Imatinib mesylate therapy of chronic phase chronic myeloid leukemia resistant or intolerant to interferon: results and prognostic factors for response and progression-free survival in 150 patients

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Background and Objectives. Imatinib mesylate has recently been shown to be highly effective in chronic-phase chronic myeloid leukemia (CML). The results of imatinib treatment in chronic-phase CML patients resistant or intolerant to interferon (IFN) and the factors predicting therapeutic response and progression-free survival were analyzed.

Design and Methods. One hundred and fifty patients with chronic-phase CML resistant (n=111) or intolerant (n=39) to IFN were treated with imatinib. Prognostic factors for response and disease progression were assessed by multivariate analysis.

Results. The median time from diagnosis was 43 months (0.5-188), median IFN therapy 21.5 months (0.5-140) and median follow-up from starting imatinib 13.6 months (range: 3-23). Complete hematologic response was achieved in 96 of 97 patients. Complete, partial and minor cytogenetic responses were present in 44%, 22%, and 8% of patients at 12 months. Grade III-IV neutropenia, thrombocytopenia, and anemia developed in 33%, 16%, and 6% of patients, respectively. Sixty-five patients discontinued treatment for a median of 4 weeks (1-36) due to toxicity. The rate of progression-free survival (lack of accelerated/blastic phase with persistent response) was 89.2% (95% CI: 84-94.4) at 12 months and 80.2% (95% CI: 72.2-88.2) at 18 months. Platelets > 450×10^9/L and treatment discontinuation > 4 weeks were associated with a lower rate of major (complete plus partial) cytogenetic response. Patients in Sokal's high-risk group and those who did not achieve a major cytogenetic response had significantly shorter progression-free survival.

Interpretation and Conclusions. Imatinib is highly effective in chronic-phase CML patients resistant or intolerant to IFN, especially in those with normal platelet counts and in those not requiring prolonged treatment discontinuation due to neutropenia.

Key words: chronic myeloid leukemia, treatment, interferon, imatinib mesylate, Glivec.

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Chronic myeloid leukemia (CML) is a neoplastic disorder of a pluripotent hemopoietic stem cell harboring the Philadelphia (Ph) chromosome,[1] the result of a reciprocal translocation between chromosomes 22 and 9.[2] This cytogenetic abnormality has its molecular counterpart in the BCR/ABL fusion gene,[3] which produces the BCR/ABL protein, a tyrosine kinase that mediates cellular transformation and is considered the cause of the disease.[4] To date, allogeneic stem cell transplantation is the only therapy with the potential to cure CML but, due to the lack of a suitable donor, it can be applied only to a minority of patients and is associated with substantial morbidity and mortality.[5] For those patients who are not eligible for transplantation, interferon-α is considered the treatment of choice, since it can induce cytogenetic responses and prolong the patients' survival.[6,7] However, many patients do not respond to interferon, while others have to discontinue the treatment because of poor clinical tolerance.[6,7] Imatinib mesylate (formerly STI571) is a 2-phenylaminopyrimidine derivative that has recently been introduced for the treatment of CML: it acts through the selective inhibition of the BCR-ABL protein.[8,9] The drug is highly effective in patients with chronic phase CML who are resistant or intolerant to interferon, and has an acceptable toxicity.[8,10] Responses are better in patients who have had the disease for a shorter period, as well as in those with a previous response to interferon.[10] However, the published experience on imatinib treatment of CML patients is still scarce.

The aim of the present study was to analyze the efficacy and toxicity of imatinib treatment in 150 chronic phase CML patients resistant or intolerant to interferon treated in five Spanish institutions, as well as to determine the factors associated with a favorable response to treatment and a shorter progression-free survival.

Design and Methods

One hundred and fifty adult patients with chronic-phase Ph-positive CML resistant or intolerant to interferon treated within an international Novartis-sponsored protocol (expanded access 113) are the subject of the present study. Chronic-phase CML was defined by the presence of less than 10% blasts in the blood, less than 20% basophils in the blood, and less than 20% blasts plus promyelocytes in blood and bone marrow, a platelet count of at least 100×10^9/L, and the lack of cytogenetic abnormalities other than the Ph-chromosome. Hematologic failure to benefit from interferon treatment was defined

as either hematologic resistance (i.e., failure to achieve a complete hematologic response after at least six months of treatment) or a relapse after having obtained a hematologic response. Cytogenetic failure was considered as either primary (i.e., failure to achieve < 65% Ph-positive bone marrow metaphases after a minimum of one year of treatment) or secondary (i.e., an increase in the proportion of Ph-positive metaphases by > 30% over the previous value or to higher than 65% of the marrow metaphases) after having obtained a major cytogenetic response (Ph-positive metaphases < 35%). Intolerance to interferon was defined as any non-hematologic toxic effect > grade 3 of the WHO scale persisting for more than two weeks despite appropriate treatment interruption and dose adjustments.

Exclusion criteria were: an ECOG performance status > 3, serum levels of aminotransferases, bilirubin and creatinine above 2.5 times the upper normal limit, functional class III or IV heart failure according to the New York Heart Association classification, and a positive pregnancy test in women. The use of barrier contraceptive measures was required for all individuals with childbearing potential. Patients were not included in the study if they had received hydroxyurea within the 7 previous days, interferon or cytarabine within the previous 14 days or any other investigational drug within 28 days. The study was performed according to the Helsinki declaration and written informed consent was obtained from all patients.

Imatinib mesylate (Glivec) was kindly supplied by Novartis Pharmaceuticals (Basel, Switzerland). Patients received 400 mg of the drug orally once a day after breakfast. Dose-escalation to 600 mg per day was permitted in patients in whom a complete hematologic response had not been achieved after 3 months of treatment, in those whose disease relapsed, and in those in whom a major cytogenetic response had not been obtained after 12 months of therapy. If response remained unsatisfactory after at least 3 months of treatment with the 600 mg dose, imatinib dose could be further increased to 400 mg twice daily. Patients received continuous therapy unless unacceptable adverse effects or disease progression occurred. Complete blood counts with differential count and serum biochemical tests were performed weekly for the first four weeks of therapy and then monthly unless toxicity requiring treatment interruption or dose modifications developed. Toxicity was graded according to the WHO scale. If grade 3-4 hematologic toxicity occurred (i.e., a neutrophil count of less than 1×10^9/L or a platelet count of less than 50×10^9/L), treatment was discontinued until amelioration to grade < 2 and then resumed at 400 mg/day in the case of resolution within two weeks or at 300 mg/day if this took more than two weeks; grade 1-2 hematologic toxicity did not require treatment interruption or reduction. There were no dose modifications because of anemia, with blood transfusions being given at the discretion of the investigator. In the case of grade 3-4 non-hematologic toxicity, treatment was discontinued until the toxicity decreased to grade < 1 and then treatment was resumed at 300 mg/day. In the case of grade 2 non-hematologic toxicity, therapy was interrupted until amelioration to grade < 1 and then treatment resumed at 400 mg/day and when there was a recurrence, treatment was discontinued until amelioration to grade < 1 and then resumed at 300 mg/day.

Rates of complete hematologic and cytogenetic response and time to progression (i.e., loss of hematologic or cytogenetic response and evolution into the accelerated or blastic phases, defined according to standard criteria)[11,12] were used to assess treatment efficacy. Cytogenetic bone marrow studies were performed every 3 or 6 months using the Giemsa banding technique, with at least 20 metaphases being analyzed. Fluorescence *in situ* hybridization (FISH) analysis was not used in the present study.

Fisher's exact and Student's t tests were used to compare categorical and continuous variables, respectively. Time to disease progression and survival were analyzed by the Kaplan-Meier method. Univariate and multivariate analyses were used to assess the effects of potential prognostic factors for major cytogenetic response achievement and disease progression. Univariate analysis was performed with the χ^2 or log-rank tests and prognostic factors with a significance level of less than 0.2 were then included as terms in logistic regression or multivariate Cox models. A backward stepwise procedure was used to build the final multivariate model. Factors attaining a significance level of less than 0.05 in the multivariate analysis were considered as independently predictive of the corresponding efficacy outcome.

Results

The main characteristics of the 150 patients are summarized in Table 1. The criteria for imatinib treatment were hematologic (n= 54) or cytogenetic failure (primary, n= 30; secondary, n= 27) to IFN and intolerance to this treatment (n= 39). Forty-two patients had previously been submitted to an autologous stem cell transplantation. At the time of the analysis, the median time of imatinib treatment was 13.6 months (3-23). Fifty-three patients were in complete hematologic response at the start of treatment. Complete hematologic response was achieved in 96 of the remaining 97 cases, at a median of 3 weeks (range, 1-24) after the start of treatment. Table 2 shows the rates of cytogenetic response obtained at different time intervals from the start of imatinib treatment. As can be seen, 53% of patients achieved a complete (0% Ph-positive metaphases) or a partial (1-35% Ph-positive metaphases) cytogenetic response by 6 months of treatment and 66% of them did so by 12 months. The actuarial probability of having achieved a major cytogenetic

Table 1. Main characteristics of 150 patients with chronic phase chronic myeloid leukemia resistant or intolerant to interferon treated with imatinib.

Feature	
Median age, years (range)	53 (16-79)
Males/Females	91/59
Sokal risk-group at diagnosis*	
Low-intermediate	69%
High	31%
Median duration of interferon therapy, months (range)	21.5 (0.5-140)
Best cytogenetic response to interferon°	
Complete	22 (16%)
Partial	20 (14%)
Minor	22 (16%)
Minimal/none	76 (54%)
Cytogenetic status prior to starting imatinib	
Complete	0%)
Partial	6 (4%)
Minor	9 (6%)
Minimal/none	132 (88%)
Unknown	3 (2%)
Time from diagnosis to imatinib treatment, months	
Median (range)	43 (0.5-188)
Previous autologous stem cell transplantation	28%
Hemoglobin, g/L, median (range)	130 (85-167)
Platelets $\times 10^9$/L, median (range)	282 (62-1428)
% marrow blasts, median (range)	0 (0-12)

**out of 104 patients with available data; °out of 140 assessable patients.*

Table 2. Response to imatinib treatment in 150 patients with chronic myeloid leukemia in chronic phase resistant or intolerant to interferon.

Cytogenetic response	3 months	6 months	12 months
Complete	11 (16%)	37 (30%)	46 (44%)
Partial	17 (24%)	29 (23%)	23 (22%)
Minor	10 (14%)	16 (13%)	8 (8%)
Minimal/none	32 (46%)	43 (34%)	27 (26%)
No. of patients evaluated	70	125	104

Table 3. Univariate analysis of prognostic factors for the achievement of a major cytogenetic response to imatinib.

Variable	*No. of evaluable patients*	*No. of patients with response (%)*	*p value*
Age, years			0.73
< 60	107	68 (64)	
>60	36	24 (67)	
Gender			0.39
Male	88	59 (67)	
Female	55	33 (60)	
Sokal's risk group			0.59
Low	41	29 (71)	
Intermediate	27	19 (70)	
High	30	18 (60)	
Time from diagnosis to imatinib, years			0.43
< 1	6	5 (83)	
1-2	27	19 (70)	
> 2	110	68 (62)	
Duration of prior interferon therapy, years			0.4
< 1	37	26 (70)	
> 1	99	62 (63)	
Best response to interferon			0.28
Major cytogenetic response	40	28 (70)	
Lesser degree of response	93	56 (60)	
Prior autologous stem cell transplantion			0.09
Yes	41	22 (54)	
No	102	70 (69)	
Reason for imatinib treatment			0.10
Primary cytogenetic resistance to interferon	82	47 (57)	
Cytogenetic relapse	26	18 (69)	
Intolerance to interferon	35	27 (77)	
Hematologic status at starting imatinib			0.001
Complete response	49	40 (82)	
Other	94	52 (55)	
Hemoglobin level, g/L			0.03
< 120	36	18 (50)	
> 120	105	73 (70)	
Platelet count, $\times 10^9$/L			0.002
< 450	101	73 (72)	
> 450	42	19 (45)	
Blasts in peripheral blood			0.005
0%	76	52 (68)	
> 1%	17	5 (29)	
Blasts in bone marrow			0.02
< 5%	104	72 (69)	
> 5%	8	2 (25)	
Duration of suspension of imatinib treatment		< 0.0001	
No stop or < 4 weeks	101	77 (76)	
> 4 weeks	37	13 (35)	

response at one year was 69.4% (95% CI: 61.2-77.5%). Table 3 summarizes the results of the univariate study of prognostic factors for the achievement of a major cytogenetic response to imatinib. At multivariate study, a platelet count higher than 450×10^9/L at the start of therapy (p=0.01) and the need for treatment discontinuation for 4 weeks or longer (p< 0.001) proved to be the factors independently associated with a significantly lower rate of major cytogenetic response (Table 4). Twenty-two patients progressed while on treatment (loss of complete hematologic response, 9 cases; loss of cytogenetic response, 6 cases; and evolution into accelerated or blastic phase, 5 and 2 cases, respectively). Blast-cell phenotype during the blast crisis was myeloid in one case and lymphoid in the other one.

Table 4. Multivariate analysis of prognostic factors associated with the achievement of a major cytogenetic response to imatinib.

Variable	*p value*	*Relative risk*	*95% confidence interval*
Imatinib discontinuation > 4 weeks	< 0.001	0.11	0.04-0.31
Platelet count > 450×10^9/L	0.01	0.27	0.10-0.74

The actuarial probability of survival without evolution to the accelerated or blastic phase was 96.4% (95% CI: 93.3-99.5) at 12 months of treatment and 92.8% (95% CI: 87-98.6) at 18 months (Figure 1).

The probability of progression-free survival (including both lack of progression to the accelerated or blastic phase and persistence of the hematologic and cytogenetic response) was 89.2% (95% CI: 84-94.4%) and 80.2% (95% CI: 72.2-88.2%) at 12 and 18 months of treatment, respectively. The univariate analysis identified five prognostic variables associated with a shorter progression-free survival: Sokal's high risk score at CML diagnosis ($p = 0.004$), presence at the start of imatinib of a platelet count higher than 450×10^9/L (p=0.01), > 1% blasts in peripheral blood (p=0.03) or > 5% blasts in bone marrow (p=0.007), and failure to achieve a major cytogenetic response during the first year of treatment ($p<$ 0.0001). However, the only two factors independently predictive of a shorter time to disease progression in the multivariate analysis were Sokal´s high risk score (p=0.01) and the failure to achieve a major cytogenetic response to imatinib (p=0.003). Figures 2 and 3 depict the time to disease progression according to the latter two variables. Table 5 shows the toxicity associated with imatinib treatment in the 150 patients. The most frequent hematologic toxicity was grade III-IV neutropenia, which was observed in 49 patients (33%). With regard to non-hematologic toxicity, muscle cramps and edema were the most frequent side-effects (33 patients each, or 22%), followed by gastrointestinal symptoms and skin rash. Severe complications were seen only in a few patients and included infection (6 cases), renal failure (2 patients), and intestinal hemorrhage and digital ischemia (one case each). Treatment was discontinued in 73 patients (49%), for a median of 4 weeks (1-36), with the primary reason for withdrawal being myelosuppression in 60 cases (82%). However, only in 10 patients did imatinib have to be definitively withdrawn due to lack of response (4 cases), toxicity (renal failure and generalized erythematous skin rash, one case each) or progression (4 cases). At the time of the analysis, two patients had died, one from progression to blast crisis and the other from allogeneic stem cell transplant-related toxicity.

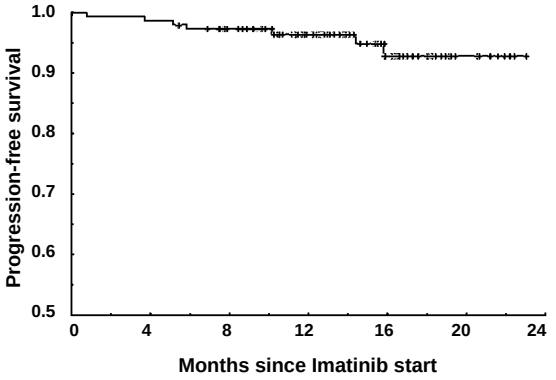

Figure 1. Actuarial probability of survival without evolution to the accelerated or blastic phase in 150 patients with chronic myeloid leukemia in chronic phase resistant or intolerant to interferon who were treated with imatinib.

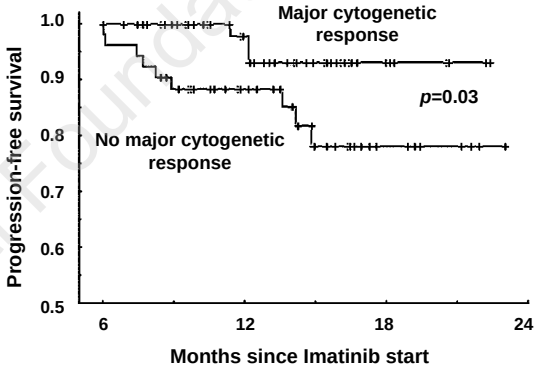

Figure 2. Land-mark analysis of progression-free survival (including lack of evolution to the accelerated and blastic phase and persistence of the hematologic and cytogenetic response) from the start of imatinib treatment in 150 patients with chronic phase chronic myeloid leukemia resistant or intolerant to interferon according to the cytogenetic response at six months.

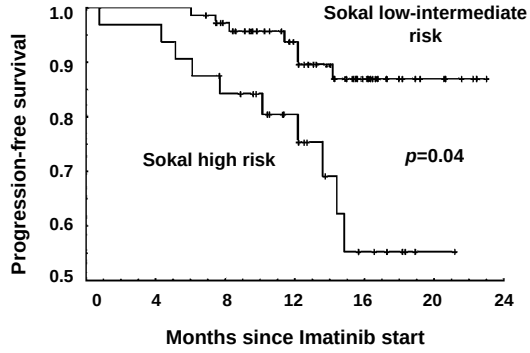

Figure 3. Time to progression from the start of imatinib treatment in 150 patients with chronic phase chronic myeloid leukemia resistant or intolerant to interferon according to Sokal's risk group.

Discussion

Allogeneic stem cell transplantation is currently the only curative treatment of chronic myeloid leukemia but, due to age limitations and the availability of a suitable donor, it can be applied only to a minority of patients.[14] For those patients who are not eligible for allogeneic transplantation, interferon-α is a therapeutic alternative that prolongs survival beyond that achieved with conventional chemotherapy.[6,7,14] Unfortunately, it is frequently associated with poor clinical tolerance, resulting in treatment discontinuation in up to a quarter of patients. In addition, a complete cytogenetic response is achieved in less than 20% of cases.[6,7,14,15]

Imatinib mesylate, a selective inhibitor of the BCR/ABL protein, was recently established as the treatment of choice for chronic phase CML patients resistant or intolerant to interferon. Thus, after the preliminary report by Druker *et al.*,[8] a phase 2 multicenter study of 454 patients treated in USA and Europe registered 60% major cytogenetic responses, including 41% complete responses.[10] However, information on the efficacy and tolerance of imatinib in other series is limited and publication restricted to abstract form.[16,17] The virtually 100% hematologic responses, and especially the 66% complete plus partial cytogenetic response rate, obtained in the present study confirms the high efficacy of imatinib in chronic phase CML patients who are refractory or intolerant to interferon. This is particularly noteworthy taking into account that in the present study the interval between diagnosis and starting imatinib treatment was longer (median 43 months, versus 34 months) and the proportion of patients resistant to interferon higher (74% versus 65%) than in the aforementioned study.[10] It must be noted, however, that in the present study stringent criteria were used to exclude, as much as possible, patients already in the accelerated phase of CML. It should also be remarked that the results of the present and the previously published study[10] are better, at least in terms of cytogenetic response, than those achieved with interferon plus Ara-C as first line therapy of CML.[7,15] Moreover, the progression-free survival probability of around 90% at 18 months of treatment is also similar to that previously registered.[10] Nevertheless, the follow-up in both series is still short and therefore a longer observation period is required to confirm that the responses to imatinib will be maintained in the long-term and thus will result in a prolongation of survival. With regard to the prognostic factors for the response to imatinib, the absence of blasts in the peripheral blood at the start of treatment, a normal hemoglobin value, less than 5% blasts in the bone marrow, a diagnosis-treatment interval of less than one year and the prior achievement of a cytogenetic response to interferon have previously been reported to be associated with a higher rate of major cytogenetic responses.[10] Moreover, early reduction of BCR-ABL mRNA transcript levels has been found to be a good predictor of the achievement of a major cytogenetic response after six months of treatment.[18] In the present series, the two factors associated with a poorer cytogenetic response to imatinib were thrombocytosis at the start of therapy and the need for treatment discontinuation > 4 weeks. Of note, grade III-IV myelosuppression occurred in 88% of the patients who suspended imatinib treatment for > 4 weeks. Myelosuppression has also been found to have a negative impact on the achievement of a major cytogenetic response and was associated with higher risk of disease progression in the Hammersmith series.[16] However, it is currently unknown whether the less favorable results in patients developing severe myelosuppression during imatinib therapy are the consequence of more advanced disease in these patients (and, therefore, lower benign hematopoietic cell reserve), insufficient treatment intensity in such cases or both. In this sense, the use of granulocyte colony-stimulating factor has been reported to reverse the dose-limiting neutropenia and thrombocytopenia associated with imatinib therapy, facilitating the achievement of cytogenetic responses in patients with recurrent cytopenias.[19]

The correlation between a Sokal's high risk score and a shorter time to disease progression deserves a specific comment. In the present series, as well as in the recently published IRIS study on newly diagnosed CML patients,[20] the rates of major cytogenetic response achieved with imatinib were not significantly different when analyzed by Sokal´s risk grouping. However, our preliminary results suggest that high-risk patients may have shorter duration of response to imatinib, similarly to what happens with IFN therapy.[21] The above finding, if confirmed with longer follow-up, could have important implications, since it may help to ascertain the potential benefit of imatinib in high-risk CML and therefore influence treatment decisions in such patients. Imatinib was generally well tolerated in our patients, with moder-

Table 5. Side-effects of imatinib treatment in 150 patients with chronic phase chronic myeloid leukemia resistant or intolerant to interferon.

Adverse effect	No. of patients (%)
Hematologic	
Grade 3-4 granulocytopenia	49 (33%)
Grade 3-4 thrombocytopenia	24 (16%)
Grade 3-4 anemia	9 (6%)
Non-hematologic	
Edema	33 (22%)
Muscle cramps	33 (22%)
GI symptoms	18 (12%)
Skin rash	13 (9%)
Arthralgia	6 (4%)
Raised transaminases	3 (2%)

ate edema, muscle cramps and gastrointestinal symptoms being the more frequent extrahematologic side-effects. On the other hand, although almost half of the patients experienced hematologic toxicity that often obliged discontinuation of treatment, therapy could be resumed in all but two cases.

In conclusion, this study confirms that imatinib is a well tolerated and highly effective therapy for patients with chronic phase CML intolerant or resistant to IFN. In this sense, the results of the IRIS study[20] have also demonstrated the superiority of imatinib over interferon plus cytarabine in newly diagnosed CML, allowing imatinib to be established as the first line therapy for this disease.

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Pre-publication Report & Outcomes of Peer Review

Contributions

FC was responsible for the design of the study, the writing of the manuscript and the control of the patients. JCHB performed the statistical analysis and was in charge of the patients. JLS, EC, JGC and JO were responsible for control of the patients and quality assessment of the data collection. AAL, JLL, SO, LV and MC collected the data. We thank Francisco Martínez Ruiz, from the Departamento de Estadística e Investigación Operativa of the University of Valencia, Spain, for his help with the statistical analysis.

Disclosures

Conflict of interest: none

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received June 3, 2003; accepted August 29, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

The efficacy of imatinib in chronic myeloid leukemia is well established.

What this study adds

This paper is an important confirmation of previously published work.