The response to imatinib and interferon-α is more rapid than the response to imatinib alone: a retrospective analysis of 495 Philadelphia-positive chronic myeloid leukemia patients in early chronic phase

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ABSTRACT

Before the introduction of imatinib, interferon α-based regimens were the gold standard for treatment of early chronic phase chronic myeloid leukemia patients. The combination of IFN-α with imatinib is currently being investigated in at least two large clinical trials, the German CML Study IV and the French SPIRIT trial.

We reviewed the cytogenetic and molecular responses of 76 early chronic phase chronic myeloid leukemia patients who were treated with imatinib and interferon-α and of 419 early chronic phase chronic myeloid leukemia patients treated with imatinib alone front-line.

The complete cytogenetic response rate was higher in the IM+IFN-α group than in the imatinib group at six months (60% *vs.* 42%; *P*=0.003), but not at 48 months (88% *vs*. 88%). The durability of the complete cytogenetic response was similar in the two groups with 94% and 91% of complete cytogenetic responders in continuous complete cytogenetic response at 48 months (*P*=0.56). The major molecular response rate was higher in the IM+IFN-α group at six months (58% *vs.* 34%; *P*=0.0001) and 12 months (67% *vs.* 47%; *P*=0.001) but not later on (65% *vs*. 57% at 48 months; *P*=0.25). Overall and progression free survival were comparable in the two groups; a significant trend to a better event free survival was observed in patients treated with PegIFNα (91% *vs.* 78%; *P*=0.02).

These data suggest that the response to the combination treatment is more rapid. It is not yet known how much a rapid reduction will influence the longer-term overall and progression free survival, and the cure rate.

Key words: imatinib, interferon α, molecular response, chronic myeloid leukemia.

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Introduction

Before 2000, interferon α (IFN-α) based regimens were the gold standard for treatment of early chronic phase chronic myeloid leukemia (ECP-CML) patients. The complete cytogenetic response (CCgR) ranged between 10% and 30%, and complete responders survived longer than ten years.[1] After the introduction of the BCR-ABL tyrosine kinase inhibitor imatinib mesylate (IM; Glivec; Gleevec, Novartis Pharma, NJ, USA),[2] imatinib became the established first-line treatment of CML where it achieved a complete cytogenetic response in about 80% of the patients.[3,4]

Despite many studies, the mechanism of action of IFN-α in CML is still poorly understood,[5-13] but it is believed that IFN-α enhances the antileukemic immune response and may target Philadelphia-positive stem cells. Currently, the role of IFN-α in combination with imatinib is being investigated in large clinical trials, like the German CML Study IV[14] and the French SPIRIT trial.[15] In an interim analysis of the French study, it has been reported that patients treated with imatinib and IFN-α had better cytogenetic responses at six months and better molecular responses at 18 months than those patients treated front-line with imatinib 400 mg alone.

Years ago, the GIMEMA CML Working Party performed an exploratory study of a combination of imatinib and IFN-α front-line and reported that the compliance to the combination was poor.[16,17] The results of this study are now compared to the results of two independent GIMEMA studies where CML patients were treated front-line with imatinib alone.

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Design and Methods

All patients were treated in early chronic phase (within six months from diagnosis and previously untreated or treated only with hydroxyurea) with imatinib 400 mg alone (*ClinicalTrials Gov. NCT00511303 and NCT00514488*) or with imatinib 400 mg and a pegylated preparation of human recombinant IFN-α2b (PegIntron; PegIFNα; Schering Plough, NJ, USA) (*ClinicalTrials Gov. NCT00511121*).

Enrolment criteria and results of these studies have already been described.[16-19] All patients gave written informed consent to the studies which were approved by the Ethics Committee of each participating institution and conducted according to the principles of the Helsinki declaration. Briefly, cytogenetic analysis was performed by standard chromosome banding analysis of marrow metaphases and cytogenetic response was rated according to the European LeukemiaNet guidelines.[4] Molecular response was assessed with a standardized methodology on peripheral blood cells by a standardized quantitative reverse-transcriptase polymerase chain reaction (RQ-PCR) method on an ABI PRISM 7700 Sequence Detector (Perkin Elmer, Faster City, CA, USA).[20] Major molecular response rate (MMolR) was defined as a BCR-ABL:ABL ratio less than 0.1% on the International Scale (IS), whereas undetectable BCR-ABL transcript levels required a BCR-ABL:ABL ratio less than 0.01% on the IS.[21] All the results (CCgR, MMolR and undetectable BCR-ABL transcript levels rates) were calculated based on all enrolled patients, according to the intention-to-treat principle.

Overall survival was calculated by the Kaplan-Meier product-limits method from the date of first imatinib dose to the date of death or last contact, whichever came first. Progression free survival (PFS) was calculated by the same method from the time of first imatinib intake to the first documentation of accelerated phase (AP) or blast crisis (BC) or to death, whichever came first. Event free survival was calculated from the date of first imatinib dose to the date of imatinib discontinuation, CCgR loss, progression to AP/BC or to death, whichever came first. Accelerated phase or blast crisis were identified as previously reported.[4]

Results

Seventy-six patients were treated with the combination of imatinib 400 mg/daily and PegIFNα, at doses ranging from 50μg to 150 μg weekly,[16] while 419 patients were treated with imatinib 400 mg/daily alone. Patients' characteristics are detailed in Table 1. More than 85% of patients received imatinib 400 mg daily throughout the follow up in both groups, and in both groups, the great majority (90% in the IM+IFN group and 84% in the IM group) were still on initial imatinib treatment at the 48 month follow up. Four percent and 5% of the patients received dose escalations to 600 and 800 mg daily in the imatinib+PegIFNα and the imatinib only group, respectively. The proportion of patients continuing PegIFNα was only 41% at 12 months, and dropped to 18% at 18 months, 13% at 24 months, and 3% at 36 months; by the end of the fourth year, all patients were off PegIFNα.[17]

The proportion of patients achieving a complete cytogenetic response, a major molecular response and undetectable BCR-ABL levels is reported in Table 2. The proportion of patients in CCgR was higher in the imatinib+PegIFNα than in the imatinib group at six months (60% *vs.* 42%; *P*=0.003) but not from 12 months on. At 48 months, the proportion of patients in CCgR was the same (82%) in both groups. After patients' stratification according to Sokal risk, there was no significant difference in high-risk patients, with a CCgR rate at six and 12

Table 1. Patients' baseline characteristics. There were no statistically significant differences between the two cohorts; **P*=0.09.

	Imatinib+IFN-α	Imatinib
N. of patients	76	419
Male/Female (%)	57%/43%	59%/41%
Median age, years (range)	47 (18-68)	50 (18-80)
Sokal Risk, n. of patients (%)		
High	18 (24%)*	66 (16%)*
Intermediate	24 (31%)	134 (32%)
Low	34 (45%)	219 (52%)
Patients with splenomegaly, n. (%)	38 (51%)	220 (53%)
Patients with palpable spleen		
≥10 cm below the costal margin, n. (%)	12 (16%)	57 (14%)
Leukocyte count, x10^9, median (range)	78 (9.1-443)	74 (8.2-491)
Platelet count, x10^9, median (range)	345 (102-3564)	332 (88-4920)
Blood blasts, %, median (range)	0 (0-10)	0 (0-10)
Blood eosinophils, %, median (range)	0 (0-20)	0 (0-20)
Blood basophils, %, median (range)	2 (0-16)	2 (0-16)
Follow up, months, median (range)	60 (40-68)	43 (12-67)

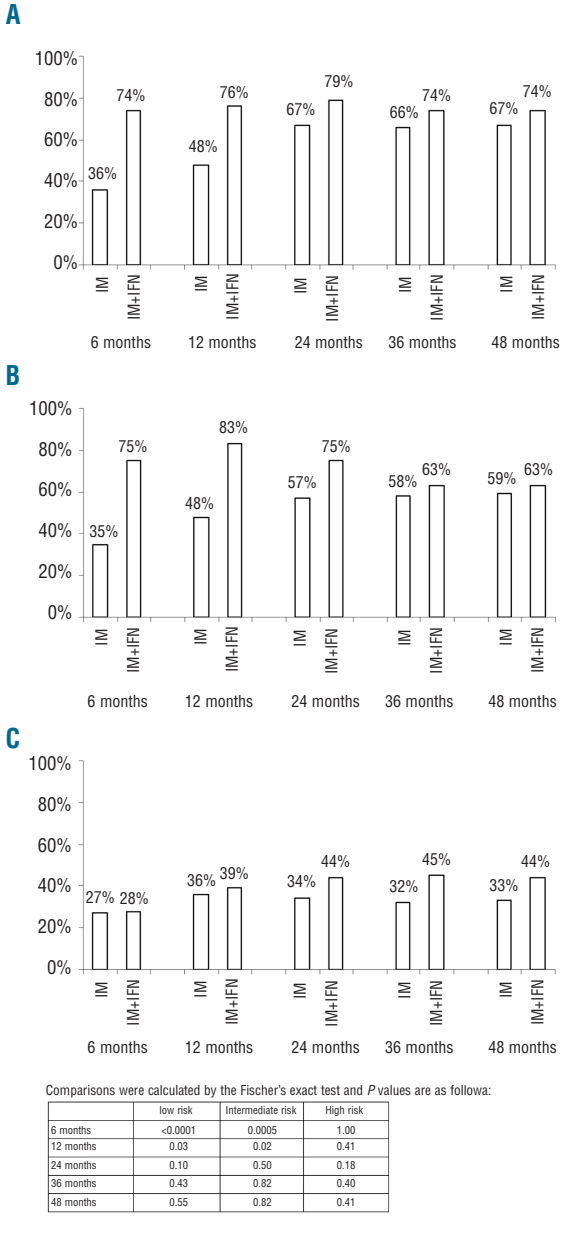
Table 2. Complete cytogenetic response (CCgR), major molecular response (MMolR) and undetectable BCR-ABL transcript in patients treated with IM 400 mg in combination with pegInterferon-alpha (IM+PegIFN) and with imatinib (IM) 400 mg alone.

Time from start IM	Patients in CCgR (%)			Patients in MMolR (%)			Patients with undetectable BCR-ABL (%)		
	IM+PegIFN (76)	IM (419)	*P* value	IM+PegIFN (76)	IM (419)	*P* value	IM+PegIFN (76)	IM (419)	*P* value
6 months	60%	42%	0.003	58%	34%	0.0001	13%	2%	0.0002
12 months	70%	68%	0.89	67%	47%	0.001	15%	5%	0.003
24 months	81%	80%	1.00	65%	62%	0.70	12%	18%	0.14
36 months	87%	82%	0.40	65%	58%	0.52	19%	24%	0.37
48 months	82%	82%	0.87	65%	57%	0.25	19%	18%	0.87

The rates are calculated on all enrolled patients according to an intention-to-treat analysis. The percentages of complete cytogenetic responders evaluable for molecular response ranged from 90% at six months to 64% at 48 months. A two-sided Fisher's exact test at the 5% alpha level was used for comparisons.

months of 17% and 28% in the patients treated with the combination, versus 8% and 36% in the patients treated with imatinib alone (P=0.39 at six months and P=0.58 at 12 months). Conversely, the difference was significant at six months for low- and intermediate-risk patients. In low-risk patients, the CCgR rate was 73% at six months and 79% at 12 months in patients treated with imatinib+PegIFNa, versus 54% at six months and 81% at 12 months in patients treated with imatinib alone (P=0.04 and P=0.81, respectively). In intermediate-risk patients, the CCgR rate was 75% at six months and 87% at 12 months in patients treated with imatinib+PegIFNa, versus 49% at six months and 78% at 12 months in patients treated with imatinib alone (P=0.025 at six months and P=0.41 at 12 months). Overall, 4 (6%) out of 66 complete cytogenetic responders lost the CCgR in the imatinib+PegIFNα group and 26 (7%) out of 370 complete cytogenetic responders lost the CCgR in the imatinib group. The durability of the CCgR was, therefore, similar in the two groups, with 94% and 91% of complete cytogenetic responders in continuous CCgR at 48 months, respectively (P=0.56).

The MMolR rate increased during follow up in both groups, but the response was more rapid in patients treated with imatinib+PegIFNα until the twelfth month. Indeed, the proportion of patients in MMolR was higher in the imatinib+PegIFNα group at six months (58% *vs.* 34%;



Comparisons were calculated by the Fischer's exact test and *P* values are as followa:

	low risk	Intermediate risk	High risk
6 months	<0.0001	0.0005	1.00
12 months	0.03	0.02	0.41
24 months	0.10	0.50	0.18
36 months	0.43	0.82	0.40
48 months	0.55	0.82	0.41

Figure 1. Frequency of major molecular response (MMolR) and during follow up in the IM+PegIFNα and in the IM groups according to Sokal risk (A) low, (B) intermediate and (C) high Sokal risk.

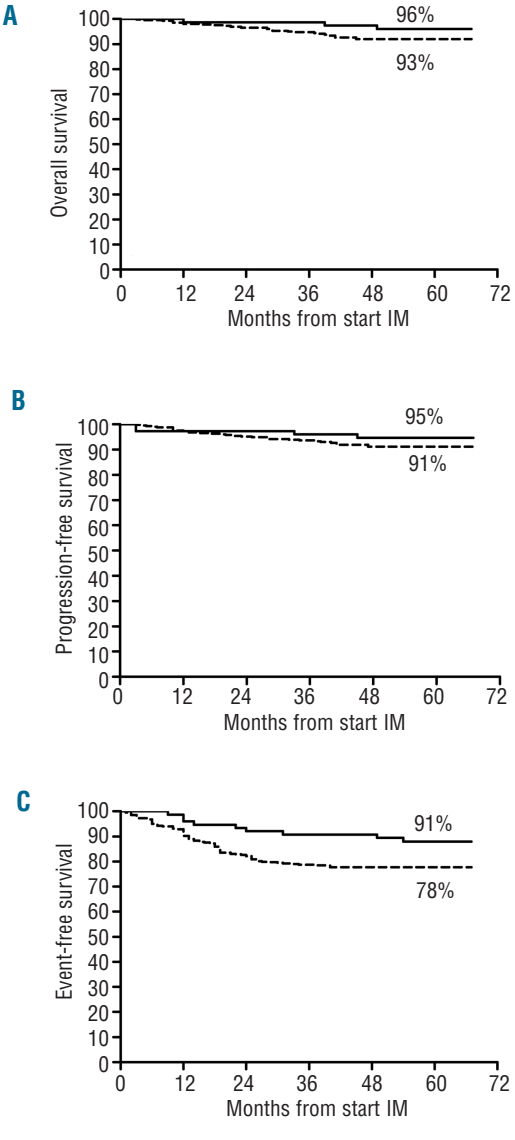


Figure 2. Historical comparison of overall survival (OS), progression free survival (PFS) and event free survival (EFS) rates between patients treated with imatinib+PegIFNα (solid lines) and patients treated with imatinib alone (dotted lines).

P=0.0001) and 12 months (67% *vs*. 47%; *P*=0.001) but not after 12 months (65% *vs*. 57% at 48 months; *P*=0.25) (Table 2).

Figure 1 reports the comparison of MMolR rates after stratification according to Sokal risk, although the number of patients in the imatinib+PegIFNα group was not sufficient to detect small differences. Patients at low and intermediate Sokal risk showed MMolR rates significantly higher than patients treated with imatinib alone. Namely, in low-risk patients, the MMolR rate was 74% at six months, 76% at 12 months and 79% at 24 months in patients treated with the combination versus 36% at six months, 48% at 12 months and 67% at 24 months in patients treated with imatinib alone (*P*<0.0001, *P*=0.03 and *P*=0.10, respectively). In intermediate-risk patients, the MMolR rate was 75% at six months, 83% at 12 months and 75% at 24 months in patients treated with the combination, versus 35% at six months, 48% at 12 months and 57% at 24 months in patients treated with imatinib alone (*P*=0.0005, *P*=0.02, *P*=0.50, respectively). In high-risk patients, the difference between the two groups never reached a statistical significance (27% and 28% at six months; *P*=1.00).

The proportion of patients with undetectable BCR-ABL transcript levels was higher in the imatinib+PegIFNα group, being 13% at six months and 15% at 12 months (*vs*. 2% and 5%, respectively, in the imatinib group; *P*=0.0002 and *P*=0.003). The difference was no longer significant beyond the first year of treatment (19% *vs*. 18% at 48 months) (Table 2).

A historical comparison of overall survival (OS), progression free survival (PFS) and event free survival (EFS) rates was also performed (Figure 2). Overall and progression free survival were comparable in the two cohorts (OS 96% in the imatinib+PegIFNα group *vs*. 93% in the imatinib group; *P*=0.19; Figure 2A). Progression free survival was 95% and 91%, respectively, *P*=0.31; Figure 2B). Conversely, there was a significant trend towards a better event free survival (EFS) in patients treated also with PegIFNα (91% *vs*. 78%; *P*=0.02; Figure 2C).

Discussion

With the limitations of a retrospective study of a large and a small cohort of patients, who were, however, comparable under all characteristics (Table 1), the data show that the response to the combination of imatinib and IFN-α was more rapid than to imatinib alone, but the difference was lost after 12 months for the CCgR and after 24 months for the MMoIR.

The difference was significant only in low and intermediate Sokal risk, while in high-risk patients the benefit of the addition of IFN-α was never observed at a molecular level, confirming the lower response rate of this risk category.

The loss of the difference in CCgR cannot be accounted for by the early discontinuation of IFN-α, because at 24 months and after there was a high CCgR rate which was identical in both groups. However, the discontinuation of IFN-α could account for the lack of increase in the MMolR rate from six months on (58% at six months and 65% at 48 months) and for the relatively small proportion of patients with undetectable BCR-ABL transcript level at 48 months (19%).

In the recent presentation of the results of the SPIRIT trial, the French group reported a significant correlation between the MMolR rate at 12 and 18 months and the duration of IFN-α treatment (less than four months as compared to more than 12 months)[15]. Also in our trial, the MMolR rate was lower in patients who discontinued IFN-α treatment within four months (56% *vs*. 72% at 12 months; *P*=0.41), although the difference did not reach a statistical significance. However, the GIMEMA study was not designed for a subgroup analysis and was not powered enough to provide a clear answer to this question.

It is expected that any improvement in molecular response will result in an improvement in survival, which is the best measure of outcome. As yet, we have not been able to detect any difference in overall and progression free survival, but there was a small positive trend in event free survival for the patients who were treated with imatinib and IFN-α. Since event free survival takes into account not only deaths and progressions but also failures (which were identified according to the ELN criteria[4]) and imatinib discontinuations for any cause, it is possible that switching to a 2nd generation tyrosine kinase inhibitor (TKI) may have obscured any effect on overall and progression free survival.

The present analysis of the responses during the first 24 months of therapy supports that of the French SPIRIT group, reporting a higher rate of MMolR after initial treatment with imatinib+IFNα compared to imatinib alone (62% *vs*. 41% at 18 months).[15] Both analyses also confirm that feasibility of the combined treatment is not without problems: in fact, IFN-α was discontinued in 45% of the patients in the French SPIRIT study and in 59% of the patients in our study at 12 months. This high rate of discontinuation makes it very difficult to fully understand the effect of an uninterrupted co-administration of IFN-α.

The possibility that a sustained co-administration of IFN-α may contribute to a reduction in minimal residual disease and, therefore, to an improvement in the long-term outcome and the cure rate, although not shown, cannot be ignored. However, several major issues require further investigation. What is the effective dose of IFN-α, and could such a dose be tolerated? Should IFN-α be administered in combination with imatinib or according to a rotatory scheme? When and for how long should IFN-α be taken?[22]

It is acknowledged that a more rapid reduction in the size of minimal residual disease can be achieved with imatinib 600 or 800 mg,[15,23,24] nilotinib[25,26] or dasatinib[27] front-line. It is not yet known how much a rapid reduction will influence the longer-term outcome in terms of overall and progression free survival, and the cure rate. IFN-α could also have a role in the setting of the front-line use of 2nd generation tyrosine kinase inhibitors.

Authorship and Disclosures

GR and MB, conception and design; FC, II, GM, MA, GG, AP, NT, MB, MB, MC, GR-C, BM, IP, FR, GS, FP and GS, provision of study materials or patients; FP, collection and assembly of data; FP and GR, data analysis and interpretation, and writing the manuscript; MB, final approval of manuscript.

GR is a consultant with Novartis and serves on the speakers' bureaus of Novartis and Bristol-Myers Squibb. MB receives research support from Novartis, Bristol-Myers Squibb, and Wyeth-Lederle, is a consultant for Novartis,

Bristol-Myers Squibb, and Wyeth-Lederle, and serves on the Novartis speaker's bureau. GM serves on the speakers' bureaus of Novartis, Bristol-Myers Squibb, and is a consultant for Merck Sharp & Dohme. FP receives research support from Novartis, is a consultant for Novartis and Bristol-Myers Squibb, and serves on the Novartis speaker's bureau. GS is a consultant for Novartis and Bristol-Myers Squibb and serves on the speakers' bureaus of Novartis and Bristol-Myers Squibb. The remaining authors declare no competing financial interests.

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