

## INTERFERON ALFA-2b COMBINED WITH CYTARABINE VERSUS INTERFERON ALONE IN CHRONIC MYELOGENOUS LEUKEMIA

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## ABSTRACT

**Background** Treatment with interferon prolongs survival in chronic myelogenous leukemia. We conducted a clinical trial to assess the efficacy of treatment with a combination of interferon and cytarabine.

**Methods** Previously untreated patients with chronic myelogenous leukemia were randomly assigned to receive either hydroxyurea (50 mg per kilogram of body weight per day) and interferon alfa-2b (5 million units per square meter of body-surface area per day), or hydroxyurea and interferon in the same dosages plus monthly courses of cytarabine (20 mg per square meter per day, for 10 days). The end points were overall survival, complete hematologic remission at 6 months, and major cytogenetic response (less than 35 percent Philadelphia chromosome-positive cells in the bone marrow) at 12 months.

**Results** The trial was stopped when a sequential analysis showed a benefit of interferon and cytarabine. A significant improvement in survival was observed in the interferon-cytarabine group (360 patients) as compared with the interferon group (361 patients) ( $P=0.02$ ; relative risk of death, 0.64; 95 percent confidence interval, 0.44 to 0.93). After three years, the survival rate was 85.7 percent with interferon and cytarabine and 79.1 percent with interferon alone. The rate of hematologic response was higher in the interferon-cytarabine group than in the interferon group ( $P=0.003$ ). Major cytogenetic responses were observed 12 months after randomization in 126 of 311 patients treated with interferon and cytarabine (41 percent) and in 75 of 314 patients treated with interferon only (24 percent,  $P<0.001$ ).

**Conclusions** The combination of interferon and cytarabine, as compared with interferon alone, increases the rate of major cytogenetic response and prolongs survival in patients in the chronic phase of chronic myelogenous leukemia. (N Engl J Med 1997; 337:223-9.)

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CHRONIC myelogenous leukemia has a poor outcome when treated with hydroxyurea or busulfan. These agents can control the disease, but they do not eliminate Philadelphia chromosome-positive stem cells from the bone marrow. Allogeneic bone marrow transplantation, considered to be the only curative treatment, prolongs survival in up to 70 percent of a

small subgroup of young patients.<sup>1</sup> An antileukemic effect of interferon alfa has been demonstrated and cytogenetic responses (the reduction or elimination of Philadelphia chromosome-positive cells in the marrow) have been reported in patients with chronic myelogenous leukemia.<sup>2-4</sup> Three randomized clinical trials comparing interferon alfa with conventional chemotherapy have shown a significant survival benefit among patients receiving interferon,<sup>5-7</sup> but complete cytogenetic responses were found in only 10 to 20 percent of patients. Cytarabine has an antileukemic activity in vitro,<sup>8</sup> and when given subcutaneously, it can reduce the number of Philadelphia chromosome-positive cells in the marrow.<sup>9,10</sup> After a pilot study<sup>11</sup> suggested an additive effect of low-dose cytarabine and interferon, a multicenter, sequential, randomized trial was begun to compare interferon and cytarabine with interferon alone.

## METHODS

## Patients

Patients with chronic myelogenous leukemia were eligible if they were under 70 years of age, had tested positive for the Philadelphia chromosome, were in the chronic phase of the disease, had been given a diagnosis within the preceding six months, and had previously been treated only with hydroxyurea. Patients with features of accelerated or blastic phases of chronic myelogenous leukemia were not eligible, nor were those with a history of depressive illness or another psychiatric disorder or severe hepatic, renal, or cardiovascular disorders.<sup>12</sup> All the patients gave informed consent to participation in the study, which was approved by the institutional review board of the Hôpital Saint-Louis, Paris.

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\*Additional participating institutions, with their principal investigators, are listed in the Appendix.

### Study Design

Using Sokal's formula,<sup>13,14</sup> we calculated a prognostic score for each patient based on the patient's sex, age, spleen size, platelet count, percentage of blast cells in peripheral blood, and hematocrit. Patients were considered at low risk if the score was below 0.8, at intermediate risk if it was between 0.8 and 1.2, and at high risk if the score was above 1.2. If a family member was available to be a donor, allogeneic bone marrow transplantation was required for all patients under 35 years of age regardless of their Sokal score, and also for high-risk patients from 35 to 50 years of age. Stem-cell collection was recommended at diagnosis for patients under 60 years of age. Those without donors and the remaining eligible patients were enrolled and randomly assigned to one of the two groups by the Biometric Center.

Hydroxyurea and interferon alfa-2b were given simultaneously to all patients as induction treatment. Hydroxyurea was given at a daily dose of 50 mg per kilogram of body weight or less, depending on the patient's white-cell count. Hydroxyurea was discontinued when a complete hematologic remission was achieved. Interferon alfa-2b was given subcutaneously at an initial dose of 5 million units per square meter of body-surface area, once a day. The dose of interferon was reduced by half when the granulocyte count dropped below 1500 per cubic millimeter, the platelet count dropped below 100,000 per cubic millimeter, or both; interferon was discontinued when the granulocyte count fell below 1000 per cubic millimeter, the platelet count below 50,000 per cubic millimeter, or both.

The patients in the interferon-cytarabine group received the same induction regimen and in addition, after 2 weeks, monthly courses of subcutaneous cytarabine in a single daily dose of 20 mg per square meter for 10 days. Each course of cytarabine was begun if, at the time of the planned treatment, the white-cell count was above 3000 per cubic millimeter and the platelet count above 100,000 per cubic millimeter. Cytarabine was discontinued if the granulocyte count dropped below 1000 per cubic millimeter or the platelet count dropped below 50,000 per cubic millimeter. If suitable hematologic control was not achieved, the total dose of cytarabine could be increased to 40 mg per day for 15 days each month. Cytarabine was discontinued if karyotyping on two consecutive occasions revealed a complete cytogenetic response. The administration of interferon was continued unless there were serious adverse effects as defined by the World Health Organization.<sup>15</sup> Blood counts were performed weekly during the first month and every other week thereafter. Interferon and cytarabine were administered in the patients' homes by nurses.

Patients in complete hematologic remission after six months continued to receive the assigned treatment. Patients in the interferon group who did not have complete hematologic remission could receive cytarabine after six months. However, if a related donor was found, allogeneic bone marrow transplantation was proposed if the patient's age and condition were appropriate. Patients receiving interferon and cytarabine who were not in complete hematologic remission could discontinue the study treatment or consider an allograft as soon as possible. An autologous reinfusion of unmanipulated stem cells could be performed after high-dose chemotherapy if there was no suitable donor. Other patients who were not in remission after six months were given standard oral chemotherapy, mainly hydroxyurea. After 12 months of treatment, the same possibilities applied to patients who did not have at least a partial cytogenetic response (those with  $\geq 35$  percent Philadelphia chromosome-positive cells in metaphase).

### End Points

The end points were overall survival, the presence of a hematologic response at 6 months, and the presence of a cytogenetic response at 12 months. Hematologic responses were evaluated six months after randomization. The criteria for a complete hematologic response were the absence of disease-related symptoms and splenic enlargement by physical examination, a white-cell count below 10,000 per cubic millimeter and a normal differential count

(the presence of 1 to 5 percent immature granulocytes was also acceptable), a platelet count below 350,000 per cubic millimeter, and no treatment with hydroxyurea. Cytogenetic responses were determined according to the percentage of Philadelphia chromosome-positive cells in metaphase. Karyotypic analysis was required after 6 and 12 months of treatment and was optional at months 3 and 9; after 12 months, it was required every 4 months. A complete cytogenetic response was defined by the absence of detectable Philadelphia chromosome-positive cells in metaphase; partial and minor cytogenetic responses were defined as decreases in the proportion of such cells to 1 to 34 percent and 35 to 94 percent, respectively; major responses included complete and partial responses. During follow-up, a median of 30 metaphases were examined. A karyotype with less than 5 cells in metaphase was discarded and had to be repeated. If there were fewer than 10 cells in metaphase, the data were skipped unless the results fitted into a pattern observed on previous tests. The karyotypes were analyzed by members of the Groupe Français de Cytogénétique Hématologique.

### Statistical Analysis

The study was designed to have a type I error of 5 percent with a power of 90 percent for the detection of increased survival (82 percent vs. 72.5 percent) after three years due to treatment with interferon and cytarabine as compared with interferon alone. To minimize the sample size and obtain results more rapidly, we conducted the study as a sequential trial using the triangular test.<sup>16</sup> The accumulated data were examined after approximately every 15 deaths. At each sequential analysis, the *z* and *V* statistics were calculated. A positive *z* value indicated that interferon plus cytarabine was superior to interferon alone, and a negative value indicated that interferon plus cytarabine was inferior. The *V* statistic is related to the number of deaths. Once the sequential values of *z* and *V* were calculated, they were plotted, and the sample path was compared with the stopping boundaries. If the plotted point lay above the upper boundary (indicating that interferon plus cytarabine was more effective than interferon alone) or below the lower boundary, the trial had to be stopped.

The statistical analysis was performed on an intention-to-treat basis, provided that the patients fulfilled the major criteria for inclusion in the study. The study groups were compared by the Wilcoxon test in the case of continuous variables, by Fisher's exact test in the case of binary variables, and by the chi-square test in the case of categorical variables. Survival distributions were estimated by the Kaplan-Meier method<sup>17</sup> and compared by the log-rank test.<sup>18</sup> To determine the factors predictive of death and adjust the comparison of treatments for the patients' base-line characteristics, we used a Cox model.<sup>19</sup> All the tests were two-sided except the triangular test. Because it takes time to achieve a cytogenetic response, survival was measured from a prespecified "landmark" time of one year after randomization in a landmark analysis.<sup>20</sup> The median duration of treatment and the time to a hematologic response were analyzed with data on the time to treatment failure. The analysis used SAS (SAS Institute, Cary, N.C.) and PEST (MPS, Reading, United Kingdom) software.

### RESULTS

From January 1991 to May 1996, 810 patients were enrolled in the study. Randomization occurred immediately for 623 patients and was delayed for 187 patients, for whom a search for a related donor was required. Among these 187 patients, 65 were referred for allogeneic bone marrow transplantation; the other 122 patients were subsequently randomized because of the lack of a related donor. Thus, a total of 745 patients were included in the study.

At the fifth sequential analysis of the study, per-

formed in 1996 with data as of July 1, 1995, 75 deaths were reported: 26 in the interferon–cytarabine group and 49 in the interferon group. Since with these data the sample path crossed the upper boundary of the continuation region, the study was ended and it was concluded that the combination of interferon and cytarabine increases survival ( $P=0.01$ ).

The analysis reported here was performed with data as of July 1, 1996, at which time one patient had been lost to follow-up. Among the 745 patients in the study, 12 in each group were excluded for the following reasons: 6 in each group were Philadelphia chromosome–negative, although they each had evidence of a *BCR-ABL* molecular rearrangement; 5 had evidence of other myeloproliferative disorders; 3 declined immediately to participate in the study; and 4 did not fulfill the major criteria for inclusion. Thus, 721 patients were studied: 360 had been randomly assigned to the interferon–cytarabine group, and 361 to the interferon group. The median period of follow-up was 35 months. There were no imbalances between the two groups at the time of randomization with respect to the patients' main clinical and laboratory features, and the risk categories (low, intermediate, and high) determined on the basis of the Sokal score were evenly distributed between the groups (Table 1).

#### Hematologic and Cytogenetic Responses

The rate of complete hematologic response was higher in the interferon–cytarabine group (237 of 360 patients, or 66 percent) than in the interferon group (198 of 361 patients, or 55 percent;  $P=0.003$  by Fisher's exact test). For the interferon group, the relative risk of a complete hematologic response was 0.83 (95 percent confidence interval, 0.74 to 0.94). However, the time needed to reach a complete response was similar in both groups (three months).

As Table 2 shows, the proportion of patients with a major cytogenetic response was significantly higher in the interferon–cytarabine group than in the interferon group ( $P<0.001$  by Fisher's exact test). The relative risk of a major cytogenetic response in the interferon group was 0.59 (95 percent confidence interval, 0.46 to 0.75). In both groups, the degree of risk was significantly correlated with the occurrence of a major cytogenetic response: in the interferon–cytarabine group, 47 percent of patients at low risk, 39 percent of those at intermediate risk, and 19 percent of those at high risk had such responses ( $P=0.006$ ), as compared with 40, 13, and 12 percent, respectively, of the patients in the interferon group ( $P=0.001$ ). The frequency of major cytogenetic responses remained significantly higher with interferon plus cytarabine after adjustment for Sokal's index ( $P=0.001$ ).

Among the 721 study patients, the probability of having a major cytogenetic response at 24 months

**TABLE 1.** CLINICAL AND BIOLOGIC CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.\*

CHARACTERISTIC	INTERFERON–CYTARABINE (N=360)	INTERFERON (N=361)
Sex — M/F	195/165	203/158
Age — yr		
Median	50	51
Range	7–71†	2–71†
Splenomegaly		
No. of patients (%)	164 (46)	188 (52)
Distance below costal margin — cm	8±6	8±6
White-cell count — $\times 10^{-3}/\text{mm}^3$	120±120.6	131±121.3
Hemoglobin — g/dl	12.3±1.9	12.1±2.1
Hematocrit — %	37±6	36±6
Platelet count — $\times 10^{-3}/\text{mm}^3$	467±336	519±436
Peripheral-blood blast cells		
No. of patients (%)	119 (33)	132 (37)
Percent of cells	2.25±1.62	2.71±2.42
Sokal risk group — no. of patients (%)‡		
Low	168 (47)	144 (40)
Intermediate	142 (39)	151 (42)
High	50 (14)	66 (18)

\*Plus–minus values are means  $\pm$  SD.

†Four patients (one in the interferon–cytarabine group and three in the interferon group) were 70 or 71 years old, but they were retained in the study because that violation of the protocol was considered minor.

‡“Low” denotes a score below 0.8 on the Sokal scale, “intermediate” a score between 0.8 and 1.2, and “high” a score greater than 1.2.

was estimated to be 54 percent in the interferon–cytarabine group and 41 percent in the interferon group ( $P=0.006$ ; relative risk, 0.73; 95 percent confidence interval, 0.59 to 0.91).

#### Survival and Prognostic Factors

The patients in the interferon–cytarabine group survived significantly longer than those in the interferon group ( $P=0.02$  by the log-rank test; relative risk of death, 0.64; 95 percent confidence interval, 0.44 to 0.93). At three years the estimated survival rates were 85.7 percent in the interferon–cytarabine group and 79.1 percent in the interferon group (Fig. 1). The difference in survival rates remained statistically significant when the data on patients who received allogeneic bone marrow transplants were censored ( $P=0.03$ ), as well as when the data on patients who received any type of transplant or who died for reasons unrelated to chronic myelogenous leukemia were censored ( $P=0.02$ ). Table 3 shows the causes of death; blastic transformation was the predominant cause in each group. In the univariate analysis, five disease-related variables influenced survival significantly: spleen size, hematocrit, hemoglobin level,

**TABLE 2. CYTOGENETIC RESPONSES AT 12 MONTHS, ACCORDING TO TREATMENT ASSIGNMENT.**

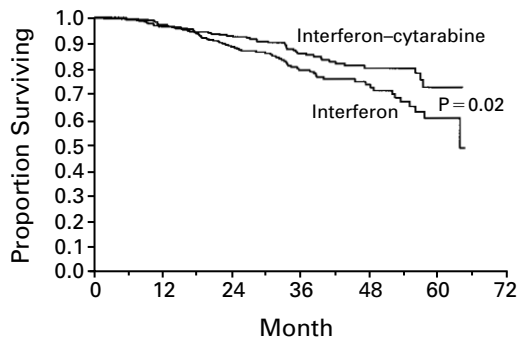
RESPONSE*	INTERFERON-CYTARABINE (N=311)†	INTERFERON (N=314)†
	no. of patients (%)	
Major‡	126 (41)	75 (24)
Complete	46 (15)	28 (9)
Partial	80 (26)	47 (15)
Minor	77 (25)	88 (28)
Treatment failure	53 (17)	78 (25)
Data not available§	55 (18)	73 (23)

\*The levels of response were based on the proportion of Philadelphia chromosome-positive cells in metaphase: complete responses, no such cells; partial response, 1 to 34 percent cells; minor response, 35 to 94 percent; and treatment failure, 95 to 100 percent.

†Only data for patients randomized at least 12 months before the reference date are shown; follow-up was insufficient for 49 patients in the interferon-cytarabine group and 47 patients in the interferon group.

‡The relative risk of a major cytogenetic response was 0.59 in the interferon group (95 percent confidence interval, 0.46 to 0.75;  $P < 0.001$ ).

§Cytogenetic data were missing in the interferon-cytarabine group and the interferon group for the following reasons: the patient died within one year (10 and 11 patients, respectively); no cytogenetic analysis was performed because the study treatment was discontinued (33 and 49 patients); the cytogenetic response was unknown while the patient was still in the study (3 and 1); and the analysis was not done or its results could not be evaluated (9 and 12).



Interferon-cytarabine							
No. at risk	360	303	228	148	74	19	0
No. of deaths	0	9	23	36	44	47	47
Interferon							
No. at risk	361	302	219	131	60	16	0
No. of deaths	0	12	34	52	60	67	68

**Figure 1.** Kaplan-Meier Estimates of Overall Survival among the Patients with Chronic Myelogenous Leukemia, According to Treatment Group.

$P = 0.02$  for the comparison of the groups by the log-rank test. Data are based on an intention-to-treat analysis.

white-cell count, and presence of blast cells in blood. After stepwise backward Cox proportional-hazards analysis, only the hemoglobin level remained significant ( $P = 0.005$ ). After adjustment for disease-related variables and the Sokal score, overall survival remained significantly higher in the interferon-cytarabine group ( $P = 0.03$ ; relative risk of death, 0.67; 95 percent confidence interval, 0.46 to 0.97).

**Effect of Cytogenetic Response on Survival**

Survival rates were also analyzed according to cytogenetic response by the landmark method. In the interferon-cytarabine group, patients who had a partial or complete cytogenetic response survived longer ( $P < 0.001$ ) than patients with no response or a minor response (Fig. 2A). This difference was also significant in the interferon group ( $P < 0.001$ ) (Fig. 2B).

**Doses of Interferon Alfa-2b and Cytarabine and Compliance with the Protocol**

One patient in the interferon-cytarabine group and two patients in the interferon group were not treated with interferon. During the first 12 months of the study, the mean daily dose of interferon was 5.4 million units in the interferon-cytarabine group and 5.8 million units in the interferon group; the median duration of treatment with interferon (as estimated by the Kaplan-Meier method) was 34 months in the interferon-cytarabine group and 28 months in the interferon group. Among the 360 patients assigned to receive interferon and cytarabine, 31 patients did not receive cytarabine during the study period. During the first 12 months, the median number of courses of cytarabine was 10 (range, 1 to 12), and the mean daily dose of cytarabine administered was 30 mg. The median duration of treatment with cytarabine was 14 months (range, 9 days to 52 months).

Among the 118 patients in the interferon group who crossed over to receive cytarabine, cytogenetic responses were recorded in 18 (complete in 7 and partial in 11). According to the design of the study, allogeneic or autologous stem-cell transplantation was performed in 105 patients with resistance to treatment: 58 patients (22 in the interferon-cytarabine group and 36 in the interferon group) received allogeneic marrow, and 47 patients (24 in the interferon-cytarabine group and 23 in the interferon group) received autologous stem cells. The two-year survival rate after allogeneic transplantation was 56 percent in the interferon-cytarabine group and 59 percent in the interferon group; after autologous transplantation, these rates were 61 percent and 68 percent, respectively. The main causes of death were graft-versus-host disease after allogeneic bone marrow transplantation and blast crisis after autologous stem-cell transplantation (Table 3).

**TABLE 3. CAUSES OF DEATH IN THE STUDY PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA (CML), ACCORDING TO TREATMENT ASSIGNMENT.**

CAUSE OF DEATH	INTERFERON-CYTARABINE (N=360)	INTERFERON (N=361)
Blast crisis and accelerated phase of CML*	29	42
Allogeneic bone marrow transplantation†	8 (22)	13 (36)
Blast crisis	0	2
Graft-versus-host disease	5	8
Infection	3	3
Autologous stem-cell transplantation‡	5 (24)	6 (23)
Blast crisis	3	5
Thrombocytopenia	1	0
Graft failure	0	1
Infection	1	0
Suicide	1	0
Other		
Related to CML	0	3‡
Unrelated to CML	4	4
Total	47	68

\*These deaths were due to the progression of disease in patients who did not undergo transplantation.

†Numbers in parentheses indicate the numbers of patients who underwent allogeneic or autologous transplantation because of treatment failure.

‡These three deaths were due to hemolytic anemia with cardiac failure, cardiac failure with pericarditis, and busulfan-induced bone marrow hypoplasia.

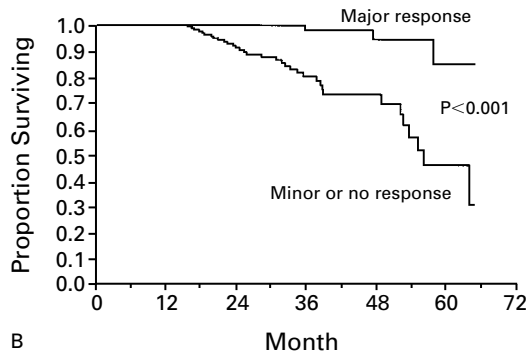
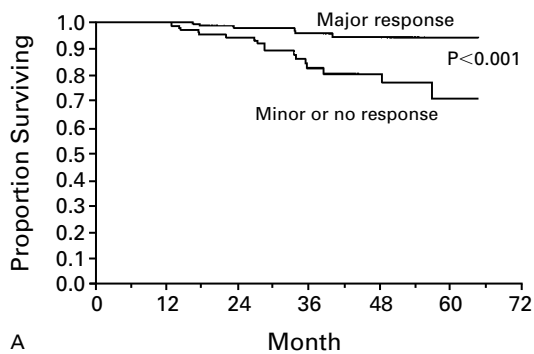
**Toxicity and Side Effects**

Major side effects led to the discontinuation of interferon treatment in 94 patients in the interferon-cytarabine group (Table 4). Cytarabine alone was assumed to have caused side effects in 85 patients, most commonly nausea, vomiting, diarrhea, and mucositis. The chief hematologic toxic effect of cytarabine was thrombocytopenia, but no life-threatening episodes of bleeding were recorded. Skin rashes and irritations at the sites of subcutaneous injections were attributed to cytarabine. In one patient hepatitis resolved after the discontinuation of cytarabine, although interferon treatment was continued.

In the interferon group, adverse events prompted the discontinuation of interferon in 97 patients. The main side effects were myalgia, arthralgia, asthenia, weight loss, and headache. Moreover, severe symptoms of depression led to the discontinuation of interferon in patients in both groups. Among the 118 patients who crossed over to the combination treatment, 32 discontinued cytarabine because of side effects.

**DISCUSSION**

In this sequential randomized trial, we found a survival benefit for patients with chronic myelogenous leukemia in the chronic phase who were treated with interferon and cytarabine. Patients given this combination also had higher rates of hematologic



		0	12	24	36	48	60	72
Major response								
No. at risk	160	160	126	89	39	11	0	
No. of deaths		0	3	5	6	6	6	
Minor or no response								
No. at risk	137	137	85	45	24	7	0	
No. of deaths		0	7	15	17	18	18	

		0	12	24	36	48	60	72
Major response								
No. at risk	106	106	81	51	26	7	0	
No. of deaths		0	0	1	2	3	3	
Minor or no response								
No. at risk	186	186	116	54	22	6	0	
No. of deaths		0	13	23	27	33	34	

**Figure 2. Landmark Analysis of Survival at 12 Months in the Interferon-Cytarabine Group (Panel A) and the Interferon Group (Panel B), According to Cytogenetic Response.**

All the patients remaining alive at 12 months were classified according to whether they had a major cytogenetic response as compared with a minor response or no response. Data were censored as of the date of transplantation for the patients who underwent transplantation and as of the date of death for the patients who died of causes other than chronic myelogenous leukemia.

**TABLE 4.** MAJOR SIDE EFFECTS THAT LED TO THE DISCONTINUATION OF TREATMENT, ACCORDING TO TREATMENT ASSIGNMENT.

SIDE EFFECT	INTERFERON-CYTARABINE (N=360)*	INTERFERON (N=361)†
Hematologic toxicity		
Thrombocytopenia	20	8
Other	31	9
Gastrointestinal		
Nausea, vomiting, diarrhea	45	14
Mucositis	21	2
Other	1	1
Weight loss, asthenia	48	20
Skin rash	19	7
Fever, flu-like syndrome, or both	10	7
Neurologic symptoms		
Peripheral	2	4
Central	7	4
Psychiatric disorder		
Depression	15	21
Other	13	19
Cytolytic hepatitis	9	3
Other side effects	31	32
Total no. of patients‡	179	113

\*Eighty-five patients in this group discontinued cytarabine treatment, 45 discontinued interferon, and 49 discontinued both treatments.

†Sixteen patients in this group who did not have complete hematologic remission after six months subsequently received cytarabine and then discontinued that treatment, 81 discontinued interferon, and 16 (who also crossed over to receive interferon and cytarabine after six months) discontinued both treatments.

‡The total number of side effects exceeds the total number of patients who discontinued treatment, because some patients discontinued treatment because of more than one side effect.

and cytogenetic responses than did patients who received only interferon. Other investigators have also found that a major cytogenetic response correlates with prolonged survival.<sup>5-7,21</sup>

The study design allowed patients in the interferon group to cross over to the interferon-cytarabine group if they did not have complete hematologic responses by 6 months or major cytogenetic responses by 12 months. Among the 118 patients who crossed over to the combination treatment, 50 did so after 6 to 12 months of treatment with interferon. Among these 50 patients, 3 had partial cytogenetic responses and 1 had a complete response. Thus, the intention-to-treat comparison of the 6-month and 12-month end points was not affected by the crossover. In addition, since 31 patients in the interferon-cytarabine group did not actually receive cytarabine, the true benefit of cytarabine may exceed that actually observed. Because of treatment failure, transplantation was performed during the first year in 7 patients in the interferon-cytarabine group and 12

patients in the interferon group; only 2 of these patients (both in the interferon group) had major cytogenetic responses at one year.

We gave every study patient hydroxyurea beginning at the time of diagnosis. The intent of this treatment was to lower the leukocyte count rapidly and reach hematologic remission quickly. Interferon alone requires a long period before its effects on the blood count become apparent.

Differences among trials in the rates of cytogenetic response may be related to various factors, including the phase of the disease, the patients' characteristics before treatment, the dose of interferon alfa, and the frequency of cytogenetic analysis. The Italian Cooperative Study Group reported an 8 percent rate of complete cytogenetic response and an 11 percent rate of partial response.<sup>5</sup> They found that the time needed for the disease to progress from the chronic phase to an accelerated or blastic phase was greater in the group treated with interferon than in the group that received standard therapy.<sup>5</sup> Other studies have confirmed the survival benefit of interferon treatment even among patients with no cytogenetic response.<sup>6</sup> However, Hehlmann et al., who found a 7 percent rate of complete cytogenetic response among patients treated with interferon alfa, did not observe a significant survival advantage among patients who had a cytogenetic response.<sup>22</sup> Using a landmark approach and a time-dependent covariate model, Ozer et al. also failed to find a correlation between cytogenetic responses and the duration of remission or survival.<sup>23</sup> However, these discrepancies between trials have been explained.<sup>24</sup>

Because only a minority of patients treated with interferon have a major cytogenetic response, additional strategies are needed. In vitro studies suggested an additive effect of interferon and cytarabine.<sup>25</sup> Patients in the advanced chronic phase of chronic myelogenous leukemia who were treated with the combination of interferon and cytarabine had a high incidence of hematologic remission and a trend toward a high rate of cytogenetic response, although the study was not randomized.<sup>26</sup> This combination of drugs is currently under investigation in patients in the early chronic phase of chronic myelogenous leukemia.<sup>27</sup> In our study, a substantial number of patients discontinued the combined treatment because of side effects, but the patients who were able to continue the treatment had significantly better survival than those treated with interferon alone. Perhaps a new oral formulation of cytarabine will have less toxicity than the form of the drug currently available.<sup>28</sup>

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APPENDIX

The following additional centers and investigators in the French Chronic Myeloid Leukemia Study Group participated in the study: Amiens, Centre Hospitalier Régional Universitaire (CHRU) Hôpital Sud (B. Desablens); Amiens, Centre Hospitalier Universitaire (CHU) Nord (C. Traulle); Anancy, Centre Hospitalier (C. Martin); Avignon, Hôpital Henri Duffaut (G. Le Peu); Bayonne, Centre Hospitalier de la Côte Basque (F. Bauduer); Beauvais, Centre Hospitalier (J.L. Dutel); Bobigny, Hôpital Avicenne (P. Casassus); Bondy, Hôpital Jean Verdier (F. Lejeune); Bourg en Bresse, Centre Hospitalier Fleyriat (H. Orfeuvre); Châlon sur Saone, Centre Hospitalier (D. Baudet-Klepping); Chambéry, Centre Hospitalier (M. Blanc); Clamart, Hôpital d'Instruction des Armées de Percy (G. Nedellec); Clermont-Ferrand, Centre Jean Perrin (M. Legros); Clermont-Ferrand, Hôpital Hôtel Dieu (F. Tavernier); Clichy, Hôpital Beaujon (J. Brière); Colmar, Centre Hospitalier Louis Pasteur (B. Audhuy, F. Kohser); Corbeil-Essonne, Centre Hospitalier (A. Devidas); Dunkerque, Centre Hospitalier (M. Weterwald); La Roche sur Yon, Centre Hospitalier Départemental les Oudairies (H. Maisonneuve); Le Kremlin Bicêtre, Hôpital de Bicêtre (G. Tertian); Le Mans, Centre Hospitalier (F. Duguay); Lyons, Hôpital Edouard Herriot (N. Philippe); Martigues, Centre Hospitalier (M. Nezri); Meaux, Centre Hospitalier (C. Allard and G. Netter-Pinon); Metz, Hôpital Notre Dame du Bon Secours (B. Christian); Metz, Hôpital Sainte Blandine (F. Rumilly); Montfermeil, Centre Hospitalier Intercommunal (M. Lenoble); Montpellier, Hôpital Lapeyronie (A.J. Ciurana); Mulhouse, Centre Hospitalier (J.C. Einsenmann); Nice, Centre Antoine Lacassagne (A. Thyss); Nice, Hôpital Cimiez (J.G. Fuzibet); Orléans, CHRU La Source (M. Schoenwald); Paris, Hôpital Bichat (M.J. Grange); Paris, Hôpital Cochin (F. Dreyfus); Paris, Hôpital La Pitié-Salpêtrière (L. Sutton); Paris, Hôpital Lariboisière (J.M. Zini); Paris, Hôpital Necker (C. Belanger); Paris, Hôpital Saint-Louis (P. Brice, A. Devergie, H. Esperou-Bourdeau); Pierre Bénite, Centre Hospitalier Lyon Sud (B. Salles); Pontoise, Centre Hospitalier René Dubos (Y. Kerneis); Rennes, Hôpital Sud (R. Leblay); Rouen, Centre Henri Becquerel (P. Piguet); Saint Etienne, Hôpital Nord (J. Jaubert); Saint-Cloud, Centre René Huguenin (E. Turpin and M. Janvier); Suresnes, Hôpital Foch (E. Baumelou); Troyes, Hôpital des Hauts Clos (G. Dine); Valenciennes, Centre Hospitalier (M. Simon and J.P. Pollet); Vannes, Hôpital Chubert (H. Jardel); Villejuif, Institut Gustave Roussy (E. Goldschmidt and M.P. Lemonnier).

The following members of the Groupe Français de Cytogénétique Hématologique performed the karyotyping: M.F. Bertheas, S. Briault, A. Brizard, C. Charrin, A. Dauvignon, P. Jonveaux, M. Lafage-Pochitaloff, J.L. Lai, J. Lespinasse, M. Lessard, M. Poissonnier, P. Talmant, F. Uettwiller, and J. van der Akker.

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