Treatment of Hairy Cell Leukemia With Recombinant α-Interferon

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Thirty patients with hairy cell leukemia were treated with recombinant interferon α-A (rIFNaA; Roferon-A); seven were previously untreated. Nine complete and 17 partial remissions were documented by bone marrow core biopsies. All patients’ peripheral blood hematologic indexes either improved or normalized. Twelve of 13 patients with retroperitoneal or mediastinal adenopathy obtained remissions of tumor masses. All seven patients with splenomegaly showed prompt reduction in the size of the spleen to normal size. The incidence of complete remissions was significantly higher (P = .02) in previously untreated patients (5 of 7) than in those in whom splenectomy had been performed (4 of 23), a result presumed to be related to the pretreatment tumor burden. rIFNaA was well tolerated: mild fatigue was the most frequent complaint. In most patients, tumor remissions resulted in an improved quality of life: they eliminated the need for transfusing blood products and reduced the incidence of infections, and immune deficits were apparently restored in some of the patients. We conclude that rIFNaA is an effective therapy for all stages of hairy cell leukemia including previously untreated or newly diagnosed patients.

We have previously shown that partially purified α-interferon (IFNa) consistently induces bone marrow remissions in patients with hairy cell leukemia (HCL), resulting in improved or normalized peripheral blood indexes. Subsequent experience with IFNa has shown that patients with all clinical stages of HCL, including those with profound pancytopenia, active life-threatening infections, or large retroperitoneal lymph node involvement, responded well to daily administration of this agent. The objective of the present study was to investigate whether a highly purified cloned IFNa had similar activity. Recombinant IFNa (rIFNaA) has been shown to induce remissions in other B-cell malignancies, including low-grade lymphomas and multiple myeloma.

We present data indicating that IFNa is indeed primarily, if not solely, responsible for the antitumor activity observed in HCL. Furthermore, rIFNaA induced tumor remissions in patients who had not had splenectomy, perhaps indicating that this surgical procedure may not be necessary for these patients.

MATERIALS AND METHODS

The diagnosis of HCL was made on the basis of clinical characteristics and laboratory demonstration of typical hairy cells in peripheral blood, bone marrow, or tissue specimens; included a positive tartrate-resistant acid phosphatase stain. The effects of treatment were assessed by standard hematologic methods. Bone marrow was obtained every 4 to 12 weeks from multiple sites in the iliac crests and was evaluated under light microscopy and by flow cytometry, using monoclonal antibodies to leukocyte surface antigens. A complete remission (CR) was defined as an absence of hairy cells from peripheral blood, bone marrow aspirate, and biopsy specimens on at least two consecutive occasions and restoration of the hemoglobin level to ≥12 g/dL, the absolute granulocyte count to ≥1,500/μL, and the platelet count to ≥100,000/μL. A partial remission (PR) was defined as a decrease of ≥50% in the bone marrow leukemic infiltrate (percentage of cellularity times percentage of hairy cells) from pretreatment values and restoration of the peripheral blood values as indicated above. In patients who initially had splenomegaly or in whom computerized tomography (CT) of the abdomen revealed retroperitoneal adenopathy, remission criteria also included: CR, spleen size reduced to normal or disappearance of nodal masses; and PR, ≥50% reduction in size of the spleen or nodal masses. Minor responses were defined as restoration of one or more abnormal hematologic indexes or as bone marrow remission, but without recovery of all hematologic indexes.

rIFNaA (Roferon-A) was provided by Hoffmann LaRoche (Nutley, NJ). The purified protein was homogenous by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and had a specific activity of 2 to 4 × 10^9 U/mg of protein. rIFNaA was administered either intramuscular or subcutaneous injection daily for the first 4 to 6 months and three times a week until completion of 1 year of treatment. The first 12 patients received an initial dose of 10 to 12 × 10^6 U which was subsequently reduced to 3 × 10^6 U due to the more pronounced side effects of the higher induction dose. The remaining patients received 3 × 10^6 U throughout the study. All patients signed informed consents in accordance with institutional policies.

Surface markers. Bone marrow and peripheral blood mononuclear cells were fractionated according to cell volume and granularity with an Ortho Spectra III cell analyzer. Cell-surface markers were determined using the fluorescein-labeled monoclonal antibodies OKT3, OKT4, OKT11, OKT8, OKM-1, and OKla (Ortho Diagnostic Systems, Raritan, NJ) and the B-1 antigen (Coulter Electronics, Hialeah, Fla). Surface immunoglobulins were determined after incubation with (Fab')2 fragments of polyclonal antibodies specific for heavy or light immunoglobulin chains of goat anti-human IgM and IgD (Kallested, Austin, Tex). Anti-T-cell activation antigen (anti-Tac) antibodies were a gift from Dr Thomas Waldmann (National Cancer Institute, Bethesda, Md).

Delayed hypersensitivity tests. Delayed hypersensitivity to recall antigens was determined by using the multitest battery (Merieux Institute, Miami, Fla). This battery consists of tetanus (5.5 × 10^6 tetanus U/mL), Streptococcus (2 × 10^6 Streptococcus U/mL), tuberculin (3 × 10 US tuberculin U/mL), Candida (2 × 10 Candida U/mL), trichophytn (150 trichophytn U/mL), Proteus (150 Proteus U/mL), and a glycerol control. Simultaneous delayed hypersensitivity was determined using the Staphylococcus aureus Cowper strain (American Type Culture Collection, Rockville, Md).

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application of the antigens and control was accomplished by a single-stroke inoculation using the Multitest-CMI device. The scoring and interpretation of the responses have been described previously. Anergy was defined as reactivity to 0 or 1 antigen(s), hypoergy as reactivity against 2 or 3 antigens, and adequate reactivity as a positive reaction to >3 of 7 antigens.

Statistics. Chi-square and Mann-Whitney tests were used for analysis. All P values <.05 were considered statistically significant.

RESULTS

Twenty-five men and five women, aged 25 to 59 years (median: 48 years) were treated beginning in January 1984. Twenty-three patients had undergone splenectomy, and 11 of these (48%) had subsequently received chemotherapy or hormonal therapy prior to treatment with rIFNaA. In all 23 patients, either prior treatment had failed or there was evidence of progressive disease at the time the patient was started on treatment. The remaining seven patients had not received any prior treatment and had splenomegaly and various degrees of pancytopenia initially. Twenty of the 30 patients (67%) had required transfusions of RBCs and 23 (77%) had a history of infections or fever of undetermined origin. The phenotype of the leukemic cells in the bone marrow was obtained in 21 patients. Hairy cells were larger and more granular than normal marrow mononuclear cells and exhibited surface immunoglobulins, Ia antigen, or B1 antigen, indicating their B cell origin. Hairy cells expressed the Tac antigen as previously reported in all patients, whereas the MO1 antigen was present in only 65% of them.

Nine complete and 17 partial remissions were observed (Table 1). The remaining four patients had shown hematologic improvement but have not achieved a remission status, either because of persistent granulocytopenia (two patients), thrombocytopenia (1 patient), or a lack of bone marrow remission (2 patients).

Figures 1 through 3 depict the pretreatment and posttreatment values over time for platelets, leukocytes, and hemoglobin, respectively. All patients, regardless of their remission status, benefited from treatment, as evidenced by the progressive rise in these hematologic indexes. The platelet counts of 21 of the 22 patients with thrombocytopenia normalized within 4 months (Fig 1). Platelet count was usually the first blood index to improve, often within 2 to 3 weeks of initiating treatment. No adverse effects were seen in patients with normal pretreatment platelet counts. Figure 2 illustrates the decline in the leukocyte count of seven patients who had leukocytosis. Figure 2 also illustrates a rapid clearance of circulating leukemic cells in 18 of the 20 patients who had hairy cells in the peripheral blood. No patient had circulating leukemic cells beyond 6 months of therapy. Concomitantly, we observed a steady upward trend in the granulocyte counts of all patients (Fig 2), and the absolute monocyte counts increased from a pretreatment mean value of 0.02 x 10^3 monocytes/μL to 0.16, 0.18, and 0.27 x 10^3 monocytes/μL at 4, 8, and 12 months, respectively.

Figure 4 depicts the results of serial bone marrow core biopsies. rIFNaA consistently produced a steady reduction in the cellularity of the bone marrow and a decrease in the leukemic infiltrate. The time required to achieve a remission status in the bone marrow varied from 1 to 10 months (median: 3.5 months).

Thirteen previously treated patients presented with retroperitoneal adenopathy, identified by CT of the abdomen: eight of these patients had extensive nodal involvement, including four who also had mediastinal adenopathy. Size of the tumor masses decreased 50% to 100% within 2 to 6 months of therapy in all but one patient.

Remissions of previously untreated patients. Five of the 7 (71%) previously untreated patients achieved a CR in contrast to 4 of 23 (17%) previously treated (P = .02). A comparison of these two groups showed that the median time between diagnosis and onset of treatment with rIFNaA was 15 months (range 2 to 21 months) in the untreated patients and 23 months (range 9 to 121 months) in those previously treated (P = .01). The leukemic infiltrate was also significantly different (P = .01) among previously untreated patients (median: 10%; range 5% to 85%) and those previously treated (median: 55%; range 15% to 86%). All seven previously untreated patients had splenomegaly, and two also had hepatomegaly. The spleen and liver were clinically undetectable within the first 3 months of therapy. The median platelet count in untreated patients at 12 months from the onset of treatment (154,000/μL) was however significantly lower (P = .005) than the platelet counts of splenectomized patients (266,000/μL). No differences in the posttreatment hemoglobin values or granulocyte counts were found between these two groups of patients.

Duration of remissions. All patients completed 12 months of treatment, and in 25 rIFNaA was discontinued.

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Patients Responding</th>
<th>Duration of Remission (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>9/30</td>
<td>10+</td>
</tr>
<tr>
<td>Partial remission</td>
<td>17/57</td>
<td>10+</td>
</tr>
<tr>
<td>Minor responses</td>
<td>4/13</td>
<td>—</td>
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rIFNaA, recombinant interferon αA.
All patients are alive with a median follow-up >20 months (range 15 to 26 months). In eight of the 25 patients (33%) in whom treatment was discontinued, a progressive decline in the granulocyte count, increase in the bone marrow index, and reappearance of circulating hairy cells (two patients), were observed (Fig 2). This clinical relapse occurred within 3 to 10 months (median 6 months) after cessation of treatment in six patients who attained PRs, and one patient each with a CR and minor response. Reinitiation of treatment resulted in reinduction of remission in five of the eight patients who have completed 3 months of administration. Furthermore, in 11 other patients (42%) an increase in the bone marrow leukemic index has become evident, but has not warranted reinitiation of treatment because all hematologic indexes remain stable. In six patients (three CRs and three PRs) remission is sustained at 6 to 22+ months (median 12+ months) after discontinuation of rIFNαA.

**Toxicity.** In general, tolerance and compliance were excellent. Initial side effects consisting of transient fever and mild fatigue occurred in most patients. Symptoms were more intense in the first 12 patients who received the higher dose and therefore had the dose reduced. As treatment continued and hematologic indexes improved, most patients reported no or only mild adverse effects, mainly consisting of fatigue. However, all patients were able to continue or resume normal daily life activities, including strenuous exercise for some young patients.

Ten patients reported a decrease in libido during treatment. Three patients developed arthritis and/or vasculitis with mild inflammation of small joints of the hands while...
receiving rIFNaA. These symptoms resolved spontaneously in two patients and required administration of corticosteroids in one. Screening for collagen disease-related antibodies or antigens was negative. A causal relationship with rIFNaA therapy is considered remote, because features of autoimmune antigens was negative. A causal relationship with nIFNaA in two patients and required administration of corticosteroids to receiving nIFNaA. These symptoms resolved spontaneously.

Infections. Twenty-three patients had a history of previous infections or episodes of fever of unknown origin prior to treatment, ranging from one to four episodes (median: 2.5), but none of the patients had active clinical infection at the onset of treatment. Two of 12 (17%) patients who received the higher dose and 2 of 18 (11%) who received 3 x 10^6 U had major infections in the first 8 weeks of treatment (cryptococcal pneumonia, meningococcemia, gram-negative bacilli pneumonia and soft tissue abscess, and S viridans endocarditis). In four additional patients from each group, the initial treatment course was complicated by minor upper respiratory, soft-tissue, or skin infections, or by fever of undetermined origin that merited antibiotic prescription. Among these, in three patients in the high-dose and four in the low-dose groups, circulating granulocytes decreased within the first 2 weeks of treatment. This decrease did not correlate with the onset of infection. No major or minor infections have been observed beyond the first 8 weeks of rIFNaA therapy in any of the patients.

Immunologic tests. Twenty-one patients underwent delayed hypersensitivity skin testing before and after 12 months of treatment. The number of positive reactions increased in 6 of 12 anergic and 3 of 5 hyperergic patients (Fig 5). In addition, 11 of 26 patients tested showed an inverted T helper/suppressor (T/S) ratio prior to treatment. In 5 of the 11 patients, a normal T/S ratio was restored at 6 or 12 months after beginning treatment with rIFNaA (data not shown).

DISCUSSION

This study confirms the efficacy of IFNa in treating hairy cell leukemia. Furthermore, it proves that the IFN molecule itself is almost certainly responsible for the antitumor effects originally described with a partially purified preparation of IFNa.3 While we were preparing this report, other groups of investigators reported the activity of rIFNaA and lymphoblastoid IFN in HCL.11-13 The scantiness of complete remissions in some of these studies11-13 may be explained by their different treatment-induction schedule (three times a week), their shorter follow-up periods, or the more advanced stages of disease of their patients (none of these studies included untreated patients).11-13).

An important contribution of the current work is the result observed in previously untreated patients with splenomegaly. rIFNaA was effective in inducing tumor remission and reducing the size of the spleen, producing a significantly higher incidence of complete remissions than was achieved in previously splenectomized patients. The most likely explanation for this finding is the earlier stage of the disease of the untreated patients, as shown by a shorter interval between diagnosis and initiation of treatment and a lower level of bone marrow leukemic infiltrate. Other studies that have included untreated patients also report a larger number of complete remissions9,10 similar to the results of this study.

The significant difference between the median platelet count after 12 months of treatment of previously untreated patients and of those who had been splenectomized suggests that the spleen may continue to consume platelets. Conceivably, some of these patients may benefit further from splenectomy. If so, the surgical risk should be decreased by their improved peripheral blood indexes resulting from rIFNaA therapy.

Discontinuation of rIFNaA after 12 months of administration resulted in clinical relapse of the disease in 33% of the patients within 3 to 10 months, suggesting the need for prolonged therapy beyond 1 year in some patients. In patients treated for 2 years with partially purified IFNa, only 3 of 21 (14%) have required reinitiation of treatment at 10, 12, and 14 months after discontinuation of therapy (unpublished observations, April 1986). Because reinduction of tumor response may be accomplished with reinitiation of treatment, periodic administration of rIFNaA may prove satisfactory for some of these patients.

rIFNaA demonstrated an excellent therapeutic index. Daily doses of 3 x 10^6 U were as effective as higher doses and better tolerated. Tumor remissions have resulted in an improved quality of life for our patients, including no further need for transfusion of blood products and an apparent reduction in the incidence of infections, the major morbidity factors associated with HCL. Furthermore, our preliminary data suggest that tumor response may also improve some of the immunologic deficits present in these patients. In this regard, we have also reported on the ability of rIFNaA to improve deficient humorab immunity in responsive patients with multiple myeloma.5

Caution must be exerted during the initial 2 months of treatment because of the possibility of complicating infections. It is unclear whether the initial decrease in circulating granulocytes observed in some patients may increase the risk of infections. IFN-induced leukopenia has not been associated with a higher incidence of infections in other cancer patients.3

Other B cell malignancies, including both low-grade lym-
phomas and multiple myeloma, have been shown to be sensitive to the antitumor effects of IFNα.3-5 In contrast, advanced cases of intermediate or high-grade lymphomas or chronic lymphocytic leukemia have been resistant to IFNs.3,18-21 It is presently unknown whether such differential sensitivity may be related to the stage of differentiation or the expression of cellular receptors in the malignant cells. In this regard, the expression in hairy cells of plasma cell-associated antigens is consistent with a stage of differentiation immediately preceding that of plasma cells.22 Similarly, the expression of the Tac antigen, initially described as a marker of T lymphocytes, led Korsmeyer and collaborators8 to suggest a unique stage of differentiation of hairy cells or a particular stage of activation. The sensitivity of cutaneous T cell lymphomas to IFNα could have in common with HCL the expression of this cell surface antigen.23

We conclude that rIFNaA is an effective method of treatment for all stages of HCL. rIFNaA can be reasonably indicated as initial treatment of newly diagnosed or untreated patients whose disease is progressing, although its use prior to splenectomy should still be reserved for patients participating in controlled clinical studies or for patients with a high surgical risk.

We are presently addressing further questions regarding duration of remissions, the need for prolonged maintenance therapy, the incidence of infections, and the impact on the survival of IFNα of >80 patients with HCL being followed at our institution.

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REFERENCES

10. Westbrook LA, Golde DW: Clinical problems in hairy cell leukemia: diagnosis and management. Semin Oncol 11:514, 1984 (suppl 2)
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