all cytogenetic response categories after imatinib had survival outcomes better than the historical control population. Within each cytogenetic response category, survival was also better with imatinib than with other therapies. Their analysis provides evidence for a survival advantage with imatinib. Another study was performed by Marin et al[23] on 143 patients treated with imatinib after IFN-α failure and compared with 246 historical controls who received conventional treatment. Those patients who achieved cytogenetic response by 6 months had a survival improvement. However, in contrast with the study of Kantarjian et al[22], those patients treated with imatinib who did not achieve cytogenetic response had a significantly worse survival.

Although these studies provide interesting information, they were based on retrospective observational trials involving historical cohorts of patients who were more heterogeneous regarding their baseline characteristics, period of recruitment, and for the IFN-α–based regimens they received. Our study was conducted on cohorts of patients included in 2 prospective randomized trials. All these patients were newly diagnosed CP CML, enrolled within exactly the same period of time of 6 months from initial cytogenetic diagnosis. Moreover, despite the different period of time during which the CML91 and IRIS trials were conducted, baseline characteristics of the selected patients were similar, and rigorous comparison of these 2 large groups of patients contributes to the strength of our analyses.

Of interest, the outcome of patients who achieved major or complete cytogenetic responses was similar, irrespective of the treatment. For IFN-α–treated patients, this statement is in accordance with previous work. Indeed, the achievement of CCyR after IFN-α therapy has been associated with an excellent long-term prognosis in several studies.[4,5,24] In both treatment groups, the achievement of MCyR at 12 months conferred a survival advantage. A similar relationship was observed for CCyR patients treated with imatinib. However, it was a trend only for CCyR patients treated with IFN-α plus Ara-C, probably because of the low rate of complete response (14%) in this group. Nevertheless, this observation is consistent with the concept that achieving a minimal disease state early was independently associated with better survival reported in several studies and has become the early therapeutic research goal. Thus, the impressive higher rate of CCyR within the first year of treatment with imatinib contributed primarily to the 36-month overall survival rate. The superiority of imatinib over the

combination IFN-α plus Ara-C was observed in all 3 Sokal risk categories. In treatment groups, the Sokal risk was associated with cytogenetic responses and survival. However, a recent analysis performed on patients treated with IFN-α in 10 prospective studies suggested that cytogenetic response per se is not a valid surrogate marker.[25] The combination of risk assessment using the New (Hasford) CML score and cytogenetic response does, however, provide useful clinical information. The higher rate of CCyR observed in the CML91 trial is explained by the better compliance of patients who, at the time of the trial, did not have any other therapeutic option.

The high rate of CCyR and impressive progression-free survival were sufficiently convincing to emphasize the central place of imatinib in the therapeutic algorithm for patients with chronic-phase CML. Despite unquestionable efficacy of the combination of IFN-α plus Ara-C, and some durable responses for a minority of patients, even after discontinuation of the treatment, the standard combination IFN-α and Ara-C cannot be recommended for front-line therapy because of dose-limiting toxicities and the greater efficacy of new well-tolerated tyrosine kinase inhibitors of Bcr-Abl. However, both agents are still of interest in combination with imatinib, since synergism has been observed in vitro. Phase 2 studies have been recently conducted with preliminary interesting results.[26,27] Improvement of tolerance and efficacy with pegylated formulation of IFN-α is another promising approach.[27]

The potential beneficial effect of IFN-α or Ara-C combined with imatinib is being evaluated in large phase 3 trials.

In summary, this study demonstrates that imatinib—the current recommended first-line therapy for newly diagnosed CP CML—provided a significant survival benefit over the previous standard IFN-α plus Ara-C combination. The results of our study suggest that, irrespective of the particular treatment, the achievement of major and complete cytogenetic responses improves survival.

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