Interferon α plus intermittent oral Ara-C ocfosfate (YNK-01) in chronic myeloid leukemia primarily resistant or with minimal cytogenetic response to interferon

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Background and Objectives. Subcutaneous Ara-C plus interferon (IFN) produces more cytogenetic responses than IFN in chronic myeloid leukemia (CML) but a greater toxicity. The objective of this study was to determine the efficacy and tolerance of IFN plus oral Ara-C ocfosfate (YNK-01) in IFN-resistant CML patients.

Design and Methods. A phase II pilot study was conducted in 19 CML patients primarily resistant or with minimal cytogenetic response to IFN. Patients were scheduled to receive 6 monthly 14-day cycles of YNK-01 (500 mg/day), with progressive escalation if tolerated, in addition to IFN. Cytogenetic assessment was performed thereafter.

Results. Of the first 7 patients, 5 had severe hematologic and 5 moderate gastrointestinal toxicity; IFN was reduced in 6, YNK-01 in 5, and treatment discontinued in 2; hematologic response was achieved in 2 of the 5 evaluable patients. In the following 4 patients the Ara-C was reduced to 300 mg: 2 had severe hematologic and 2 moderate gastrointestinal toxicity; IFN and Ara-C were reduced in 2 patients and treatment discontinued in 2 due to progression or toxicity; the other 2 achieved a minor cytogenetic response, progressing in one to a major response after 6 more cycles. In 8 patients the starting Ara-C dose was 200 mg: 5 had moderate-severe hematologic and 5 mild gastrointestinal toxicity; IFN was reduced in 5, Ara-C in 1, and treatment discontinued in 1; Ara-C was increased in 7 cases; hematologic response was obtained in 4 patients, 2 of whom attained a minor and 1 a major cytogenetic response.

Interpretation and Conclusions. These results provide background for future studies aimed at ascertaining the role of oral Ara-C combined with IFN or STI571 in newly diagnosed CML.

Key words: chronic myeloid leukemia, treatment, interferon, oral Ara-C ocfosfate.

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Interferon α (IFN) is considered the first-line treatment for patients with chronic myeloid leukemia (CML) not eligible for allogeneic bone marrow transplantation.[1-3] Recently, based on early *in vitro* studies showing the preferential inhibition of CML progenitors by Ara-C[4,5] as well as clinical studies demonstrating the therapeutic efficacy of low-dose Ara-C in CML,[6] this latter drug has been combined with IFN. Thus, IFN plus subcutaneous low-dose Ara-C produces higher cytogenetic responses rates[7-11] and, in some studies,[8,9] longer survival than IFN alone, but also a higher toxicity. An additional disadvantage of the intravenous and subcutaneous administration of Ara-C consists of the resulting short plasma half-life of the drug, due to its rapid inactivation by systemic deamination.[12] This limitation might be overcome by the use of cytarabine ocfosfate (YNK-01), an oral Ara-C analog prodrug that is metabolized to the active drug by the liver and is resistant to systemic deamination.[13] The antitumor activity and safety of YNK-01 have been shown in small groups of patients with several hematologic disorders.[14,15] As far as CML is concerned, experience with the use of YNK-01 is scarce.[16-21] The aim of the present phase II multicenter pilot study was to assess the efficacy, tolerance to, and safety of the combination of IFN and intermittent oral Ara-C ocfosfate in CML

Table 1. Main characteristics of 19 CML patients primarily resistant to interferon according to the starting oral dose of Ara-C.

	Ara-C dose		
	500 mg	*300 mg*	*200 mg*
No. of patients	7	4	8
Sex (M/F)	4/3	3/1	2/6
Age (range)	42 - 65	43 - 57	38-60
Sokal risk group			
Low	2	3	6
Intermediate	3	1	1
High	2	0	1
Time from diagnosis			
≤ 2 years	2	3	7
> 2 years	5	1	1

patients with primary hematologic resistance or poor cytogenetic response to IFN.

Design and Methods

Patients

Between October 1997 and September 2000, 20 individuals with Ph+ CML from four Spanish institutions were considered eligible for being enrolled into a phase II pilot multicenter study after having given written informed consent approved by the local Ethics Committee. The protocol entry criteria were the following: a) chronic phase CML; b) age 18-65 years; c) hematologic resistance or minimal cytogenetic response (bone marrow Ph-negative metaphases < 10%) after more than one year of IFN treatment; d) normal renal, hepatic and cardiac function; and e) ECOG performance status < 2. Exclusion criteria included pregnancy and platelet counts < 100×10^9/L. Since one of the 20 patients was diverted to allogeneic bone marrow transplantation when an unrelated donor was found after the patient had given informed consent to enrollment, 19 patients were finally included in the protocol.

Treatment schedule

At diagnosis, after cytoreduction with hydroxyurea, patients had been treated with IFN, administered subcutaneously at an initial dose of 5 MU per square meter of body surface and subsequently adjusted to the patient´s hematologic tolerance, with the goal of maintaining the leukocyte counts between 3 and 4×10^9/L and the platelet counts above 50×10^9/L. Following the failure of IFN treatment, the combined therapy consisted of the daily IFN dose that the patients were receiving at the time of protocol entry plus monthly 14-day cycles of oral Ara-C ocfosfate (YNK-01, kindly provided by Schering-Plough, Spain) at a starting dose of 500 mg/day, with progressive dose escalation (100 mg per cycle, up to a maximum total dose of 900 mg/day) if tolerated. Patients were initially scheduled to receive 6 oral Ara-C cycles and to continue on treatment in the case of response. Causes of treatment discontinuation included: 1) unacceptable hematologic (grade > 3 of the WHO scale) or extra-hematologic (grade > 2 of the WHO scale) toxicity in spite of appropriate reductions in the IFN and Ara-C doses in subsequent cycles; 2) progression of the CML to accelerated or blastic phase, defined according to standard criteria;[22-25] and 3) persistence of high leukocyte counts in spite of successive increases in the Ara-C and IFN doses.

Response criteria and toxicity assessment

In addition to a complete medical history, physical examination, serum chemistry analysis and blood counts, pretreatment evaluation included bone marrow morphologic and cytogenetic study, in which a minimum of 20 metaphases was required. During the first month of therapy, and following each dose escalation, blood counts were obtained every two weeks. Otherwise, medical history, physical examination, blood counts, and serum chemistry were obtained prior to the start of every Ara-C cycle. Bone marrow cytogenetic analysis was performed one month after completion of the 6 Ara-C cycles and thereafter every 6 additional cycles in responding patients.

Conventional criteria were employed for assessment of hematologic and cytogenetic response[1] and the WHO criteria for toxicity assessment.

Results

Table 1 summarizes the main characteristics of the patients. Although the starting Ara-C dose was initially planned to be 500 mg/day 14 days a month, due to the toxicity observed with this dose, the starting dose had to be decreased twice in the course of the study. Because of this, both the patient characteristics and the results are presented separately for each dose subgroup.

In the first 7 patients the starting Ara-C dose was 500 mg/day. The distribution of the patients according to Sokal´s prognostic score[24] and the time elapsed between diagnosis and protocol entry are shown in Table 1. At the start of Ara-C treatment, the IFN dose that the patients were receiv-

ing ranged from 7 to 56 MU/week. As shown in Table 2, 5 patients experienced grade III-IV hematologic toxicity (mainly thrombocytopenia), which led to treatment discontinuation in 2 cases (after having received 2 and 3 Ara-C cycles). With regard to extrahematologic toxicity, 5 patients experienced grade I gastrointestinal toxicity. In all patients but one a reduction in the IFN dose was required, with the weekly IFN dose actually administered during the treatment period ranging from 3 to 52.5 MU. In its turn, the Ara-C dose had to be reduced in 5 patients and could be escalated up to 900 mg in the remaining two. One patient left the protocol after having received 5 oral Ara-C cycles due to progression to the accelerated phase. Overall, a hematologic response was achieved in 2 of the 5 evaluable patients, one of whom also had a minimal cytogenetic response.

Considering the marked toxicity associated with the above Ara-C dosage, in the following 4 patients the starting Ara-C dose was reduced to 300 mg. As shown in Table 1, at protocol inclusion, 3 patients were in the early chronic phase of CML. At the time of starting Ara-C, the IFN dose that the patients were receiving ranged from 7 to 56 MU/week. Two patients developed grade III hematologic toxicity (thrombocytopenia) and 2 grade II gastrointestinal toxicity (Table 2). The IFN dose had to be decreased in 2 cases; the IFN dose actually administered during the treatment period ranged from 3 to 35 MU/week. The Ara-C dose had to be reduced in 2 patients, whereas it could be escalated in the other 2 patients. Treatment had to be discontinued in 2 patients, due to toxicity and disease progression, after they had received 3 and 4 Ara-C cycles. In the remaining 2 patients, at completion of the 6 Ara-C cycles a minor cytogenetic response was obtained, progressing in one case to a major cytogenetic response after administration of 6 additional Ara-C cycles.

Due to the hematologic toxicity still observed with the 300 mg Ara-C starting dose, this already adjusted dose was further reduced to 200 mg in the following 8 patients, whose main characteristics are summarized in Table 1. At the time of starting Ara-C, the IFN dose that the patients were receiving ranged from 9 to 70 MU/week. Three patients developed moderate to severe hematologic toxicity (mainly thrombocytopenia) and 5 had mild gastrointestinal toxicity (mainly abdominal discomfort) (Table 2). The IFN dose had to be decreased in 5 cases, so that the IFN dose actually administered during the treatment period ranged from 6 to 70 MU/week. A reduction in the Ara-C dose (to a mean of 170 mg/day) was necessary in 1 patient, whereas the dose could be escalated to 300-600 mg in the remaining seven. Treatment had to be discontinued in 1 patient after 4 cycles due to hematologic toxicity (thrombocytopenia). Among the remaining 7 patients, at completion of the 6 Ara-C cycles a hematologic response was observed in 4 patients, of whom 3 also attained a minor cytogenetic response, and 1 a major cytogenetic response.

Table 3 shows the characteristics of the 5 patients who achieved a minor or a major cytogenetic response following the addition of oral Ara-C to IFN. As can be seen, all responders were in the subgroup of 11 low-risk patients, in contrast with the lack of

Table 2. Side effects in 19 CML patients treated with interferon plus oral Ara-C according to the starting dose of Ara-C.

Side effects	*Ara-C dose*		
	500 mg n = 7	*300 mg n = 4*	*200 mg n = 8*
Hematologic toxicity	5	2	5
Grade III-IV	5	2	3
Grade I-II	0	0	2
Thrombocytopenia	5	2	3
Leukopenia	2	0	2
Anemia	0	0	1
Extrahematologic toxicity	5	2	5
Grade III-IV	0	0	0
Grade I-II	5	2	5
Abdominal pain	2	1	3
Diarrhea	2	0	1
Nausea/vomiting	1	0	1
Oral mucositis	1	1	0
Liver enzyme increase	1	0	0
Conjunctivitis	0	0	1

Table 3. Data of the 5 CML patients achieving a cytogenetic response after the addition of oral Ara-C to interferon (IFN) treatment.

Patient no.	*Sokal risk score*	*Time of IFN treatment**	*Daily IFN dose°*	*Months to first HR*	*Ph⁻ cells at Ara-C start*
1	low	22	3	3	6%
2	low	18	6.5	12	0%
3	low	21	3	6	10%
4	low	15	2	5	8%
5	low	13	7.5	Not reached	5%

**months; °mean in MU; °mean MU; HR: hematologic response.*

responders among the 8 patients with intermediate or high-risk disease ($p = 0.04$, Fisher´s exact probability test). However, one of the responders had not obtained a complete hematologic response after one year of IFN treatment, whereas the remaining four showed only minimal or absent cytogenetic response after having received IFN for 15 to 22 months. Finally, when the possible relationship between the risk score and the development of adverse effects was analyzed, the distribution of the 10 patients with grade III-IV hematologic toxicity was as follows: 5 out of the 11 patients with low-risk CML and 5 out of the 8 with intermediate or high-risk disease (difference not significant).

Discussion

In the last decade IFN has become the gold standard for the treatment of CML patients who are not candidates for allogeneic hemopoietic stem cell transplantation. In addition to achieving hematologic responses in the majority of patients treated in the early chronic phase of CML, IFN is able to reduce the number of Ph^+ cells in a substantial proportion of cases, with this translating into a significant survival prolongation.[1-3] Based on *in vitro* studies showing the selective suppression of CML progenitors by Ara-C[4,5] and clinical studies demonstrating the therapeutic efficacy of low-dose Ara-C when used as a single agent in CML,[6] the latter drug has been added to IFN in the treatment of this disease. Indeed, the combination of IFN and subcutaneous low-dose Ara-C results in higher hematologic and, more importantly, higher cytogenetic responses rates than IFN alone. Thus, IFN plus low-dose Ara-C produces major cytogenetic responses in 40 to 50% of CML patients treated in early chronic phase,[7-11] and this has been found to be associated with longer survival in some studies.[8,9] In this sense, it must be pointed out that ongoing meta-analyses will determine the survival benefit, if any, that could be derived from the addition of low-dose Ara-C to IFN treatment.

The good therapeutic results of IFN plus low-dose Ara-C are, however, obtained at the price of a higher toxicity than when IFN is given alone. Besides this, subcutaneous administration of Ara-C results in a short plasma half-life of the drug, due to its rapid inactivation by systemic deamination.[12] To overcome this disadvantage, cytarabine ocfosfate (YNK-01), an oral Ara-C prodrug resistant to systemic deamination following oral administration, has been synthesized. This drug has shown antitumoral activity in small groups of patients with several hematologic disorders, such as acute leukemia, non-Hodgkin's lymphoma, myelodysplasia, multiple myeloma, chronic lymphocytic leukemia, and chronic myeloproliferative disorders.[14,15]

As far as CML is concerned, the experience with the use of YNK-01 is limited.[16-21] Thus, Kühr *et al.*[18] recently reported the results of IFN plus oral Ara-C treatment in 9 patients with CML primarily resistant or with poor cytogenetic response to IFN. In this study, YNK-01 was given at a starting dose of 300 mg/day on a continuous basis. It must be remarked that the patients´ disease duration was highly variable, ranging from 0.7 to 10.9 years. Dose escalation was difficult, since dose levels higher than 300 mg/day were associated with a high incidence of severe toxicity, mainly fatigue, gastrointestinal symptoms, and thrombocytopenia. Thus, due to the adverse side effects, a total of 7 patients went off study. Overall, a complete hematologic response was obtained in 4 patients, and a complete cytogenetic response at 18 months of treatment in one of them. In the present study, involving a population of CML patients refractory to interferon after having received this drug for a minimum of one year (and most of them for more than one and a half years), oral Ara-C was given on an intermittent basis. In spite of this, Ara-C dosages of 300 mg/day or higher were associated with substantial hematologic and extrahematologic (mainly gastrointestinal) toxicity, which led to treatment discontinuation in more than a quarter of patients. By contrast, in the present study a better tolerance was observed when the starting Ara-C dose was reduced to 200 mg/day, allowing a further dose escalation in the majority of patients and apparently not resulting in a lower therapeutic effect, since major cytogenetic responses could be obtained.

With regard to the use of IFN plus oral Ara-C in newly diagnosed CML, four studies have been communicated in abstract form.[17,19-21] In all cases oral Ara-C was administered at a dose of 600 mg/day, 10 to 14 days a month, in addition to baseline continuous IFN treatment. Thus, Guilhot *et al.*[17] reported a 21% major cytogenetic response rate at 6 months in 98 patients with newly diagnosed CML. Of note, 35 of the patients discontinued YNK-01 within 6 months of starting treatment because of adverse effects, which consisted mainly of gastrointestinal toxicity and cytopenia. Because of this, in order to improve the tolerance, the above authors suggested administering YNK-01 at a lower dose on a daily basis. More recently, of the 31 evaluable patients included in the study by Mollee *et al.*,[19] therapy was prematurely discontinued in 15, primarily because of toxicity, including asthenia, gas-

trointestinal symptoms, cytopenia, and hepatitis. Complete hematologic response at 6 months was achieved in 87%, and major cytogenetic response at 6, 9, and 12 months was 36%, 43%, and 39%, respectively. In their turn, Kalmantis *et al.*,[20] in a randomized study comparing IFN plus hydroxyurea versus IFN and oral Ara-C, obtained 25% major cytogenetic responses in 18 patients receiving oral Ara-C, with acceptable gastrointestinal and hematologic toxicity, versus 0% responses in the IFN-hydroxyurea group. Finally, the Italian Co-operative Study Group on CML recently reported 23% major plus complete cytogenetic responses in a group of 92 newly diagnosed patients using the combination of IFN and oral Ara-C, but they also reported low treatment compliance due to the gastrointestinal toxicity associated with the oral Ara-C dose of 600 mg 14 days a month.[21]

All patients in the present study attaining a minor or a major cytogenetic response after the addition of oral Ara-C to IFN had low-risk CML. It might, therefore, be argued that the cytogenetic response could also have been achieved by continuing IFN alone. However, the fact that among the responders one had not attained a complete hematologic response after one year of IFN, whereas the remaining four obtained only a minimal or absent cytogenetic response after 15 to 22 months of treatment makes such a possibility unlikely.[26] On the other hand, it is noteworthy that none of the patients with intermediate or high-risk CML gained benefit, in terms of cytogenetic response, from the addition of oral Ara-C.

From the above results it can be concluded that in CML patients primarily resistant or with poor response to IFN the addition of oral Ara-C at starting doses higher than 200 mg/day, 14 days a month, is associated with substantial hematologic and, to a lesser degree, gastrointestinal toxicity. In contrast, reasonable tolerance is observed to the starting dose of 200 mg/day, and this dose does not apparently jeopardize the possibility of obtaining cytogenetic responses. Use of oral Ara-C at this lower starting dosage in patients with less advanced disease will allow us to determine the possible role of the above drug as an alternative to subcutaneous Ara-C in CML. In this regard, the results of the present study and those recently reported with the use of STI571 in chronic phase CML patients refractory to IFN[27] would support the possible combination of oral Ara-C with the above tyrosine-kinase protein inhibitor.

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FC was responsible for the design of the study, the analysis of the results and the writing of the paper; AS, RM, SB, DB, and J-L A contributed by including patients and collecting the data; J-C H-B helped in the data collection and analysis of the results and EM contributed to the writing of the paper.

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Disclosures

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Potential implications for clinical practice

A few clinical studies have already shown the potential role of oral cytarabine ocfosfate in combination with subcutaneous interferon alpha in inducing major cytogenetic responses in chronic-phase CML patients.[28] This preliminary study suggests that this combination may be effective also in CML patients primarily resistant to interferon-α,[29] but treatment strategies should now account for the newly introduced tyrosine kinase inhibitor STI571.[30]

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