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Hydroxyurea versus Interferon Alfa-2b in Chronic Myelogenous Leukaemia: Preliminary Results of an Open French Multicentre Randomized Study

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In order to compare the effects of interferon versus hydroxyurea for the treatment of chronic myelogenous leukaemia (CML), 58 CML patients, having received no previous treatment, were randomized into two treatment groups (hydroxyurea or interferon) for an open multicentre study from 1 May 1987 until 1 July 1990. Fifty patients were evaluable: 24 in the interferon group and 26 in the hydroxyurea group. Haematological response was obtained in 16/24 interferon-treated patients and 23/26 hydroxyurea patients. Failure to obtain haematological remissions occurred in eight of 24 interferon-treated patients and in three of 26 hydroxyurea patients. Four interferon-treated patient failures and one hydroxyurea-treated failure were due to drug intolerance. Progression occurred in one interferon-treated patient and in three patients given hydroxyurea. Fourteen of 16 patients in the interferon group and 17/23 in the hydroxyurea group continue on study and show no progression.

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INTRODUCTION

THE INTRODUCTION of recombinant alpha interferon allowed Talpaz and colleagues [1] and then other groups [2-5] to observe the efficacy of this drug in the treatment of chronic myeloid leukaemia (CML). Moreover, the partial and sometimes apparently complete disappearance of the Philadelphia (Ph^1) chromosome in the bone marrow of patients thus treated prompted the hope that this drug would have a higher efficacy than the cytoreductive drugs thus far utilized.

The aim of this study was therefore to compare the effects of recombinant alpha interferon versus hydroxyurea in recently diagnozed, previously untreated CML patients, who were placed randomly into one of the two treatment groups.

ELIGIBILITY

Patients were selected for this study according to the following criteria:

- diagnosis of Ph^1-positive chronic myeloid leukaemia.
- absence of previous treatment (chemotherapy, radiotherapy or treatment with cytokines) with the exception of leukapheresis.
- disease diagnosed less than 3 months prior to study.
- age > 18 years.
- absence of the following karyotypic abnormalities: trisomy 8, isochromosome 17, double chromosome Ph^1.
- consent of the patient.

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The patients were rather old (average age 57 years) as there was an almost complete exclusion *a priori* of patients who might benefit from an allograft.

PROTOCOL

The study was carried out in four centres; randomization of the patients to hydroxyurea and recombinant alpha interferon treatment was performed by one centre according to a centralized randomization list, equilibrated every four patients.

Hydroxyurea was administered at doses allowing the white blood cell count to be maintained between 4 x 10^9/L and 10 x 10^9/L. Patients selected for interferon treatment received a daily dose of 4 million units (MU)/m^2 by subcutaneous administration. These doses were maintained until there was evidence of disease progression, as manifested by irreducible splenomegaly or thrombocytosis > 700,000/ml, a blood level of blast cells > 5%, or a medullary blastosis > 30%. Drug doses were modified in cases of cytopenia or other side effects.

Patients were assessed monthly and underwent a bone marrow examination every 6 months. The cytogenetic analysis included 30 to 100 mitoses, always with study of the G and R bands. In certain patients, determinations of molecular rearrangement were occasionally carried out:

- haematological remission (HR) was defined as a white cell count lower than 10 x 10^9/L in the absence of circulating myeloblasts.
- cytogenetic remission was defined as:
  - minimal cytogenetic response (MCR): Ph^1-negative mitoses < 25%.
  - incomplete cytogenetic response (ICR): Ph^1-negative mitoses between 25 and 99%.
  - complete cytogenetic response (CCR): 100% Ph^1-negative mitoses.

PATIENT CHARACTERISTICS

Fifty-eight patients were enrolled in the study between 1 May 1987 and 1 July 1990: 30 in the interferon group and 28 in the hydroxyurea group.

Eight of these patients could not be evaluated: six in the interferon group, including one due to violation of the protocol, one due to progression to acute disease within the first 15 days of treatment, three voluntary withdrawals from the study, and one treatment too recent; and two in the hydroxyurea group, due to loss of contact with one patient and voluntary withdrawal from the study by another. The voluntary withdrawals from the study did not have disease progression but left before a result could be evaluated.

Fifty patients were thus evaluable, 24 from the interferon group and 26 from the hydroxyurea group. There were no significant differences in age or sex between these two groups (Table 1). For the most part the patients were older than usual for this indication.

The 50 evaluable patients were classified according to risk-type following the criteria of Sokal *et al.* [6] (Table 1). This classification was identical between the interferon and hydroxyurea groups.

Table 1. Evaluable patient characteristics (age, sex, risk using Sokal classification [6]) *

	Interferon alfa-2b (n = 24)	Hydroxyurea (n = 26)
Sex		
Male n	15 (62.5%)	16 (61.5%)
Female n	9 (37.5%)	10 (38.5%)
Age (years ± S.D.)	55.6 ± 10.6	58.6 ± 7.1
Low risk	7	7
Intermediate risk	12	12
High risk	5	7

* Six patients on alpha interferon treatment and two on hydroxyurea were inevaluable. S.D. = standard deviation.

RESULTS

Haematological response

Haematological response (HR) was obtained in 23 of the 26 patients treated with hydroxyurea, and in 16 of the 24 patients treated with interferon (Table 2). Two of the failures in the hydroxyurea group were related to progression of the disease. Four of the eight failures in the interferon group were related to signs of intolerance that led to a rapid discontinuation of treatment. The other four failures were associated with a discontinuation of treatment at 0.5, 3, 4 and 4 months, respectively, due to therapeutic inefficacy.

Of the 23 patients treated with hydroxyurea who achieved a HR, three withdrew from the study due to secondary intolerance, loss to follow up, and concurrent illness, respectively, and in three others the disease evolved toward an acute phase. Seventeen patients continue in the study.

Of the 16 patients treated with interferon who were in HR, two were withdrawn from the study at a later date. None of the remaining 14 patients continuing in the study show progression of their disease.

Table 2. Haematological remission (evaluable patients)

	Haematological response		Failure to respond
Interferon (n = 24)	16 (66.7%)		8*
		NS	
Hydroxyurea (n = 26)	23 (88.5%)		3

*Four out of eight were withdrawn for therapeutic inefficacy at 0.5, 3, 4 and 4 months of interferon treatment, respectively. NS = not significant

An analysis of the initial treatment failures and disease progressions according to the risk groups described by Sokal *et al.* [6], demonstrates no progression of disease in patients treated with interferon. Furthermore, the treatment failures were equally distributed in the low- and intermediate-risk groups but occurred predominantly in the high-risk group.

The average length of treatment (± S.D.) was 13.9 ± 11.8 months and 20.4 ± 10.3 months in the interferon and hydroxyurea groups, respectively.

Cytogenetic response

Among the 26 evaluable patients in the hydroxyurea group, six had a minimal cytogenetic response (MCR) evaluated on a large number of mitoses (Table 3). Two patients presented more significant responses (incomplete cytogenetic response (ICR)), while 18 of the patients did not show any cytogenetic response.

Table 3. Cytogenetic response (number of patients evaluated, and respective percentage of Ph'-negative mitoses in each case)

	Interferon alfa-2b (n = 24)	Hydroxyurea (n = 26)
Minor	2 (8%, 11%)	6 (7%, 9%, 16%, 16%, 17%, 24%)
Incomplete	9 (25%, 35%, 45%, 46%, 47%, 47%, 62%, 82%, 90%)	2 (32%, 38%)
Complete	2 4 months and 12+ months bcr-abl-negative*	0

* By Southern blot.

Among the 24 evaluable patients in the interferon group; two achieved MCR, nine ICR, and two patients CCR (Table 3). In these, one has lasted 4 months and the other 12+ months. Thirteen of the interferon-treated patients showed no cytogenetic response. No conversions were observed before 3 months of treatment, and the two cases of CCR occurred late (18 months) (Fig. 1). (Ten interferon-treated patients and 14 hydroxyurea-treated patients had cytogenetic analyses at 18 months and all were continuing on the study.)

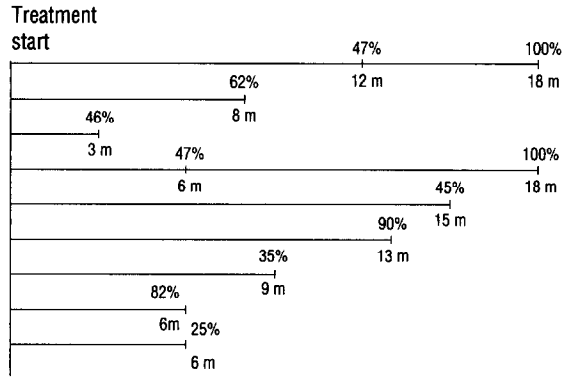

Fig. 1. Delay to cytogenetic response (incomplete and complete) in interferon treated patients.

Mean time (± S.D.) to obtain an incomplete cytogenetic response: 8.67 ± 3.94 mths. Mean time (± S.D.) to obtain a complete cytogenetic response: 18 mths

Toxicity

In patients receiving hydroxyurea, three cases of intolerance arose, one of which led to discontinuation of the treatment.

In patients receiving interferon there were 10 cases of intolerance. In six of these the treatment was stopped: two cases of hepatitis with elevated levels of gamma glutamyl transpeptidase, one case of flu-like syndrome, two cases involving the central nervous system, and one dermatitis. In four cases, interferon could be continued: two cases of thyroid insufficiency, most likely pre-existing in latent form at the start of treatment, one case of unexplained inflammatory anaemia, and one case of depression.

DISCUSSION

In this study, the groups treated with interferon or with hydroxyurea were homogeneous with regard to age, sex and distribution of risk groups. However, it should be noted that the average age of the two groups was old for this indication (average 57 years), which was due in part to the patient eligibility criteria (almost complete exclusion *a priori* of patients who might benefit from an allograft). Although the age factor does not appear significant in the scores according to Sokal *et al.*, Tura *et al.* or Kantarjian *et al.* [6-9], the average age in our study was not in itself a good prognostic factor, and may also have played a role in the tolerance to interferon.

The 67% rate of haematological remission obtained on interferon in the present study is comparable to rates reported in the literature. As expected, failures are more frequently observed in the high-risk group. Among the 16 interferon-treated patients with HR, we have obtained several good quality ICRs and two CCRs, one of which has been stable for 1 year.

The study follow up has not yet been long enough to judge the duration of these remissions or their influence on the duration of the chronic phase.

Haematological remissions were more numerous in the hydroxyurea treatment group than in the interferon group; however, the difference is not significant. One surprising observation was the MCR and two ICRs in the hydroxyurea group. The length and significance of these partial cytogenetic conversions remain to be seen. Three patients had a percentage of Ph¹-negative mitoses at the start of treatment.

More patients treated with hydroxyurea achieved HR and tolerated their treatment better than interferon-treated patients. However, among the evaluable patients, evolution towards the acute stage occurred early in two patients and later in three others. Here again, conclusions cannot be drawn until the study has ended.

The toxicity of interferon was high in an appreciable number of patients. Other than the classical problems, two neurological effects [10] (encephalitis and severe depressive syndrome) led to discontinuation of the treatment. One should also note a decompensation of two thyroid insufficiencies that were latent up until the time of treatment [11], and two cases of hepatitis, in one of which serum gamma glutamyl transpeptidase levels, apart from other biological parameters, rapidly increased to more than 20 times the normal value in one patient, leading to discontinuation of the treatment. This effect was completely reversible and in one case the reintroduction of interferon led to the same effects, which disappeared again after final discontinuation of the drug.

In conclusion, we can currently state that interferon administered as primary treatment for CML patients leads to a slightly lower level of HR than hydroxyurea, that the incomplete cytogenetic conversions are more numerous and more significant than those obtained with hydroxyurea, and that the side effects of interferon treatment are not negligible.

Furthermore, and as shown in other studies, the patients who respond to interferon and who pursue this treatment have a tendency to have a long-lasting chronic phase. These patients, are however, more or less correlated at the onset to factors indicating a good prognosis, and it will be interesting to evaluate these results in relation to similar patients treated with hydroxyurea.

For patients with a poor prognosis who are not amenable to bone marrow allografts, other options must be taken into consideration, such as autologous graft during the chronic phase [5] or combination therapies [12].

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Several New Approaches to Improvement of Alpha Interferon Therapy in Chronic Myelogenous Leukaemia

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Several basic experimental and clinical studies were carried out in an attempt to improve the efficacy of alpha interferon therapy for chronic myelogenous leukaemia (CML). First, the combined use of hydroxyurea (HU) and interferon (500-1000 mg daily) in interferon-resistant cases facilitated maintenance of reduced leucocyte production, or a reduction in the dose of interferon, although suppression of Philadelphia chromosome (Ph^1)-positive clones was not observed in most cases. In order to try and decrease the rate of lymphoblastic crisis during the course of interferon therapy, we recently added methotrexate (MTX) (10-15 mg, weekly) to the treatment protocol. Since then, no lymphoblastic crisis has been observed. Second, the *in vitro* expression of alpha interferon-stimulated gene (ISG) mRNA was shown to be markedly decreased in granulocytes of one representative interferon-resistant case, compared to that in granulocytes of the three interferon-sensitive cases. Interestingly, it was found that the transcriptional activity in this case became almost normal when the blood granulocytes were controlled by the addition of HU. These findings suggest that the *in vitro* transcriptional assay of ISG mRNA may be clinically useful for predicting alpha interferon efficacy. Third, when genetically manipulated, alpha interferon-producing NIH/3T3 cells were co-transplanted using diffusion chambers into nude mice bearing a CML cell line, KU812, the CML tumour growth was shown to be markedly suppressed. This experimental model for alpha interferon replacement gene therapy suggests some directions for future studies on interferon therapy.
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INTRODUCTION

CHRONIC MYELOGENOUS LEUKAEMIA (CML) is one of the myeloproliferative disorders caused by the appearance of abnormal haemato-lymphopoietic stem cell clones with a Philadelphia chromosome (Ph^1) marker as a result of 9;22 reciprocal translocation. These clones generally have two biological characteristics: (1) the extensive ability to differentiate into a neutrophilic cell lineage with some growth advantages (chronic phase), and (2) the occasional transformation into more malignant clones (blastic phase) [1]. Recent molecular biology studies have revealed that the 9;22 translocation is responsible for the abnormal hybrid bcr-abl gene products which may determine the characteristics of CML cell clones [2, 3]. However, actual molecular mechanisms for blastic transformation have not yet been elucidated. Because blastic transformation is the major cause of death in most CML patients, it is of particular importance to address this issue.

For CML, a major advance was the introduction of alpha

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