Recombinant Alfa-2b-Interferon Therapy in Untreated, Stages A and B Chronic Lymphocytic Leukemia

A Preliminary Report

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Ten patients with B-chronic lymphocytic leukemia (B-CLL) (Six Stage A and four Stage B), who had not received therapy previously, were treated with recombinant alfa-2b-interferon (Schering Corporation, Kenilworth, NJ). The low dose of 1.5 MU was administered by intramuscular (IM) injection three times a week for the first week. The dose was increased to 3.0 MU thereafter until 3 months of therapy were completed. In the responding patients, treatment was continued in the same dose and schedule for 3 additional months. Interferon was tolerated without major toxicity by most patients. Objective tumor response (one complete response and four partial hematologic responses [PHR]) was observed in five of ten patients (50%). Severe autoimmune hemolytic anemia developed in one of the nonresponders at 8 weeks. Therefore, treatment had to be discontinued. Our study demonstrated single alfa-2b-interferon antitumor activity in untreated B-CLL patients with stable disease, and indicated that further trials of alfa-2b-interferon, possibly combined with chemotherapy, may be justified.

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ALPHA-INTERFERON (α-IFN) therapy is highly effective in hairy cell leukemia[1–6] but less effective in other B-lymphocytic proliferations.[7–17] Reports on the treatment of chronic lymphocytic leukemia with a α-IFN refer mostly to pretreated patients with advanced disease.[10,14–17]

The current study was undertaken to determine the effectiveness of α-IFN in early B-chronic lymphocytic leukemia (B-CLL) patients, untreated previously, and in excellent clinical condition.

Patients and Method

Patient Characteristics

Ten immunologically proven B-CLL patients were included in this study. There were seven men and three women with a mean age of 60 years (range, 51 to 73 years of age). The mean follow-up time from diagnosis was 30.7 months (range, 5 to 128 months). Six patients were Stage A and four were Stage B.[18] The Stage A patients were Rai Stage 0, whereas the Stage B patients were Rai Stage II.[19] A diffuse pattern of bone marrow disease appeared in two patients and a nondiffuse pattern in eight.[20,21] The mean pretreatment hematologic values for Stage A and B patients are shown in Table 1.

Treatment Program

Our patients were untreated previously. The treatment protocol provided 1.5 MU of recombinant alfa-2b-interferon, (Intron-A, Schering Corporation, Kenilworth, NJ) administered IM every Monday, Wednesday, and Friday for the first week. Thereafter, this increased to 3.0 MU three times a week until the completion of 3 months of therapy. In responding patients, treatment was continued in the same dose and schedule for 3 additional months. Patients with intolerable side effects had the option of stopping therapy at any time, and therapy was discontinued when serious hematologic toxicity was evident. The flu-like symptoms were controlled easily with paracetamol administration. This protocol is similar to that used in splenectomized hairy cell leukemia patients.[3] Follow-up liver and kidney function tests were performed weekly during the first month, and monthly thereafter.

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TABLE 1. Recombinant Alfa-2b-Interferon Therapy in B-CLL Patients: Comparison of the Mean Hematologic Values Before and After 3 Months of Therapy

Hematologic parameters	Stage A		Stage B	
	Before	After	Before	After
Hgb (g/dl)	13.6	12.8	13.4	12.4
WBC × 10^9/l	29.2	17.0	59.7	63.0
Lymphs × 10^9/l	26.0	14.0*	57.2	58.5
Polys × 10^9/l	2.7	3.0	2.4	4.5
Platelets × 10^9/l	230.0	220.5	195.0	171.2

B-CLL: B-chronic lymphocytic leukemia; Hgb: hemoglobin; WBC: leukocyte count.
* $P < 0.005$.

Response Criteria

The following response criteria were used: patient stage (upstaged or downstaged); blood findings, with particular emphasis on the absolute lymphocyte and polymorphonuclear neutrophils counts; and bone marrow findings by aspiration and core biopsy at the completion of 3 months of therapy.

Results

Some of the results obtained in these series are shown in Table 1 and Figures 1 and 2.

Clinical Findings

None of our stage A (0) patients were downstaged after the completion of 3 months of α-IFN therapy. The following occurred in the Stage B (II) patients: one with lymphadenopathy and hepatosplenomegaly had a complete disappearance of all palpable disease after the first week of therapy and thereafter, and was therefore upstaged to Stage A (0); one had stable disease; one had a 20% reduction of palpable disease (lymphadenopathy and splenomegaly); and severe anemia due to an autoimmune hemolytic mechanism developed in one who was therefore downstaged to Stage C.

Hematologic Findings

At the completion of 3 months of α-IFN therapy, the mean hematologic values were as indicated in Table 1. The overall blood lymphocyte population was reduced in the Stage A (0) patients by almost 50%, compared with the pretreatment numbers (Table 1). In the four responding patients, the pretreatment blood lymphocyte counts and the corresponding counts at the completion of 3 months of α-IFN therapy were as follows: 32 × 10^9/l and 15 × 10^9/l, 16 × 10^9/l and 7.5 × 10^9/l, 29 × 10^9/l and 15 × 10^9/l, and 60 × 10^9/l and 29 × 10^9/l. In the Stage B (II) patients, the overall blood lymphocyte population remained approximately the same as the pretreatment one, with the exception of the upstaged patient in whom a 50% lymphocyte reduction was observed. Of significance was the gradual reduction of hemoglobin (Hgb) in one patient (Stage B) from 12g/dl before therapy to 6g/dl 8 weeks after initiation of α-IFN therapy, without evidence of blood loss or disease progression. This dramatic reduction of Hgb proved to be

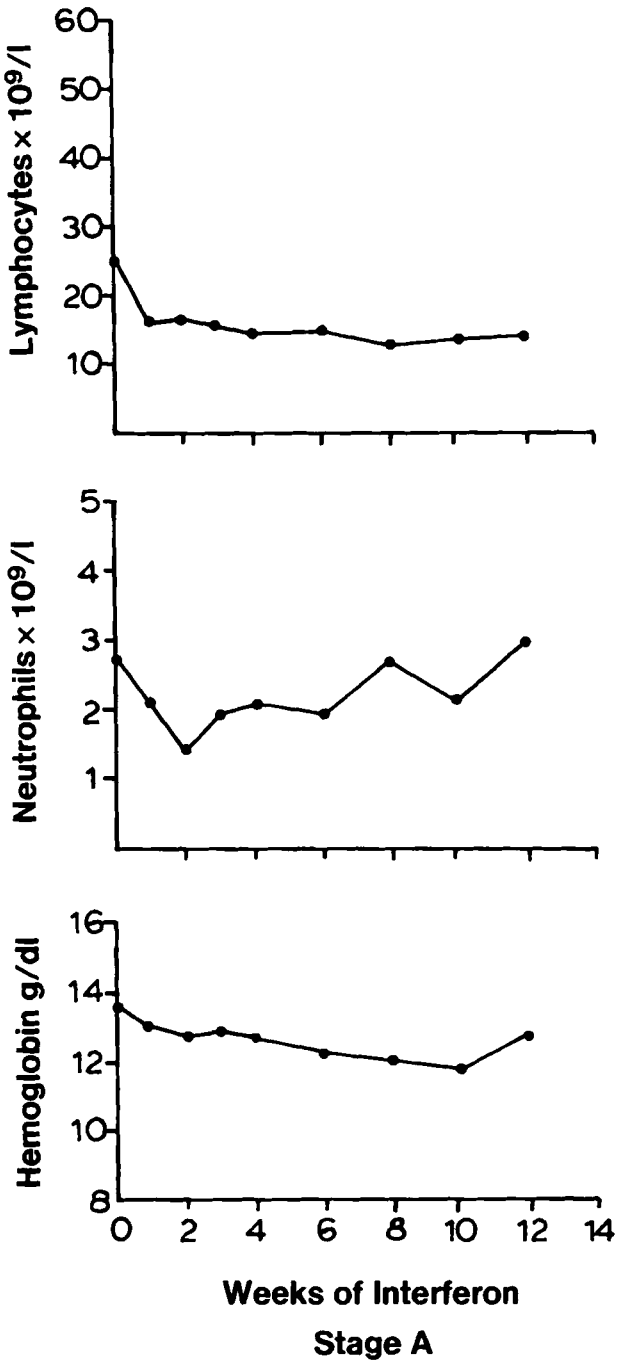

FIG. 1. Stage A patients. Changes of lymphocytes, neutrophils, and hemoglobin during a 3-month administration of alfa-2b-interferon.

related to the development of an autoimmune hemolytic mechanism while on α-IFN therapy. Therefore, in this patient α-IFN treatment had to be discontinued.

Bone Marrow Findings

In the Stage A (0) patients, the bone marrow involvement pattern and the lymphocyte percentage remained the same approximately. In the Stage B (II) patients, the bone marrow pattern also remained the same overall. However, some changes observed in this group should be mentioned. When severe anemia developed in one patient, increased numbers of islands of erythroid precursors were observed. This finding is consistent with the autoimmune mechanism of anemia. In the patient with complete disappearance of all palpable disease (upstaged), the percentage of bone marrow lymphocyteswas reduced by 50%. This finding is consistent with the reduction of blood lymphocytes by the same percentage. In the patient with no observable clinical or hematologic response to α-IFN, the almost 100% diffuse bone marrow lymphocytes were reduced by 50%. In the remaining Stage B patient, the bone marrow remained unchanged after α-IFN therapy.

TABLE 2. Objective Response

Stage	No. of patients	Response				
		CR*	PHR	MR	Stable	Progression
A	6	0	4	0	2	0
B	4	1	0	1	1	1†

CR: complete response; PHR: partial hematologic response; MR: minor response.
*: as defined by physical examination; †: due to the development of autoimmune hemolysis.

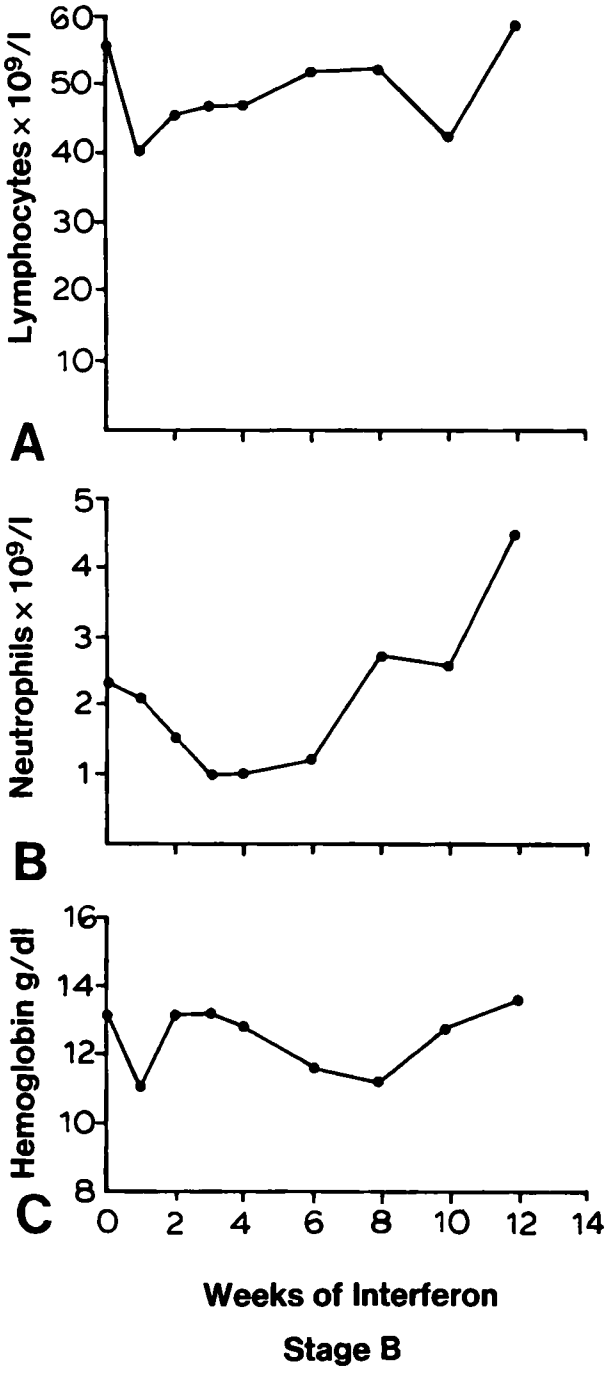

FIG. 2. Stage B patients. Changes of lymphocytes, neutrophils, and hemoglobin during a 3-month administration of alfa-2b-interferon.

Alpha-Interferon Toxicity

Alpha-interferon toxicity was well tolerated by most patients. A flu-like syndrome was observed in five and appetite loss in two. As mentioned previously, therapy had to be discontinued in one patient at 8 weeks because of severe anemia due apparently to an autoimmune hemolysis while on α-IFN.

Overall Response

Of the six Stage A patients (Rai 0), partial hematologic response (PHR) was observed in four with a 50% reduction of the blood lymphocytes (Table 2; Fig 1). It should be mentioned that all Stage A patients did not have palpable disease and their bone marrow remained unchanged at the completion of 3 months of α-IFN therapy. Of the four Stage B patients (Rai II), complete response was observed in one and minor response (20% reduction of palpable disease, 50% reduction of bone marrow lymphocytes in biopsy sections, but no reduction of blood lymphocytes) in one (Table 2). Therefore, in this series of untreated B-CLL patients, 50% response rate overall was observed with one complete responder (10%). In the responding patients, the reduction of blood lymphocytes started the first week of therapy.

Discussion

The α-IFN response rate of B-CLL patients is unknown. However, some α-IFN activity in CLL has been reported.[10,13,14-17] In a recent review by Roth and Foon,[14] an 18% response rate among 67 patients with CLL was observed. However, it should be emphasized that in previous studies most patients had advanced disease, previous therapy, and administration of higher doses of α-IFN. O'Connel *et al.* reported recently a partial responder among four untreated CLL patients.[13]

In our study, the effectiveness of α-IFN in early B-CLL patients was observed in 50% of them. Our results were achieved using a very low α-IFN dose, compared with the doses of other investigators.[13,14] We adopted the three times a week administration schedule because previous studies in hairy cell leukemia have shown significant activity with excellent results using a similar administration strategy.[3] The antileukemic activity observed in our B-CLL patients with a low-dose α-IFN program further supports the assumption that biological response modifiers do not need to be administered at the maximal tolerated dose level, because improved results may be seen at less toxic doses.[13] In addition to the observed antileukemic activity, α-IFN was well tolerated by our patients with fewer side effects when compared with higher doses.[13,14] This factor is of significance when dealing with elderly patients (mean, 60 years of age) which may not necessarily need to be treated. The 3-month treatment period also was selected based on our previous experience with hairy cell leukemia.[3-6] Of particular interest is the fact that during the first week of therapy and while all our patients were receiving 1.5 MU of α-IFN, a significant response was observed (Figs. 1 and 2). The mechanism of this rapid response is not understood clearly. At the completion of 3 months, α-IFN therapy was continued in the responding patients at the same dose level.

Our results on the effectiveness of the relatively low dose of α-IFN used and the rapid response in 50% of our paitents are provocative. Because we observed no major toxicity with our treatment schedule, we believe that further studies of the early stages of B-CLL in a randomized clinical trial comparing 1.5 MU with 3.0 MU of α-IFN three times a week are justified. It remains to be seen, at least in our patients, whether the response achieved already could be sustained or improved with the continuation of therapy. Also, the best dose of α-IFN and its length of administration over time need to be determined. It may be proven that α-IFN can be used in combination with some of the chemotherapeutic agents to improve the life quality and survival of B-CLL patients.

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