# Recombinant $\alpha_2$-Interferon in the Treatment of B Chronic Lymphocytic Leukemia in Early Stages

By Ciril Rozman, Emilio Montserrat, Nuria Viñolas, Alvaro Urbano-Ispizua, José M. Ribera, Teresa Gallart, and Chris Compernolle

**Ten previously untreated patients with early B cell chronic lymphocytic leukemia (B-CLL) (seven in Rai's stage 0, three in stage I) were given recombinant $\alpha_2$-interferon ($\alpha_2$IF) ($2 \times 10^6$ U/m$^2$ intramuscularly three times a week for a minimum of 14 weeks) to assess its effectiveness. All patients were evaluable for response to therapy and toxicity. No complete response was achieved. In all cases a definite, although transient reduction in the absolute number of peripheral blood lymphocytes was observed. In eight patients an increase in the absolute number of granulocytes was detected. None of the patients experienced severe hematologic toxicity. Fatigue, malaise, and fever were the more common side effects, but all patients were able to finish their treatment as planned. The results of this pilot study suggest that low doses of recombinant $\alpha_2$-IF have some activity in early and previously untreated B-CLL and that further studies of IF effectiveness in B-CLL seem warranted.**



INTERFERONS are a group of naturally occurring substances that are being actively investigated in the treatment of different hematologic neoplasms. $\alpha_2$-Interferon ($\alpha_2$IF) has proved to be particularly useful in therapy for hairy cell leukemia[1-3] and has shown promising results in low-grade malignant lymphomas,[4] cutaneous T cell lymphomas,[5] multiple myeloma,[6] and chronic granulocytic leukemia.[7] In chronic lymphocytic leukemia (CLL) it is thought that $\alpha$IF does not produce significant therapeutic results.[8-12] It should be noted, however, that so far most CLL patients entering trials with $\alpha$IF had rather advanced disease and had been extensively treated with chemotherapy before receiving $\alpha$IF. In this setting it is not surprising that $\alpha$IF had failed to show definite activity. We report herein the results of therapy with $\alpha$IF on previously untreated patients with CLL in early clinical stages.

## MATERIALS AND METHODS

Ten previously untreated patients with B cell CLL (B-CLL) (four males, six females; median age, 55 years; range, 42 to 78) in early clinical stages (seven in Rai's stage 0, three in stage I) were included in this study after informed consent. The B-CLL diagnosis was performed according to standard clinical, cytological, and immunologic parameters. Human recombinant $\alpha$IF (specific activity, $3.2 \times 10^8$ U/mg protein, 98% pure), provided by Boehringer-Ingelheim, SA, Barcelona, Spain, was administered at a dose of 2 MU/m$^2$ by the intramuscular route three times each week for a minimum of 14 weeks. Four patients were treated for 22, 21, 18, and 17 weeks, respectively. All remaining patients were treated for 14 weeks. No escalation of the dose was carried out during therapy. Before treatment all patients underwent a complete physical examination, radiographic studies, abdominal computed tomography, ECG, and analytical determinations including hemoglobin, WBC and platelet counts; serum immunoglobulin (IgG, IgA, IgM) levels; SGOT, SGPT, bilirrubin, glucose, BUN, and hepatitis B surface antigen. The B-CLL phenotype was studied by means of SmIg, $\kappa$ and $\lambda$ light chains, mouse rosettes and the following monoclonal antibodies: Chris-1 (CD5), Edu-1 (HLA-DR), B-1 (CD20), and BC-2 (CD24). T lymphocytes were studied by means of OKT3 (CD3), OKT4 (CD4), and OKT8 (CD8). In addition, Leu 7 and Leu 11 were used to study natural killer (NK) cells. Before, during, and after treatment anti-IF antibodies were routinely screened by enzyme-linked immunosorbent assay (ELISA) and, occasionally, by measuring the cytopathic effect. After starting therapy all patients were seen once each week. Criteria for response were as follows: complete remission (CR), total disappearance of signs and symptoms related to the disease, normalization of peripheral blood counts and impossibility to demonstrate the persistence of the B-CLL lymphocyte abnormal clone as defined by immune markers; partial response (PR), any type of improvement in basal clinical and/or hematologic data; failure, persistence of clinical or hematologic data with or without progression of the disease. No repeated bone marrow studies were planned except in the case in which a complete clinical remission might be observed. The paired $t$ test was used to compare pretreatment and postreatment values. To avoid the influence of extreme values, the logarithmic transformation of lymphocyte counts was done before performing the $t$ test.

## RESULTS

*Objective response.* Table 1 gives details concerning the age, sex, clinical stage, and hematologic response of patients included in this study. In all cases a definite decrease in the number of leukocytes and absolute peripheral blood lymphocyte count was observed. Lymphocyte counts declined from a median of $18 \times 10^9$/L (range, 10 to $176 \times 10^9$/L) to a median of 9 (range, 4 to $50 \times 10^9$/L) during therapy ($P < .01$). The nadir of lymphocyte counts was observed after 4 to 12 weeks of therapy (median, 8 weeks). Figure 1 depicts lymphocyte decreases during $\alpha$IF administration. Once the nadir of lymphocyte counts was achieved, no further decrease was observed in spite of continuing therapy, this fact being apparent in both patients treated for 14 weeks and those receiving $\alpha$IF for longer periods (22, 21, 18, and 17 weeks). As far as the duration of the response is concerned, at

*From the Postgraduate School of Hematology "Farreras Valentí" and Service of Immunology, Hospital Clínic i Provincial, University of Barcelona, and Boehringer Ingelheim, SA, Spain.*

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*Address reprint requests to Professor Ciril Rozman, MD, Postgraduate School of Hematology "Farreras Valentí," Hospital Clínic i Provincial, Villarroel 170, 08036 Barcelona, Spain.*

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**Table 1. Patient Characteristics**

| Patient/Age/Sex/ Clinical Stage | Treatment Duration (wk) | Before Treatment | | | | During Treatment | | | | After Treatment | | | | Follow-up* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hb (g/dL) | Lymphocytes (×10⁹/L) | Granulocytes (×10⁹/L) | Platelets (×10⁹/L) | Hb (g/dL) | Lymphocytes (×10⁹/L) | Granulocytes (×10⁹/L) | Platelets (×10⁹/L) | Hb (g/dL) | Lymphocytes (×10⁹/L) | Granulocytes (×10⁹/L) | Platelets (×10⁹/L) | |
| 1/50/F/O | 22 | 13.9 | 40 | 3 | 162 | 11.4 | 9.7 | 7.1 | 188 | 13.4 | 25.5 | 3 | 107 | 15 |
| 2/46/M/O | 21 | 15.7 | 10 | 2.7 | 219 | 15 | 4.5 | 4.1 | 130 | 15.7 | 11.4 | 2.8 | 219 | 12 |
| 3/59/F/I | 18 | 12.6 | 18 | 1.4 | 200 | 10.9 | 9.7 | 2.5 | 135 | 11 | 43 | 2.8 | 103 | 6 |
| 4/67/M/O | 17 | 15.8 | 18 | 6.1 | 233 | 14.6 | 6.1 | 10 | 151 | 13.9 | 18.4 | 5.5 | 262 | 16 |
| 5/78/F/O | 14 | 13.6 | 29 | 5.5 | 115 | 10.1 | 13.5 | 12.6 | 272 | 13 | 57.8 | 10 | 171 | 6 |
| 6/67/F/O | 14 | 13.2 | 17.5 | 4.2 | 140 | 13.1 | 11.5 | 6 | 164 | 14 | 25 | 5 | 200 | 8 |
| 7/68/F/O | 14 | 13.4 | 11.5 | 5 | 179 | 11.8 | 5 | 3.3 | 195 | 14 | 17.7 | 6.9 | 250 | 5 |
| 8/52/M/I | 14 | 13.3 | 176 | 5.7 | 137 | 11.3 | 50 | 6 | 126 | 12 | 214 | 6.6 | 148 | 13 |
| 9/74/F/O | 14 | 12.2 | 14 | 1.5 | 149 | 11.5 | 7.8 | 3.2 | 150 | 11.7 | 9.2 | 2.9 | 130 | 3 |
| 10/42/M/I | 14 | 15.1 | 15.1 | 4.1 | 122 | 14.9 | 10 | 3.1 | 104 | 14.8 | 21.7 | 0.6 | 125 | 6 |

*Months after therapy.

the time of this report the lymphocyte count of eight patients had reached pretreatment values after a period of 2 to 6 months (median, 5) after stopping therapy. The two remaining patients maintain lymphocyte counts below initial pretreatment values after 15 and 3 months, respectively. Eight patients showed an increase in the absolute number of peripheral blood granulocytes ($P < .05$) simultaneously with the decrease in lymphocyte counts. None of three patients with lymphadenopathy experienced a reduction in its size. No case of disease progression under treatment has been observed. One patient progressed from stage 0 to stage III 7 months after stopping therapy and another one from stage 0 to stage II 13 months after discontinuing therapy. With a median follow-up after therapy of 7 months, the remaining nine patients have not experienced clinical stage progression. No changes were observed in the B-CLL phenotype after therapy. The OKT4/OKT8 ratio was ≤1.5 in six patients at diagnosis. In two of them this ratio normalized after therapy. In six of eight patients in whom NK markers (Leu 7, Leu 11) could be tested, an increase in the percentage of Leu 7– and Leu 11–positive cells was observed after therapy. None of the patients developed αIF antibodies.

*Toxicity.* There were no cases of severe hematologic toxicity, infections, or bleeding. In all patients a slight, although significant ($P < .01$) decrease in the hemoglobin level that ranged from 0.1 to 3.5 g/dL was observed after therapy. The hemoglobin level returned to normal shortly after treatment was stopped. Platelet levels remained above 100 × 10⁹/L in all patients. All patients experienced the characteristic "flu-like" syndrome associated with IF therapy. Most patients, however, tolerated therapy very well and were fully active during the treatment period.

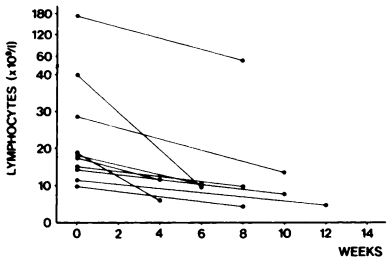


**Fig 1. Decrease in lymphocyte counts in patients with CLL treated with αIF. Pretreatment and nadir values are shown.**

## DISCUSSION

In spite of some promising early results,[13] it is generally considered that treatment of CLL with αIF offers rather disappointing results.[8-12,14] Most of the studies in which IF has been evaluated in CLL, however, have been done in previously treated patients with advanced disease. In this setting, it is not surprising that these studies have shown poor results. Foon et al[8] treated 18 patients with advanced CLL by administering recombinant αIF intramuscularly three times each week at doses of either 50 × 10⁶ U/m² (12 patients) or 5 × 10⁶ U/m² (6 patients). Most of the patients experienced toxicity requiring a reduction in the dose of αIF. Of the 12 patients in whom a response to a higher dose was evaluable, only two had transient PRs. None of the patients treated at a lower dose had a response. These authors cautioned about the fact that 11 of 18 patients showed disease progression while receiving αIF. In this context, it is noteworthy that none of our patients had disease progression while receiving treatment. As noted by Foon et al,[8] in patients with advanced and refractory disease it is difficult to ascertain whether disease progression is due to the natural history of the disease or it is triggered by treatment. Our results seem to make clear that IF therapy, at least as given in this study, is not associated with disease progression.

IF has been rarely used as first-line therapy in patients with CLL. Schulof et al[11] treated four previously untreated patients (one stage 0, two stage I, one stage II) with 20 × 10⁶ U/m² recombinant αIF intramuscularly three times each week for 8 weeks. Two patients (one stage 0, one stage I) responded with transient decreases in absolute lymphocyte counts. The Eastern Cooperative Oncology Group[9] treated four patients with CLL who had not received previous therapy with recombinant αIF (12 × 10⁶ U/m² intramuscularly three times weekly for 8 weeks) and achieved a PR in one of them. Talpaz et al[10] treated ten patients (six without previous therapy) in stages 0, I, and III with 3 to 9 × 10⁶ units of αIF administered intramuscularly daily. Three patients with disease stages 0, I, and III (and prolymphocytic leukemia) responded with partial remissions lasting from 10 to 24 months. Four additional patients had minor responses. Overall, five of nine responders did not receive any treatment before starting IF therapy.

This pilot study had two major objectives: (*a*) to test the antileukemic activity of αIF in patients with previously untreated CLL and in early clinical stages and (*b*) to analyze

the toxicity of αIF administered at a rather low dose in this particular group of patients.

We decided to treat previously untreated patients with CLL in early clinical stages for several reasons: (*a*) although early CLL has an excellent prognosis, patients eventually progress and die; (*b*) in early clinical stages the tumoral burden is low, and consequently, a higher number of responses to any form of therapy could be expected; and (*c*) previously treated patients respond less well to any form of treatment than patients previously untreated. On the other hand, we chose to use αIF at a rather low dose, which has proved to be useful in hairy cell leukemia. Higher doses are more toxic and are not accompanied by a greater number of responses. In fact, all our patients tolerated treatment remarkably well without needing dose reductions.

Although the responses observed in our patients have been minor and transient, the reduction observed in all cases in the absolute lymphocyte counts as well as the increase in granulocyte counts in eight of ten patients is noteworthy. Although our study was not specifically envisaged to ascertain the mechanisms of actions of αIF in CLL, it should be mentioned that this is by no means a settled issue. In vitro IF produces proliferation and differentiation of malignant B-CLL lymphocytes.[15] It has also been suggested that IF could act indirectly by stimulating the immune system or directly by inhibiting cell proliferation.[16,17] The increase observed in NK cells in four of six cases in which NK markers were evaluable might suggest, among other putative mechanisms, an increased NK activity. In fact, an increase in NK activity has been observed in patients with hairy cell leukemia who respond to αIF.[4] We have not observed the changes (decline in the proportion of B cells bearing surface immunoglobulin without a change in the number of B cells, decrease in the proportion of B cells bearing T1 antigen) recently reported by Talpaz et al.[10]

In summary, in spite of the fact that no cases of CR have been observed, a definite response (eg, (*a*) decrease in absolute peripheral blood lymphocyte counts, (*b*) trend for a normalization of differential leukocyte counts in all cases, and (*c*) significant increase in the absolute number of granulocytes in eight cases) has been observed in previously untreated CLL patients in early stages who are receiving αIF. Treatment toxicity has been negligible, and all patients could be treated according to the planned schedule without complications or the need for an αIF dose reduction. These results suggest that further studies of αIF as therapy for patients with CLL and a low tumoral burden are warranted. In future trials the optimal dose and treatment schedule of αIF in CLL should be elucidated. Moreover, αIF could be used in combination with alkylating agents or be given to those patients who achieve a good response and have a significant reduction in the tumoral burden after conventional alkylating agents therapy. This latter approach would be particularly interesting because in animal models it has been demonstrated that interferons act best when the tumor load is low.[18]

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