Recombinant α2-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 α2-interferon (α2IF) (2 × 10^6 U/m² 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 complete remission 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 α2IF 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. α2-Interferon (α2IF) has proved to be particularly useful in therapy for hairy cell leukemia and has shown promising results in low-grade malignant lymphomas, cutaneous T cell lymphomas, multiple myeloma, and chronic granulocytic leukemia. In chronic lymphocytic leukemia (CLL) it is thought that αIF does not produce significant therapeutic results. It should be noted, however, that so far most CLL patients entering trials with αIF had rather advanced disease and had been extensively treated with chemotherapy before receiving αIF. In this setting it is not surprising that αIF had failed to show definite activity. We report herein the results of therapy with αIF 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 αIF (specific activity, 3.2 × 10^6 U/mg protein, 98% pure) was provided by Boehringer-Ingelheim, SA, Barcelona, Spain. In addition, Leu 7 and Leu II (CD7). 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. B-CLL phenotype was studied by means of SmIg, s and λ 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). The B-CLL phenotype was studied by means of SmIg, s and λ 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. B-CLL phenotype was studied by means of SmIg, s and λ 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).

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 × 10^9/L (range, 10 to 176 × 10^9/L) to a median of 9 (range, 4 to 50 × 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 αIF administration. Once the nadir of lymphocyte counts was achieved, no further decreases were observed in spite of continuing therapy, this fact being apparent in both patients treated for 14 weeks and those receiving αIF for longer periods (22, 21, 18, and 17 weeks). As far as the duration of the response is concerned, at
Although significant (P < 0.05) 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 < 0.01) 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 × 10^9/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.

In spite of some promising early results, it is generally considered that treatment of CLL with αIF offers rather disappointing results. 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 treated 18 patients with advanced CLL by administering recombinant αIF intramuscularly three times each week at doses of either 50 × 10^6 U/m^2 (12 patients) or 5 × 10^6 U/m^2 (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., 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.

αIF has been rarely used as first-line therapy in patients with CLL. Schulof et al treated four previously untreated patients (one stage 0, two stage I, one stage II) with 20 × 10^6 U/m^2 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 treated four patients with CLL who had not received previous therapy with recombinant αIF (12 × 10^6 U/m^2) intramuscularly three times weekly for 8 weeks and achieved a PR in one of them. Talpaz et al treated ten patients (six without previous therapy) in stages 0, I, and III with 3 to 9 × 10^6 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

**Table 1. Patient Characteristics**

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* Months after therapy.

**Fig 1.** Decrease in lymphocyte counts in patients with CLL treated with αIF. Pretreatment and nadir values are shown.
the toxicity of aIF 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 aIF 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 early (a) increased proliferation might suggest, among other putative mechanisms, an indirect by stimulating the immune system or directly by inhibiting cell proliferation.5 It has also been suggested that IF could act by stimulating the immune system or directly by inhibiting cell proliferation.6,7 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 aIF.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.8

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 aIF. Treatment toxicity has been negligible, and all patients could be treated according to the planned schedule without complications or the need for an aIF dose reduction. These results suggest that further studies of aIF as therapy for patients with CLL and a low tumoral burden are warranted. In future trials the optimal dose and treatment schedule of aIF in CLL should be elucidated. Moreover, aIF 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.9

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