Front-line treatment of Philadelphia positive chronic myeloid leukemia with imatinib and interferon-α: 5-year outcome

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ABSTRACT

In 2004, we reported the short-term results of a multicentric, phase 2 study of imatinib 400 mg daily and pegylated interferon-α in the treatment of 76 early chronic phase Philadelphia-positive chronic myeloid leukemia patients. In this report, we update the results with an observation time of five years. After two years of treatment, all but 10 patients (13%) had discontinued pegylated interferon-α. The complete cytogenetic response rate at five years was 87%, and 94% of complete cytogenetic responders maintained the complete cytogenetic response after five years. All but one complete cytogenetic response also achieved a major molecular response. These data confirm the excellent response to imatinib front-line and the stability of the complete cytogenetic response. Any possible additional benefit of the combination with interferon-α remains uncertain, due to low patient compliance.

Key words: chronic myeloid leukemia, imatinib, long-term results, interferon-alpha

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Introduction

Imatinib mesylate (Glivec, Novartis Pharma) is a small molecule inhibiting, among others, the Bcr-Abl encoded protein kinase.[1,2] Imatinib was first tested and registered in a rapid sequence between 1998 and 2000, for the treatment of blast crisis,[3,4] accelerated phase[5,6] and late chronic phase patients resistant or intolerant to interferon-α.[7,8] The potency of imatinib was such that a prospective randomized study of imatinib *vs.* interferon-α in early chronic phase, treatment-naïve, patients was initiated in 2000.[9,10] This study, called IRIS (International Randomized Study of imatinib *vs.* interferon-α and low dose arabinosyl cytosine) led to an impressive change in the front-line management of CML, with imatinib almost completely replacing both interferon-α and allogeneic stem cell transplantation (alloSCT).[11] Since the mechanisms of action of imatinib and interferon-α are different, in 2001 the Italian Cooperative Study Group on CML (now the GIMEMA CML Working Party) carried out an exploratory phase 2 study of the combination of imatinib and interferon-α, to evaluate the safety of the combination, appropriate dosage and patients' compliance. Seventy-six consecutive, previously untreated, CML patients were treated with imatinib 400 mg daily and a pegylated preparation of human recombinant interferon-α2b (PegIntron; PegIFNα; Schering Plough, NJ, USA) at a variable dose (50, 100 and 150 μg/week).

The results of this study were published in 2004,[12] reporting that 45 out of 76 (59%) patients discontinued PegIFNα during the first year of treatment, that the frequency and the

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severity of all adverse events, both hematologic and non-hematologic, increased together with the increase in PegIFNα dose, and that the median administered dose of PegIFNα was significantly lower than the scheduled dose. We concluded that the toxicity profile of the combination and patients' compliance did not encourage testing the combination of imatinib and interferon-α *vs.* imatinib alone. At one year, 83% of patients achieved a major cytogenetic response (MCgR), 70% a CCgR and 47% a 3-log reduction of BCR-ABL transcript levels. The first report of the study covered the first year of treatment, and was focused on toxicity profile and dose adjustments. This cohort of patients, with a follow-up observation of five years, has now provided a valuable source of data for the assessment of the long-term efficacy, covering response duration and survival.

Design and Methods

Study protocol

The study was promoted and sponsored by the Italian Cooperative Study Group on CML (currently the GIMEMA Working Party on CML), with the support of Novartis Pharma and Schering-Plough, which provided the study drugs free of charge. The study was approved by the Ethics Committee of each participating institution and was designed and managed according to the Helsinki declaration and Good Clinical Practice guidelines. The general outline of the study, inclusion criteria and response definitions have been previously reported.[12] Briefly, patients were eligible if they were in early chronic phase, less than six months from diagnosis, and previously untreated with either study drug. According to treatment protocol, patients were assigned to receive imatinib 400 mg daily and PegIFNα at the dose of 50, 100 or 150 μg/week. Continuing PegIFNα was not mandatory after the first year and, in case of adverse events, PegIFNα was dose-reduced or discontinued first, so as to keep the imatinib dose as close as possible to 400 mg daily.

Methods

Cytogenetic studies were performed by standard banding techniques on marrow cells before treatment, every three months during the first year of therapy and at 6-12 month intervals thereafter.[12] Molecular response (MolR) was assessed on blood cells at 3-6 month intervals by a standardized quantitative reverse-transcriptase polymerase chain reaction (RQ-PCR) method on an ABI PRISM 7700 Sequence Detector[13] (Perkin Elmer, Faster City, CA, USA). The housekeeping gene was β_2 microglobulin (β_2M) until January 2004, when it was decided to substitute β_2M with ABL, to make the data more consistent with recommendations and other reports.[13,14] In order to transform BCR-ABL:β_2M data into BCR-ABL:ABL data, from January 2004 to April 2004, 50 samples were assessed in duplicate, using both β2M and ABL. The BCR-ABL:β_2M ratio was plotted against the BCR-ABL:ABL ratio, and the slope of the linear regression equation was used to obtain the estimated BCR-ABL:ABL ratios, applying the formula: BCR-ABL:ABL ratio=57.74 x BCR-ABL:β_2M ratio.[14]

Response definition

The cytogenetic response (CgR) was evaluated according to the proportion of Ph-positive metaphases.[12] A complete cytogenetic response (CCgR) required the absence of Ph-positive metaphases in two subsequent tests. We defined a major molecular response (MMolR) as a ratio BCR-ABL:ABL less than 0.05%, corresponding to 0.1% on the International Scale,[15] whereas undetectable BCR-ABL transcript levels were defined as a ratio BCR-ABL:ABL less than 0.001%, corresponding to the lowest level of detectability of the method (10^{-4}).

Statistics

Overall survival was calculated by the product-limits method of Kaplan-Meier[16] from the date of first imatinib dose to the date of death or last contact, whichever came first, with 95% confidence interval (95% CI). Progression-free survival (PFS) was calculated by the same method from the time of first imatinib intake to the first documentation of accelerated phase or blast crisis or to death, whichever came first. Accelerated phase and blast crisis were identified as previously reported.[12] The Kaplan-Meier[16] method was also used to calculate the duration of the CCgR from the date of the first CCgR to the date of CCgR loss or of last cytogenetic evaluation, whichever came first.

Patients

Seventy-six patients with early chronic phase Ph-positive CML were enrolled between July and December 2001 in 18 Italian hospitals and treated with imatinib 400 mg daily and PegIFNα at the dose of 50 μg/week (27 patients, first cohort), 100 μg/week (18 patients, second cohort), and 150 μg/week (31 patients, third cohort). The Sokal risk[17] distribution was 45%, 31% and 24% in the low, intermediate and high risk groups respectively. According to Hasford's score, 51% of the patients were low risk, 37% were intermediate risk and 12% were high risk.

Results and Discussion

Adverse events, compliance and dose intensity

The type and the frequency of the adverse events during the first year have already been reported in detail.[12] Neutropenia grade 3-4 and thrombocytopenia grade 3 occurred in 63% and in 28% of patients respectively. Non-hematologic adverse events were grade 2 in 38%, grade 3 in 38% and grade 4 in 3% of patients. Compliance to PegIFNα was low, both in terms of median administered dose and of proportion of patients who continued PegIFNα therapy over the years (Table 1). Imatinib was discontinued for adverse event in 3/76 patients (4%); one of these patients

Table 1. Number of patients on PegIFNα and median administered vs. scheduled dose of PegIFNα (μg/week) after 12, 18, 24 and 36 months.

	1st cohort (27 patients, 50 μg/week)		2nd cohort (18 patients, 100 μg/week)		3rd cohort (31 patients, 150 μg/week)	
	N. patients on PegIFNα	Median administered vs. scheduled dose (μg/week)	N. patients on PegIFNα	Median administered vs. scheduled dose (μg/week)	N. patients on PegIFNα	Median administered vs. scheduled dose (μg/week)
12 months	12 (44%)	36 (72%)	7 (39%)	35 (35%)	12 (39%)	32 (21%)
18 months	7 (26%)	50 (100%)	2 (11%)	54 (54%)	5 (16%)	112 (75%)
24 months	4 (15%)	50 (100%)	2 (11%)	100 (100%)	4 (13%)	112 (75%)
36 months	1 (4%)	50 (100%)	0	0	1 (3%)	100 (66%)

The overall proportion of patients continuing on PegIFNα dropped from 41% at 12 months to 18% at 18 months, 13% at 24 months, 3% at 36 months; by the end of the fourth year, all patients were off PegIFNα. During the first 12 months, the median administered dose of PegIFNα ranged between 32 and 36 μg/week in all three cohorts. From the second year, the median administered dose ranged between 50 and 112 μg/week, reflecting a selection of the patients who had a better compliance and tolerance to PegIFNα treatment. None of the patients tolerated PegIFNα at the dose of 150 μg/week, and only 7 patients could tolerate 100 μg/week.

resumed imatinib later, without toxicity, and obtained a CCgR. The imatinib dose was increased to 600 mg in 3 patients. Edema was not more frequent than expected with imatinib alone, being observed in 15% of patients (all grades) and in 1% of (grade 3) patients. No patient developed cardiac heart failure or myocardial infarction. The number of patients enrolled in each PegIFNα cohort was too small for a specific statistical analysis. Nonetheless, there was a trend towards a correlation between the severity of the adverse events and the scheduled PegIFNα dose, since grade 3 non-hematologic adverse events were reported in 22%, 33% and 55% of the patients of the first, second and third cohorts respectively.

Table 2. Time to complete cytogenetic response by cohort and for all 76 patients.

Time to CCgR	Low risk (34 patients)	Intermediate risk (24 patients)	High risk (18 patients)	Total
3 months	35%	33%	11%	29%
6 months	73%	75%	17%	60%
12 months	79%	87%	28%	70%
24 months	88%	92%	55%	81%
36 months	88%	96%	72%	87%

CCgR: complete cytogenetic response. Low and intermediate risk patients had similar CCgR rates, whereas the rate was significantly lower for high risk patients (p=0.005 at 12 months and 0.02 at 36 months).

Response and course

After one year of treatment, 74/76 patients (97%) had achieved a complete hematologic response; 55/76 (70%) a CCgR and 36/76 (47%) a MMolR, that was undetectable by RQ-PCR in 11 (14%) patients. After the 12th month, another 11 patients achieved a CCgR, for an overall CCgR rate of 87%. Eight of these 11 late CCgRs belonged to the high Sokal risk group, where the proportion of patients in CCgR increased from 28% at 12 months to 72% at five years (Table 2). Forty-one of 66 (67%) CCgRs achieved CCgR while on imatinib and PegIFNα, while the remaining 25 patients achieved CCgR 1-26 months (median 4 months) after the discontinuation of PegIFNα. Nine of the 10 patients who never obtained a CCgR discontinued PegIFNα within the first six months of therapy. After 3-6 years (median 5 years) from the time of first documentation of the CCgR, 62/66 patients are still in continuous CCgR, and the actuarial proportion of stable CCgRs at five years is 94% (95% CI: 88.4-99.6%). Of the patients who lost the CCgR, 2 were submitted to alloSCT in CP, 1 is currently being treated with a second generation tyrosine kinase inhibitor and 1 pro-

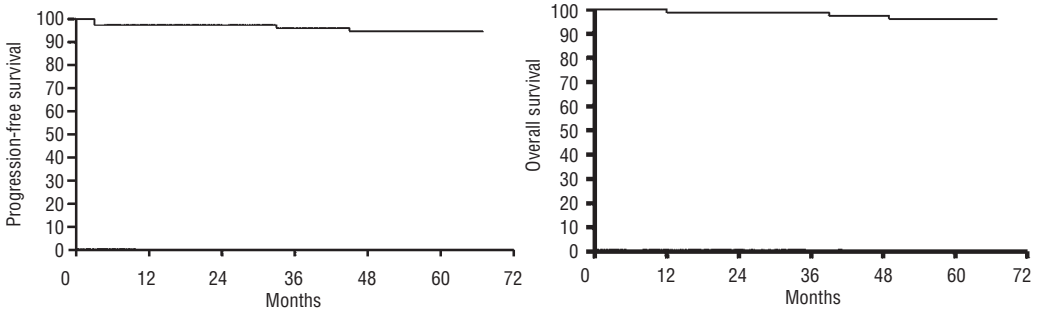

Figure 1. Kaplan-Meier estimate of progression-free survival (PFS) and overall survival (OS). PFS was calculated from the date of enrolment to the date of progression to accelerated phase/blast crisis or to death, whichever came first. OS was calculated from the date of enrolment to the date of death or to last contact, whichever came first. At 5-years, PFS was 95% (95% CI: 90-100%) and OS was 96% (95% CI: 92-100%).

gressed to blast crisis and died. The MMolR rate at one year was 47% (36/76) in all patients, and 65% (36/55) in CCgRs. At subsequent evaluations, the MMolR rate increased to 83% in all patients (63/76), and 95% in CCgRs (63/66). The BCR-ABL transcript level became occasionally undetectable in 21% of patients, but remained persistently undetectable in only 2/76 patients (3%). With an observation time of more than five years, 3 patients have progressed to accelerated phase/blast crisis and 3 patients have died (Figures 1A and 1B). iImatinib has rapidly become the front-line treatment of Ph-positive CML, thanks to the results of the pivotal IRIS study.[9,10,18] However, no other reports have been published on the front-line treatment of CML with imatinib, with the exception of two single-centre studies. These reported on 187 and 114 patients respectively, who were treated with imatinib front-line (mainly 800 mg daily) with a short follow-up (median 19 and 15 months respectively).[19,20]

This study was designed in 2001 with the specific purpose of determining the toxicity and compliance to the combination of imatinib and interferon-α, and to identify the PegIFNα dose which would be both safe and free from recurrent adverse event. The answers to these questions had already been published: the combination was safe (no severe adverse event occurred) but was hematologically more toxic, and compliance was poor, mainly due to the non-hematologic toxicity of PegIFNα.[12] After a median follow-up of 60 months, we confirm that most patients discontinued PegIFNα during the first 12 months of therapy, and we report that just a few patients continued the combined treatment beyond two years. On the other hand, compliance to imatinib was excellent, and no severe late-onset toxicities, including cardiac dysfunctions, have been observed. After a median follow-up of more than five years, we confirm that the results of this study do not support testing of this combination in longer, prospective randomized studies. However, since other exploratory studies of imatinib and interferon-α suggested that with different doses, preparations and timings, the combination could be better tolerated, some large prospective randomized studies of imatinib and interferon-α front-line are ongoing.[21,22] These studies will provide more data on the compliance and on the tolerated dose of interferon-α, and will establish whether the addition of interferon-α results in a higher cytogenetic and molecular response rate, and in a longer survival. Based on this report, the high CCgR and MMolR rate, and the durability of the responses may encourage speculation that the addition of PegIFNα had some benefits. On the other hand, it should be remembered that the great majority of the patients received PegIFNα for a short period of time and that interferon-α, when given alone, requires longer treatment durations to achieve a response.[23] Retrospectively, the role of interferon-α remains uncertain. However, in the present study all but 2 patients were regularly and continuously treated with imatinib 400 mg daily, confirming that, as in the pivotal IRIS study, the response to this treatment is excellent and durable.

Authorship and Disclosures

FP and II: collected data and wrote the manuscript. MB designed and supervised the study and gave final approval to the manuscript. GM and GR: contributed to the design and development of the study as well as interpretation of the data. NT, AP, and MA: performed cytogenetic and molecular studies. FC, MB, TI, FI, GRC, MT, MM, FP and GS: contributed in the development of the study and in data collection. GRC: speaker bureau of Novartis and Bristol Myers Squibb. FP: Research grant from Novartis, honoraria from Novartis, Bristol Myers Squibb e Roche. GS: advisory board and speaker bureau Novartis and Bristol Myers Squibb and research grant from Novartis. GR: grant and speaker bureau (Novartis), speaker bureau (Bristol Myers Squibb); MB: research grants and honoraries as speaker and consultant from Novartis Pharma. The other authors reported no potential conflict of interest.

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