Stage, percentage of basophils at diagnosis, hematologic response within six months, cytogenetic response in the first year: the main prognostic variables affecting outcome in patients with chronic myeloid leukemia in chronic phase treated with interferon-α. Results of the CML89 trial of the Spanish Collaborative Group on interferon-α2a and CML

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Abstract

Background and Objectives. Interferon-α (IFN) is increasingly being used as the drug of choice in chronic myeloid leukemia patients. The main objectives of the study were to study the influence of the classic prognostic variables and response to IFN, and to assess the influence of this response on the course of the disease and survival.

Design and Methods. Single arm, prospective, multicenter study, without a control group. Only Ph1-positive CML patients were included. The treatment scheme was biphasic: the patients first received standard chemotherapy and thereafter IFN-α2a was used as monotherapy, with a target dose of 9 MU/d/s.c.

Results. Twenty-one centers in Spain enrolled 132 patients (72 men, 60 women). The median dose of IFN given was 5.8 MU/d, and the median treatment duration was 431 days (range: 18-2597). Seventy-two percent of patients obtained a hematologic response in the first six months of IFN treatment. Genetic response was obtained in 47% of the patients, and the response was major or complete in 27% and 19%, respectively. The median time to obtain this response was 7, 9, and 18 months for minimal, partial and complete genetic response, respectively. Multivariant analysis showed that only a higher percentage of basophils at diagnosis was associated with a worse hematologic response at six months (*p*=0.001) (OR: 1.23) and with a worse cytogenetic response in the first year of IFN therapy

(*p*=0.018) (OR: 1.4). Over an observation period of 8 years, 35.6% of the patients died, and 85 (64.4%) remained alive. With a median follow-up of 42 months (3.7-98), the 6-year projected probabilities of survival and transformation-free survival were 0.61±0.07 vs. 0.54±0.07, respectively. Patients with Kantarjian's stage 3 disease or in a high-risk Sokal group had lower probabilities of survival, but these systems did not adequately discriminate in our series. Obtaining a complete hematologic response in the first six months of IFN therapy was favorable in terms of overall survival (*p*=0.05; HR=0.33). Cox's analysis demonstrated that obtaining a cytogenetic response in the first year was independently associated with better overall survival (*p*=0.04; HR=0.19) and better transformation-free survival (*p*=0.0035; HR=0.11).

Interpretation and Conclusions. Nearly half of the patients obtained some degree of Philadelphia suppression, which was major in 27% , and complete in 19%. A higher percentage of basophils at diagnosis was the only variable associated with a lower probability of cytogenetic response. Obtaining a cytogenetic response during the first year of IFN was a favorable and independent variable in terms of survival and transformation-free survival. Obtaining a major cytogenetic response during this period decreased the risk of transformation twenty times. Our results suggest that the effect of IFN on survival is independent of the classic prognostic variables.
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Key words: interferon-α, chronic myeloid leukemia, prognosis, cytogenetic response, basophils

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Clinical research on interferon-alpha (IFN-α) therapy in chronic myeloid leukemia was initiated by the MD Anderson Cancer Center (MDACC) group in 1982. These studies opened a new era in the treatment of this disease.[1,2] Interferon was able to induce hematologic control of the disease in about 70% of the patients in early chronic phase. Moreover, it could reduce the percentage of Philadelphia-chromosome below 35% in nearly forty percent of the patients,[3,4] and in one-quarter this cytogenetic response was complete. Interferon was also able to induce the disappearance of additional abnormal clones.[5] The final effect was a surge of the normal hemopoiesis,[6] and, in prolonged complete genetic responders, the reduction of leukemia cells to concentrations below 10^{-5} cells.[7] The MDACC group reported a survival advantage over historical control patients, with a median survival of 89 months.[2]

The *Italian Cooperative Study Group on CML* (ICSG) was the first to report the results of a randomized trial, comparing IFN-α and conventional chemotherapy, mainly hydroxyurea. This group showed a significant survival advantage for patients given IFN-α, mostly due to a lower probability of transformation.[8] These results were confirmed by the British MRC group,[9] but challenged by results of the German[10] and Benelux[11] trials, which did not observe a significant superiority of IFN-α over hydroxyurea treatment in terms of survival. The results of the Italian study have recently been updated and confirmed.[1,2]

Cytogenetic response was associated with longer survival in the studies by the Italian,[8] MDACC,[13] British[9] and Japanese groups.[14] However, the CALGB group[15] and the German study[10] did not find this association.

In December, 1988, we set up a trial of recombinant IFN-α2-a treatment of CML patients in chronic phase. All patients were given IFN-α. Our main objectives were to study the relationship between classic prognostic variables and response to IFN-α, and to assess the influence of hematologic and cytogenetic responses on the course of the disease and survival.

Design and Methods

Study Group

Adult patients with chronic phase, Philadelphia-positive CML were enrolled. The definition of chronic phase was that of the model proposed by Kantarjian *et al.*[16] Patients had to have a Karnofsky index higher than 70%, with adequate hepatic and renal function. Patients were entered consecutively.

Patients who had received previous IFN-α or intensive chemotherapy were excluded, but the study allowed the inclusion of patients who had received busulfan or hydroxyurea.

Therapy

Before entry, patients receiving busulfan had to stop this therapy, and hydroxyurea was used for con-

trol of the disease. In patients receiving hydroxyurea, the aim was to get the leukocyte number into the range between 15 and 20×10^9/L. After having reached this target, hydroxiurea was interrupted, IFN-α2a (Roferon A, Roche SA, Madrid, Spain) was used as monotherapy, and no further chemotherapy was allowed. The IFN-α dose was 3 MU/d during the first week of therapy, 6 MU/d during the second, and 5 MU/m²/day during the third week and thereafter. The dose was reduced by 25% if persistent WHO grade 2 toxicity occurred or if the granulocyte count was between $1–1.4\times10^9$/L, or if the platelet count was between 50 and 99×10^9/L. Case report forms were filled in during the first 24 months on a monthly basis, and then at 6-month intervals until the patient came out of the study, or died. The clinical and hematologic criteria for response in each report were checked by the monitor of the protocol. The dose of IFN-α was recorded in each report. The patients withdrew from protocol treatment when progressive disease occurred in spite of increasing the dose of IFN-α, when transformation or blastic crisis occurred, when other cytostatic drugs were added, or when stem cell transplantation was performed.

Hematologic response

A complete hematologic response (CHR) was defined as absence of symptoms and signs attributable to CML ,WBC less than 10×10^9/L, platelet less than 450×10^9/L, and no immature granulocytes in peripheral blood. Patients with partial hematologic response (PHR) were those with at least a 50% reduction of WBC (only if WBC were lower than 20×10^9/L), but with immature granulocytes in peripheral blood or splenomegaly. A response worse than partial was classified as nil (NHR). The hematologic response needed to be maintained for at least a month to be classified.

Cytogenetic response

Bone marrow karyotyping was scheduled during the first year at 6, 9 and 12 months, and at six-month intervals thereafter. Cytogenetic evaluations during the first trimester of therapy were allowed. At least 25 marrow metaphases had to be analyzed. If 5-10 metaphases were obtained, the result was not used unless it was consistent with previous and subsequent results. Data from less than five metaphases were not evaluable. The cytogenetic response was classified according to MDACC criteria[1] thus it was: a) as complete (CGR), if there were no Ph1+ve metaphases; b) partial (PGR), if there were between 5 and 34%; c) minimal (mGR), if there were between 35 and 95%; and d) nil (NGR), if more than 95% Ph1+ve metaphases were present. By convention, major cytogenetic response was defined as the presence of CGR or PGR. Cytogenetic response in the first year was defined as the last cytogenetic response the patient obtained within the first year of treatment. Best cytogenetic response was defined as the response corre-

sponding to the lowest percentage of Ph1+ve metaphases. Southern blot results were used in patients with previous CGR only if two criteria were met: 1) M-BCR rearrangement present at diagnosis, 2) M-BCR rearrangement absent in the previous evaluation with CGR.[17]

Definition of transformation

For the purpose of the study, transformation included the presence of accelerated or blastic phase. Accelerated phase was defined as follows: 1) leukocyte doubling time less than 5 days; 3) ≥ 10% blasts in peripheral blood (PB) or bone marrow (BM); 3) ≥ blasts plus promyelocytes in PB or BM; 4) ≥ 20% basophils plus eosinophils in PB 5) anemia or thrombocytopenia resistant to treatment; 6) persistent thrombocytosis; 7) clonal evolution; 8) progressive splenomegaly 9) chloromes or myelofibrosis. Blast phase was defined as the presence of ≥ 30% blasts in PB or BM.

Statistical analysis

Variables. 1) Obtained at diagnosis: age, sex, Kantarjian's stage,[16] Sokal's stage,[18] % myeloblasts PB, % basophils PB, % eosinophils PB, Hb (g/L), platelets ($\times 10^9$/L), splenomegaly (cm below costal margin, midclavicular line). 2) Obtained when IFN-α was started: time between diagnosis and IFN-α (days), hydroxyurea received (g/kg), busulfan received (mg/kg), time between cessation of chemotherapy and IFN-α, leukocytes ($\times 10^9$/L). 3) Obtained during treatment: hematologic and cytogenetic responses, as previously defined, IFN-α dose received, time to obtain hematologic or cytogenetic responses, cumulative probability of obtaining cytogenetic responses obtained by Kaplan-Meier[19] method (CGR, PGR, mGR, major genetic response, cytogenetic response). Concerning responses, the main endpoints of the study were the hematologic response in the first six months and the cytogenetic response in the first year of therapy.

Descriptive analysis. For the quantitative variables, medians and ranges, and means and standard deviations were calculated. For the qualitative variables, percentages and proportions were calculated. Normality was analyzed by the Kolmogoroff-Smirnov test.

Study of the association between variables obtained at diagnosis or at start of IFN alpha, and hematologic or cytogenetic response. t-Student's test (2 subpopulations) or Anova's test (more than 2) were used to study the differences between the means. We used the chi-square test for the quantitative variables. Table 1 describes the variables entered into the association analysis.

Study of the effect of the independent variables on the response. Logistic regression ,single and multiple.

Survival and transformation-free survival. These were calculated from the time IFN-α was started to death, the date of transformation, or the date of the last follow-up evaluation. Data from the patients who received a bone marrow transplant in chronic phase were cen-

Table 1. Association with hematologic or cytogenetic response. Variables studied.

Age
Sex
Stage (Kantarjian)
Sokal's index
Stage (Sokal)
% myeloblasts peripheral blood
% basophils peripheral blood
Hb (g/L)
% myeloblasts bone marrow
Splenomegaly (cm below rib margin)
Time diagnosis-IFN
Previous hydroxyurea (g/kg)
Previous busulfan (mg/kg)

sored as of the date of transplantation. Crude probability of survival was analyzed by the Kaplan-Meier estimator,[19] calculating the confidence intervals by Parmar and Machin's method,[20] and using the appropriate hypothesis tests (log-rank, Tarone-Ware).

Survival was also analyzed by comparing Sokal and Kantarjian stage, hematologic response in the first six months of IFN-α, and cytogenetic response during the first year of IFN-α.

Our main endpoint was to analyze the impact of cytogenetic response in the first year of therapy on survival and transformation-free survival. Because cytogenetic response is a time dependent variable, analyses of no response versus some response, and no or minimal response versus major response were done by a modification of the landmark method.[21] This method requires the time for response to be known for each individual,[22] which was the case in our study, and the survival time to be corrected accordingly. Thus, in order to study the impact of cytogenetic response during the first year of therapy and survival, the survival time was calculated discounting the time to the first evaluation (in patients with no genetic response), or the time to the first cytogenetic response (in patients with minimal or major response). Comparisons of subgroups were made by Cox's proportional-hazard model for covariate analysis of censored data on survival 23 (Table 2). In all cases, a two-tailed $p <0,05$ was required for statistical significance. All analyses were performed by the clinical epidemiology unit (Hospital de la Princesa, Madrid), with the SPSS 6.04 program package (SPSS Inc. Chicago, IL, USA).

Results

Patients' description

One hundred and thirty-two patients from 21 hospitals in Spain were entered into the study. Their characteristics are shown in Table 3. Their median age was 43 years, and 45% were women. Fifty-one

Table 2. Association with Survival. Variables entered in the Cox's model.

HR6m*
GR12m°
Age
Sex
Stage (Kantarjian)
Stage (Sokal)
% myeloblasts peripheral blood
% basophils peripheral blood
Hb (g/L)
% myeloblasts bone marrow
Splenomegaly (cm below rib margin)

*HR6m: Hematologic response in the first six months of IFN therapy;
°GR12m: Genetic response in the first year of therapy, i.e. the last cytogenetic response the patient had during the first year of therapy.

Table 3. Patients' characteristics.

Variable	N	Median	Range	Mean	SD
Age (yr)	132	43	12.2-79.4	43.5	14.3
Sex	132	M=72 (54.5%) F=60 (45.5%)			
Stage (Kantarjian)	132	1=90 (68.2%) 2=23 (17.4%) 3=16 (12.1%) NE=3 (2.3%)			
Stage (Sokal)	132	LR=68 (51.5%) IR=34 (25.8%) HR=27 (20.5%) NE=3 (2.3%)			
Karyotype (% Ph1+ve)	132	20-50: 5 51-90: 9 90-100: 115			
Splenomegaly (cm)	129	3	0-23	5.5	6.4
Myeloblasts p.b. (%)	130	0	0-12	1.1	1.8
Basophils p.b. (%)	132	4	0-18	4.07	3.1
Eosinophils p.b. (%)	130	1	0-14	1.59	2.3
Hemoglobin (g/L)	129	122	62-174	122.95	22.40
Platelets (x10⁹/L)	130	354	116-2,396	466.29	339
Myeloblasts b.m. (%)	129	0	0-9	1.48	1.7
Time from diagnosis to IFN (days)	132	89	0-4970	231.58	527.7
Hydroxyurea (previous) (g /kg)	89	1.28	0.14-25	2.36	3.5
Busulfan (previous) (mg/kg)	8	2.92	0.33-30.7	6.05	10.1
Leukocytes at start of IFN (x10⁹/L)	126	14	3-267	20.69	30.2

per cent of the patients were classified as low-risk by Sokal's index. The median time from diagnosis to IFN-α treatment was 3 months. Thirty-five patients were treated with IFN-α as front-line therapy, and the rest had received previous chemotherpy (8 of them, busulfan). The median number of leukocytes when IFN-α was started was 14×10⁹/L (range: 3-267). When IFN-α was initiated, twelve patients had a leukocyte number between 30 and 50×10⁹/L, and only five patients had more than 50×10⁹/L. Leukocyte number at that moment was not different between patients who had previously been treated with hydroxyurea and those who had not (18.8±29.8 vs 25.1±31.4). No correlation was found between the time from diagnosis and the cumulative hydroxyurea dose (r^2 = 0.08 ; p=0.05).

Patients received a mean IFN-α dose of 5.72 MU/d (SD:2.4). The median treatment time was 431 days (range: 18-2597).

Hematologic response

Of the 132 patients treated, 79 (60%) obtained a complete hematologic response. However, this figure was lower when considering the first semester of therapy, when there was hematologic control in 72% of the patients, but this was complete in only 39% of the total (Table 4). Median time to obtain PHR and CHR was 41.5 days (range: 3-349) and 98 days (range: 6-1361), respectively.

When studying the association of prognostic variables with the response in the first 6 months of therapy, univariate analysis disclosed that a lower percentage of basophils at diagnosis (p=0.003) and less splenomegaly (p=0.08) were associated with better hematologic response. The logistic regression analysis showed that only basophils were associated with worse hematologic response (subgroups: CHR & PHR vs others; OR: 1.23; p=0.001). The influence of basophils was also detected when analyzing the last hematologic response (subgroups: CHR vs others; OR:1.14; p=0.06).

Table 4. Hematologic response.

	HR6m N (%)	BestRH N (%)	LastHR N (%)
CHR	51 (38.6)	79 (59.8)	60 (45.5)
PHR	44 (33.3)	30 (22.7)	27 (20.5)
NRH	34 (25.8)	22 (16.7)	34 (25.8)
Transf.	3 (2.3)		11 (8.3)

*HR6m: hematologic response in the first six months of IFN therapy;
°Best RH: best hematologic response obtained during IFN therapy;
#Last HR: last hematologic response while on IFN therapy.

The IFN-α dose received by the patients whose last HR was complete was significantly lower than that received by the patients with no hematologic response (5.07 MU/d ±2.2 vs 6.37±2.4; p=0.004).

Fifty-six percent of the patients with PHR in the first six months of therapy obtained a CHR as best HR, as compared with only 11 % of the patients with NHR in the first six months of therapy.

Table 5. Cytogenetic response.

Response	GR12m* N (%)	BestGR° N (%)
CGR	10 (7.6)	25 (18.9)
PGR	14 (10.6)	11 (8.3)
MGR	22 (16.7)	27 (20.5)
NGR	30 (22.7)	24 (18.2)
Not evaluated	56 (42.4)	45 (34.1)
Total	132	132

*GR12m: Genetic response in the first year of therapy, i.e. the last cytogenetic response the patient had during the first year of therapy; °BestGR: Best genetic response during IFN therapy.

Table 6. Causes of IFN withdrawal.

Cause	N
Pseudogripal syndrome	5
Parkinsonism	3
Cardiac toxicity	2
Cutaneous toxicity	2
Thrombocytopenia	2
Hepatic toxicity	1
Weight loss	1
Impotentia coeundi	1
Paresthesias	1

Table 7. Secondary effects.

Grade (WHO)	Liver	Skin	GI	Hb	WBC	Plts
0	62 (47)	91 (69)	111 (84)	91 (69)	70 (53)	73 (55)
1	47 (36)	27 (20)	10 (7)	25 (19)	35 (26)	25 (19)
2	17 (13)	11 (8)	8 (6)	13 (10)	22 (17)	21 (16)
3	5 (4)	2 (1.5)	3 (2)	3 (2)	5 (4)	11 (8)
4	1 (0.8)	1 (0.8)	0	0	0	2 (1.5)

Genetic response

Out of 132 patients, 87 were evaluated cytogenetically. The mean number of evaluations was 3.1 per patient. Table 5 shows the frequencies of genetic responses. In the first year of therapy, 76 patients (58%) were evaluated, and a major genetic response was obtained in 24 patients (18.2% of the total group). Fifty-six patients were not evaluated during the first year, 36 of them because of a follow-up shorter than 6 months. Considering the best response, 48% of the patients obtained some degree of Philadelphia suppression during the treatment; this response was complete in 19% and partial in 8% of the patients. The median days to obtain a mGR, PGR and CGR

were 205 (307-1,099), 273 (145-1,158) and 555 (34-1,822), respectively. Eighty-five percent of the genetic responses and 77% of the major responses occurred in the first 18 months of therapy. Although CGR or PGR in the first year clustered in patients in Kantarjian risk's groups 1 or 2 (100% and 86% of the patients with CGR or PGR belonged to these groups), the logistic regression analysis disclosed that only basophils were associated with worse cytogenetic response in this period (subgroups: CGR/PGR/mGR vs NGR; OR:1.4; p=0.018). Interferon dose was not significantly different in patients with any degree of cytogenetic response and those without response (5.34±2 vs 5.89±2.8 MU/d).

The hematologic response at six months had a strong predicitive value over the best genetic response. A patient with CHR response was approximately three times more likely to have a major cytogenetic response as best response (OR: 3.1; CI 95%= 1.27-7.6).

Obtaining some degree of Ph1 suppression in the first year of therapy was also highly predictive of a major cytogenetic response as best response (OR= 13.6; CI 95% = 3.56-52.1).

Toxicity and side effects

In eighteen patients (13.6%) IFN-α was definitively stopped because of toxic effects, the more frequent being an influenza-like syndrome (fever, asthenia, arthromyalgias)(five cases), and parkinsonism (in three) (Table 6). No death was attributable to IFN-α. It can be appreciated from Table 7 that hepatic toxicity was the more frequent extra-hematologic toxicity, and 53% of the patients had some degree of liver function abnormality at some time. Myelosuppresion was the most frequent chronic side-effect; it must be stressed that this was not a target. However, nearly 45% of the patients at some time had less than 100×10^9 platelets /L, and 21% had less than 3×10^9 leukocytes/L. Most of the grade III toxicities needed only temporary interruption of IFN-α, and IFN could be recommenced safely at a dose 75% less than the previous dose with watchful clinical follow-up. In two patients IFN-α was definitively withdrawn because of thrombocytopenia. All the cytopenias were reversible, and no complication related to cytopenias was reported. Thirteen patients (10%) developed autoimmune alterations while on IFN therapy. A positive direct antiglobulin test was seen in nine patients, this being the most frequent laboratory abnormality. Antithyroid antibodies were seen in 4 patients (2 of them with thyroiditis), systemic lupus erythematosus was seen in one, and severe autoimmune hepatitis developed in one patient with previous thyroiditis.

Survival and transformation-free survival

The median follow-up of the alive patients was 42 months (3.7-98). At the moment of analysis, 47 patients died (35%), 28 of them due to disease pro-
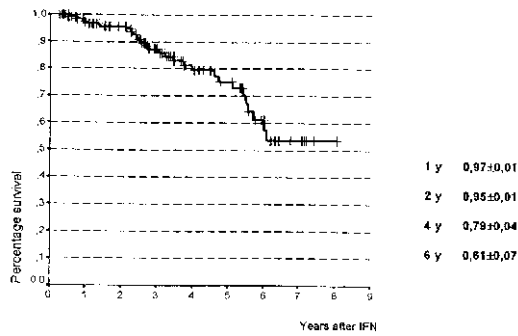
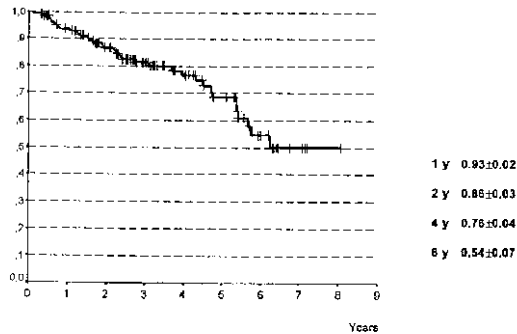**Figure 1. Overall survival. Estimated probability.**

Figure 2. Transformation-free survival. Estimated probability.

Figure 3. Overall survival. Estimated probability by Kantarjian's stage. *E/C: events/censored.*

Figure 4. Transformation-free survival. Estimated probability by Kantarjian's stage. *E/C: events/censored.*

Figure 5. Overall survival. Estimated probability by Genetic response in the first year of IFN. *E/C: events/censored; GR 1st y: genetic response in the first year of IFN therapy; Some: mùinimal, partial or complete genetic response; NGR: no genetic response.*

gression, 18 after bone marrow transplantation, and one because of a hypertensive crisis. During the observation period, 34 patients (25%) suffered transformation of their disease , and 19 of them developed blastic crisis (myeloid in 10 cases).

The predicted 6-year probabilities of survival and transformation-free survival (TFS) are 61% and 54%, respectively (Figures 1 and 2).

The projected probability of OS was higher in patients with Kantarjian's stage 1 disease than in those with stage 3 (Figure 3). Probability of TFS was higher in the patients with Kantarjian's stage 1 or 2 disease (log rank: 9.42; p=0.009) as compared with stage 3 (Figure 4). However, we found no significant differences between stages 1 and 2 (Figures 3 and 4). When Sokal's groups were compared, we found a statistically significant difference between the groups, but, surprisingly, probability of OS and TFS was higher in patients with *intermediate risk* (Table 8).

Survival according to hematologic response and cytogenetic response

Overall survival. Multivariate Cox's analysis demonstrated that patients with complete hematologic response in the first six months of therapy have a low-
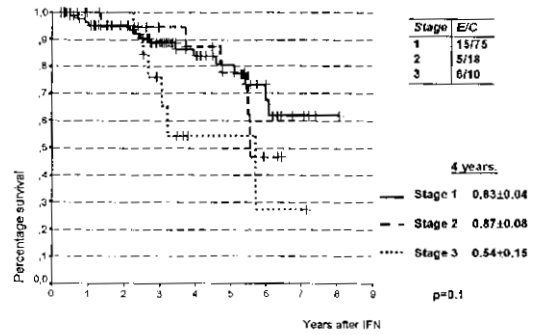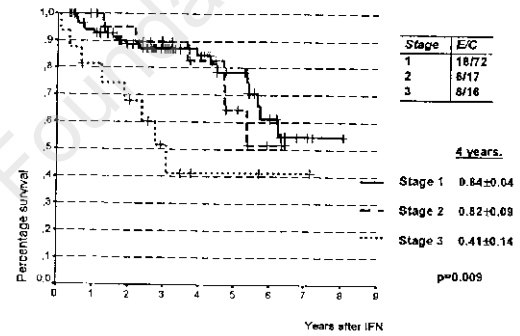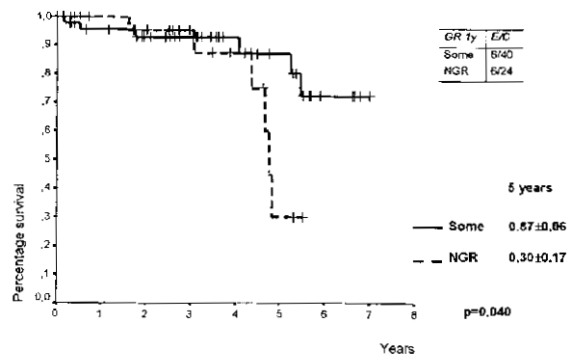
Figure 6. Transformation-free survival. Estimated probability by Genetic response in the first year of IFN. *E/C: events/censored; GR 1st y: genetic response in the first year of IFN therapy; Some: minimal, partial or complete genetic response; NGR: no genetic response.*
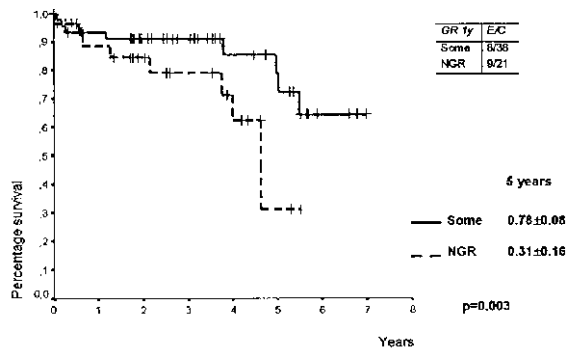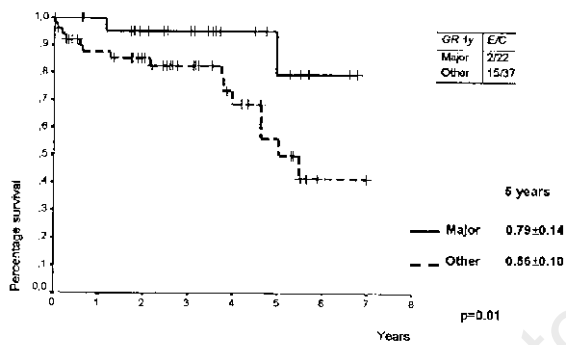

Figure 7. Transformation-free survival. Estimated probability by Genetic response in the first year of IFN. *E/C: events/censored; GR 1st y: genetic response in the first year of IFN therapy; major: partial or complete genetic response; other: minimal or no genetic response.*

er risk of death than patients with a worse response (*p*=0.05; HR: 0.33). Patients with CHR have a projected 6-year OS of 87±7%.

Concerning genetic response in the first year, after correction for the time for response, the projected 6-year survival rate was 72±11% in patients with some degree of response and 30±17% in patients with NGR (*p*=0.08). The Cox's analysis showed that the benefit of obtaining a cytogenetic response during this period was independent of the other studied variables (*p*=0.04; HR: 5.15) (Figure 5).

Transformation-free survival. According to genetic response in the first year, the projected 6-year probability of TFS was higher in patients with some cytogenetic response than in those with no response (64±11% vs 31±16; *p*=0.038). The multivariate analysis revelaed that obtaining a cytogenetic response during this period was an independent and favorable event (*p*=0.003; HR: 8.4) (Figure 6).

This effect was more evident when comparing patients with major cytogenetic response with patients with minimal or no response (*p*=0.018; HR: 20) (Figure 7).

Discussion

The study sample includes a higher percentage of low risk patients than those studied by the German or MRC UK trial.[9,10] It is fairly similar to that reported by the MDACC.[13]

Sixty-seven percent of the patients received hydroxyurea before IFN-α was started, but chemotherapy was not allowed after this point. The definition of hematologic response was more stringent than that used by other trials.[9] Seventy-two percent of the patients obtained hematologic responses during the first semester of therapy (38.6% a complete response).

Table 8. Overall and transformation-free survival by Kantarjian's and Sokal's stage.

		Overall survival				
		1 year	2 year	4 year	6 year	
Kantarjian's	Stage					
	1	0.96±0.02	0.95±0.02	0.83±0.04	0.73±0.07	Tarone-Ware =4.43P=0.1
	2	1	0.94±0.05	0.87±0.08	0.46±0.1	
	3	1	1	0.54±0.15	0.27±0.2	
Sokal's	Stage					
	Low Risk	0.96±0.02	0.95±0.02	0.82±0.06	0.67±0.09	Log Rank= 12.7P=0.001
	Intermediate	1	1	0.96±0.03	0.96±0.03	
	High Risk	0.96±0.03	0.92±0.05	0.61±0.1	0.27±0.12	
		Transformation-free survival				
Kantarjian's		1 year	2 year	4 year	6 year	
	Stage					
	1	0.94±0.02	0.88±0.03	0.84±0.04	0.61±0.08	Log Rank= 9.42P=0.009
	2	1.0000	0.95±0.04	0.82±0.09	0.51±0.15	
	3	0.81±0.09	0.67±0.11	0.41±0.14	0.41±0.14	
Sokal's	Stage					
	Low Risk	0.93±0.03	0.88±0.04	0.81±0.05	0.49±0.1	Log Rank= 8.3P=0.015
	Intermediate	0.96±0.02	0.93±0.04	0.88±0.06	0.88±0.06	
	High Risk	0.88±0.06	0.77±0.08	0.61±0.1	0.41±0.11	

These percentages are similar to those obtained by the MRC group,[9] higher than those reported by the Austrian or German trials (45% and 31%, respectively),[10,24] but lower than the eighty-percent figures achieved by the MDACC or Bordeaux teams.[25,26]

The adverse effects described in our study are similar to those described by other groups.[8,15,24,27] A flu-like syndrome was the most frequent toxic effect in those series. Myelosuppression was a major problem in two studies,[15,24] and neurologic and gastrointestinal effects were frequent in three studies.[8,10,27] We also found a high incidence of autoimmune phenomena. Sacchi *et al.* reported a 5% incidence of autoimmune disease, thyroiditis and connective disorders being the most frequent.[28] The incidence of autoimmune alterations may be even higher: one of the centers included in our study reported a 28% incidence of anti-erythrocyte autoantibodies in patients treated with different types of IFN-α.[29]

Of all the studied variables, a higher percentage of basophils at diagnosis and greater splenomegaly were shown to be associated with a worse hematologic response, but only the percentage of basophils remained significant in the multivariant analysis. The negative influence of basophils was also detected when considering the last and best hematologic responses. Patients with CHR had a lower Sokal's index than those with a worse response, but the significance of the stage was lost in the multivariant analysis. Although some studies have used IFN-α as monotherapy,[10,26,30] most allowed the concomitant use of chemotherapy, and the association between prognostic variables and hematologic response has been rarely studied. The Bordeaux group reported that the achievement of CHR was not influenced by age, sex, WBC or platelet count at diagnosis, percentage of myeloblasts, splenomegaly or Sokal's group, but we are not told if basophils were considered.[26]

Nearly half of the patients (48%) in our study obtained Ph1 suppression. This response was major in 27% of the patients, and complete in 19%. The proportion of patients with major responses is lower than that reported by the Bordeaux or MDACC group (44% and 38%, respectively),[25,26] and similar to that obtained by the Italian group.[8]

The time to cytogenetic response was long in some cases. Eight of our patients obtained CGR after two years of therapy. A time to CGR of 73 months was described in the MRC trial,[9] and Italian authors reported that 41% of the patients with CGR obtained it after two years of IFN-α.[8]

We found that a higher percentage of basophils at diagnosis was associated with a worse cytogenetic response in the first year of therapy. The influence of this variable was independent of other classic prognostic variables. It is pathologically sound that basophilia could influence the rate of response to IFN-α. Basophilia is a hallmark of CML, and two prognostic studies have described its influence on

survival.[31,32] These cells belong to the Ph1 clone,[33] have an augmented proliferation,[34] and their production is increased during transformation.[35] However, a negative impact of basophilia at diagnosis on genetic response was not found in three previous studies,[13] although in two of them we do not know whether this variable was entered into the statistic model.[8,26] It is tempting to speculate that commitment of the Ph1 clone to basophil lineage may confer some resistance to IFN-α.

The projected 6-year overall survival and transformation-free survival in our series are 61% and 54%, respectively. We found that neither Sokal's nor Kantarjian's[16] prognostic systems discriminated adequately in our series. Paradoxically, patients with Sokal's intermediate-risk had a higher probability of survival in our series, specially after 4 years. Thus, this prognostic system, when applied to our series, has lost its progressive character. Several studies have found that the discriminating ability of Sokal's system may be lower in patients treated with IFN-α.[10,11,13,36] Concerning the synthetic model, we found that the projected TFS was significantly lower in patients with Kantarjian's stage 3 disease, although we found no differences between those in stages 1 and 2, a fact which has also been found in other studies.[36] It is important to point out that 61% of our patients with Sokal's intermediate risk disease are classified as being in stage 1 by Kantarjian's system. This fact may be important in order to explain the discrepancy between the discriminating power of the two prognostic systems in our series.

Our results show that obtaining a CHR in the first six months of therapy is a beneficial factor for survival. Patients with CHR have a projected 6-year OS of 87±7%. Besides, this influence is independent of other variables, confirming the results of recent studies by other European groups.[24,26]

The Italian Group was the first to show that obtaining a genetic response was independently associated with better survival,[8] a result which conflicted with results previously reported by the CALGB group.[15] The favorable impact of genetic response on survival has now been confirmed by other groups, which have also described its independence from classic prognostic variables.[13,26] The analysis of our results reconfirm these findings. In our series, obtaining a cytogenetic response during the first year of therapy decreases the risk eight times. This effect is higher when patients obtain a major cytogenetic response in this period, and the risk is lowered twenty times in these patients. The multivariate analysis disclosed that the effect of the genetic response was independent of all the classic prognostic variables entered into the model, and we feel that this finding supports the belief that genetic response is not merely a surrogate marker of an intrinsically good prognosis in patients who obtained it, and reinforces the hypothesis of a direct effect of IFN-α on survival in CML patients.[37]

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Appendix

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Disclosures

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