Prolonged, Continuous Treatment of Hairy Cell Leukemia Patients With Recombinant Interferon-α2a

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Interferons are not curative in hairy cell leukemia (HCL), and retreatment is necessary in most patients whose therapy is stopped. In an attempt to maintain or improve responses, we administered recombinant interferon-α2a (rIFN-α2a) continuously to patients with HCL who initially responded to this therapy. Of 53 evaluable patients enrolled in this study, 32 have received rIFN-α2a continuously for a median of 5 years. Patients received 3 million units of rIFN-α2a subcutaneously (SC) daily for 6 months, followed, in responding patients, by the same dose three times weekly. Twenty-one patients (40%) discontinued IFN after a median of 29 months, seven of whom developed resistant disease in association with anti-IFN antibodies. Treatment produced high response rates: complete response plus partial response (CR + PR) = 40 of 53 (77%); CR + PR + minor response (MR) = 43 of 53 (82%), with no differences in response rates between patients with previous treatment of the patients, as well as dose, schedule, and duration of treatment.

HAIRY CELL LEUKEMIA (HCL) is a rare, chronic lymphoproliferative disorder of unknown etiology manifested by proliferation of malignant cells that tend to infiltrate the bone marrow (BM), liver, and spleen, resulting in cytopenias, splenomegaly, and an increased incidence of severe bacterial or fungal infections. In almost all cases, the malignant cell is of B-lymphocyte lineage; however, hairy cells also possess certain features of T lymphocytes and monocytes, suggesting that they may be in an unusual or abnormal stage of differentiation. Patients with HCL have been treated with splenectomy, splenic irradiation, chemotherapy, androgens, leukapheresis, transfusions of allogeneic mononuclear cells and, more recently, with interferons (IFNs), deoxycoformycin (dCF), and 2-chlorodeoxyadenosine.

Clinical trials using IFNs to treat HCL have varied with regard to the type and purity of the IFN preparation, previous treatment of the patients, as well as dose, schedule, and duration of treatment. In general, these trials have shown high overall response rates, but low complete response (CR) rates. In most trials, IFN treatment was discontinued after 1 to 2 years. After discontinuation of IFN therapy, disease progression occurs in patients regardless of their response category and most patients eventually require retreatment.

In 1984, we began a trial of recombinant IFN-α2a (rIFN-α2a) for patients with HCL to define the initial response rates and toxicity of this then-new therapy, and the preliminary results of the first 15 patients in this study have been reported previously. In time, it became clear that patients tolerated therapy well but that CRs rarely occurred. These observations and the reported high rates of disease progression after IFN treatment was discontinued prompted us to modify our protocol to provide therapy continuously for prolonged periods. We now summarize the results of long-term, continuous treatment of HCL patients with rIFN-α2a at one institution.

MATERIALS AND METHODS

Patients. All patients were treated on the same protocol at the Biological Response Modifiers Program (BRMP) of the National Cancer Institute (NCI). The protocol was approved by the Institutional Review Boards of the National Cancer Institute and the NCI-Frederick Cancer Research and Development Center. All patients voluntarily gave their written informed consent before treatment.

Fifty-six patients were enrolled in this study between April 1984 and December 1985. This analysis includes follow-up through April 30, 1990. There were 46 men and 10 women with a median age of 52 years (range 36 to 75 years). The median time from diagnosis to any treatment was 1 month (range 0 to 60 months) and to study entry was 10 months (range 2 weeks to 153 months). Thirty-two patients (57%) had previous splenectomy, 5 had previous chemotherapy, hormonal therapy, or leukapheresis, and 20 (36%) had no previous treatment. The median time from last previous treatment to study entry was 14 months (range 1 month to 108 months). Before rIFN-α2a therapy, 35 patients (63%) received blood transfusions, 4 patients (7%) received platelet transfusions, and 19 patients (34%) had infections, which required hospitalization in 47% of the cases.
Eligibility criteria. Eligibility criteria included (a) a pathologically confirmed diagnosis of HCL based on the characteristic morphologic appearance of hairy cells in the peripheral blood, BM, or tissue biopsies with positive tritrate-resistant acid phosphatase (TRAP) staining or electronmicroscopy compatible with hairy cells; (b) significant anemia (hemoglobin [Hb] < 10 g/dL or need for transfusions), thrombocytopenia (platelets < 100,000/μL), or neutropenia (granulocytes < 1,500/μL); (c) creatinine ≤ 1.8 mg/dL, bilirubin ≤ 1.4 mg/dL, calcium ≤ 12 mg/dL; (d) no antineoplastic therapy in the 4 weeks before study entry; (e) no active cardiopulmonary disease; and (f) Karnofsky performance status greater than 60%. Previous splenectomy was not required. Patients were excluded if they had severe intercurrent infection, platelet count less than 20,000/μL with clinical bleeding, previous treatment with interferon IFN-α or IFN-β, or splenectomy within 4 months of study entry unless there was evidence of progressive cytopenia. Use of aspirin and nonsteroidal antiinflammatory agents was proscribed during the study.

Initial evaluation and serial studies. Initial evaluation included a complete history and physical examination, chest radiograph, electrocardiogram, urinalysis, chemistry profile, prothrombin time, partial thromboplastin time, complete blood count with differential, platelet count, TRAP stain of peripheral blood, BM aspirate and biopsy, and liver/spleen scan in patients with hepatomegaly or splenomegaly. These studies were repeated at regular intervals and as clinically indicated. Bilateral BM aspirates and biopsies were performed at least once yearly on chronic treatment. Patients were examined monthly at the BRMP for the first 6 months and every 2 to 3 months thereafter. All BM studies were reviewed by one of the investigators (J.L.) to determine the response status.

Response criteria. The following response criteria were used: CR—absence of detectable hairy cells in peripheral blood (PB) or BM, BM granulocyte count (the sum of the percentages of myelocytes, metamyelocytes, and neutrophils) greater than 35%, complete resolution of organomegaly and adenopathy, and improvement in PB counts to Hb greater than 12 g/dL, platelet count greater than 100,000/μL and granulocytes count greater than 1,500/μL. Partial response (PR)—greater than 50% reduction of hairy cell infiltrate in the BM accompanied by improvement in PB counts as indicated above, and BM granulocyte count greater than 35%. Minor response (MR)—improvement in PB counts as compared with baseline but less than the criteria described above or a decrease in hairy cell infiltrate by less than 50%, or BM granulocytes from 25% to 35%. Stable disease was considered stabilization of baseline abnormalities of BM, PB, and physical examination. Progressive disease was considered the appearance of new, or worsening of preexistent abnormalities of PB, BM, or physical examination.

Treatment plan. Patients were treated with rIFN-α2a (Recom-A) provided by Hoffmann-La Roche (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 x 10^9 U/mg protein. Lyophilized rIFN-α2a was reconstituted with sterile water, and patients self-administered subcutaneous (SC) injections of 3 x 10^6 U rIFN-α2a daily for the first 6 months. Responding patients (criteria described above), received IFN at the same dose three times a week thereafter. Patients who did not respond to this treatment schedule received higher doses of interferon (6 to 12 million units daily). Therapy was discontinued only if the disease failed to respond or stopped responding, if intolerable side effects occurred, or if patients refused to continue. Compliance with IFN therapy was documented by vial counts performed at the study center and by medication records maintained by each patient.

Measurement of serum-soluble interleukin-2 receptor (sIL-2R) levels. sIL-2R levels were measured using the CELLMfree IL-2R test kit (T Cell Sciences, Cambridge, MA). The procedure is a sandwich enzyme immunoassay for determination of released IL-2R. The manufacturer’s directions were followed in the performance of this assay. Receptor levels in this study are expressed in units per milliliter. The mean ± SE for sIL-2R levels in our normal donor population is 320 ± 77.

Statistical methods. Several statistical techniques were used in this research. Chi-square contingency table analyses were used in comparisons of splenectomy and nonsplenectomy patients. Exploratory data analyses, regression analyses, and analyses of covariance (ANCOVA) were performed using Hb, absolute granulocyte count, platelet count, and soluble IL-2R levels as variables. Survival analysis was performed by the Kaplan-Meier (product limit) method.

RESULTS
Of the 56 patients entered in the protocol, 53 are evaluable for response. Two patients died early in their treatment, one of a Rhizopus brain abscess, another of a primary CNS malignancy. One patient with normal PB counts was enrolled because of diffuse bony pain and hairy cell infiltration of the bone and is not evaluable for hematologic response. The best response to treatment of all 53 evaluable patients is shown in Table 1. Overall, 76% of patients have had either a PR or a CR and 82% of patients had either CR, PR, or MR. One patient who had stable disease at 3 months elected to be treated with dCF and subsequently responded. The patient who never responded to rIFN-α2a and subsequently failed to respond to splenectomy, alkylating agents, dCF and IFN-γ probably had a variant form of HCL and is described elsewhere.

A chi-square test for homogeneity demonstrated that the response to treatment (CR + PR + MR) was not significantly different in patients with previous splenectomy (77%) and those without previous splenectomy (87%) (chi-square = 5.07, 2 df; P = 0.0792). Of the three patients with MR, two met the marrow response criteria for a PR but had persisting absolute granulocyte counts less than

| Table 1. Best Response to Treatment With rIFN-α2a |
|------------------------|------------------------|------------------------|
| Response | Overall, n (%) | Splenectomy, n (%) | Nonsplenectomy, n (%) |
| CR | 1 (1.9) | 0 (0) | 1 (4.3) |
| PR | 39 (73.6) | 23 (76.7) | 16 (69.6) |
| MR | 3 (5.7) | 0 (0) | 3 (13.8) |
| SD | 9 (12.0) | 7 (23.3) | 2 (8.7) |
| PD | 1 (1.9) | 0 (0) | 1 (4.3) |
| No. of patients | 53 | 30 | 23 |

Chi-square test showed no significant differences in distributions of treatment responses between patients with and without previous splenectomy. Pearson’s chi-square = 8.25 on 4 df, P = 0.0827. For purposes of analysis, zero entries in post splenectomy categories CR, MR, and PD were replaced with 0.1. Log-linear analyses performed on the data yielded an identical interpretation.

Abbreviations: rIFN-α, recombinant interferon-α; CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease.
1,500 cells/μL. One patient had an MR at 6 months of therapy but subsequently had disease progression at a time when his serum showed evidence of neutralizing antibodies to rIFN-α2a.

Of the nine patients with stable disease, one has had normalization of PB counts but little improvement in the BM hairy cell infiltrate. Four patients in this category had minor improvements in their PB counts and four patients had stabilization of their PB counts.

Overall, 41 patients (77.4%) had normalization of their PB counts. Two other patients had significant clearing of hairy cell infiltrate from their BM but had persistent low absolute granulocyte counts.

The median and range of Hb, platelet, and granulocyte counts of all patients with time on treatment are shown in Fig 1. The counts of only patients who have remained on IFN continuously were analyzed separately and showed similar results. Circulating TRAP-positive cells disappeared by 3 months (data not shown), although rare atypical lymphoid cells continued to be observed in the PB of most patients throughout therapy. The median platelet count increased rapidly in the first 2 months, slowed, and continued to increase thereafter, but at a slower rate. The median Hb values returned to greater than 12.0 g/dL after approximately 4 months. The median granulocyte values increased throughout the study, although less rapidly after 18 months. The changes in blood counts with time were subjected to more formal statistical analysis and are discussed below.

Twenty-one patients (40%) were removed from study for a variety of reasons. The seven patients who had clinical deterioration after initial improvement on IFN therapy all had anti-rIFN-α2a antibodies and are described in detail in another publication. The excellent patient acceptance of long-term low-dose IFN is evidenced by the fact that only five patients (9%) experienced unacceptable central or peripheral nervous system-related side effects, (impaired cognitive function 2, depression 1, peripheral neuropathy 1, and fatigue 1). Only one of these patients noted any improvement off treatment and three of the patients have needed to resume IFN and are tolerating therapy well. In other patients, there was no decrease in the dose or frequency of administration of rIFN-α2a because of constitutional symptoms. One elderly patient's IFN treatment was discontinued after 5 years 9 months because of recurrent cerebrovascular events believed to be unrelated to treatment. One patient was believed to have had a flare of an underlying rheumatologic syndrome induced by rIFN-α2a treatment and has been described in detail elsewhere. This patient subsequently responded to dCF therapy. One patient discontinued treatment at 3 years 5 months because of the inconvenience of continuing treatment (difficulty refrigerating medication while on frequent business travel). One patient whose sister administered the injections became noncompliant when he moved away from her after 3 years of treatment. Two patients developed erythrocytosis, and extensive workup failed to show an etiology. One patient's IFN therapy was discontinued because of concern that it was contributing to the erythrocytosis. No significant change occurred even after several months off therapy. Of the 13 patients removed from study for reasons other than disease progression, 1 had obtained a CR, 10 had obtained a PR, and 1 each had either an MR or stable disease. The median duration of treatment of the 21 patients removed from study was 29 months.

Of the 56 patients originally enrolled in the protocol, 32
(57%) have received IFN therapy without interruption. Currently, 31 are receiving the maintenance schedule described above (3 million units three times weekly), and 1 patient whose counts declined on the three-times weekly schedule is receiving 3 million units daily. The median duration of continuous IFN treatment of these 32 patients as of April 1990 was 60 months. The response status of these patients on uninterrupted treatment is PR 88% (26 of 32), MR 9% (3 of 32), and stable disease 3% (1 of 32). Fourteen of these 32 patients have less than a 5% hairy cell infiltrate bilaterally in their latest BM biopsies.

These 32 patients have tolerated prolonged treatment well without significant constitutional symptoms. To measure toxicity in a more objective manner, we performed straight-line regression analyses on these patients’ weights from the 18th to the 48th month on treatment. Forty-one percent (13 of 32) of patients showed no significant change in body weight, 28% (9 of 32) had a significant weight gain, and 31% (10 of 32) had a significant weight loss. Only 5 of 32 patients (16%) lost more than 5% of their body weight. Four patients who discontinued treatment have required reinstitution of therapy and are currently receiving rIFN-α2a at 3 million units three times weekly; all have responded (PR) to retreatment.

Major points addressed in this study were both the potential beneficial and adverse effects of prolonged IFN therapy. To investigate long-term effects, we analyzed data for trends from the eighteenth month, a point at which most other IFN trials had discontinued therapy. First, descriptive analyses were performed on distributions of Hb, absolute granulocyte count (AGC), platelet count, and sIL-2R variables at each week were reported. Median values provided a more reasonable measure of central tendency than mean values because many of the distributions were markedly skewed. Hence, we used median values in our regression analyses.

A simple straight-line regression analysis was performed on Hb data beginning at the eighteenth month. The statistical hypothesis of interest was whether the slope of the regression line was equal to zero. The parameter estimate for the slope was 0.00874, with an SE of 0.001249 (P = 0.5017), indicating that there was no significant increase in Hb count from 18 to 48 months in these patients.

A similar analysis was performed on the AGC data beginning at the eighteenth month. Again, the hypothesis of no slope against its alternative of a significant positive slope was tested. Results showed that for these data the slope differed significantly from zero, obtaining a value of 7.14 (SE = 2.08, P = 0.0075) (Fig 2A).

As with the previous two regression analyses, a straight line was fit through the median platelet count data (Fig 2A). The slope was 179.72, with an SE of 71.48 (P = 0.0331), indicating that it differed significantly from zero. A straight-line regression was performed on serum sIL-2R data. The parameter estimate for the slope was -32.19 with an SE of 7.50 (P = 0.0020), indicating a significant negative linear trend (Fig 2A).

For the group as a whole, analyses showed a significant increase in Hb count, a significant increase in platelet count, and a significant decrease in serum sIL-2R level from the eighteenth to the forty-eighth month.
increase in the AGC and platelet count with time on treatment after 18 months. At the same time, the sIL-2R levels showed a significant continuing decrease. As described elsewhere, the majority of patients (19 of 32, 59%) on continuous prolonged treatment at some time during therapy had anti-rIFN-α2a antibodies detectable in their serum; however, with time on treatment, nearly all these patients lost the antibodies. The presence of the antibodies may have inhibited the antitumor effects of IFN treatment in these patients and their disappearance might have caused hematologic improvement. Because of the possibility that this loss of antibodies accounted for the long-term improvement observed in the entire group of patients on continuous treatment, additional statistical tests were performed to determine whether differences existed between patients who never developed any type of antibodies to rIFN-α2a (Ab−) and those who did (Ab+) with respect to long-term improvement of AGC, platelet count, and sIL-2R level.

Figure 2B and C shows median AGC counts for Ab− (n = 13) and Ab+ (n = 19) subgroups from the 18th to the 48th month. ANCOVA was performed, and a test for equivalence of slopes between the subgroups was not rejected (P = .4798), indicating that the slopes between the Ab− and Ab+ subgroups were homogeneous. In addition, straight-line regression analyses were performed for each group separately, and slopes were positive and significant: 37.98 with an SE of 12.79 for Ab− (P = .0157) and 27.81 with an SE of 5.93 for Ab+ (P = .0011).

The overall survival for all 56 patients enrolled in the study is 82% (Fig 3). One patient died of a brain abscess soon after starting treatment. Two patients died of progressive disease after multiple other treatments (lymphoblastoid IFN, dCF, alkylating agents, and fludarabine). One patient who had PB count deterioration after 1 year of IFN treatment received three weekly doses of dCF, after which he developed severe prolonged thrombocytopenia and died.
of gastrointestinal hemorrhage. Autopsy revealed no hairy cell infiltrate in his BM. Three patients died of second malignancies: 1 patient whose brain tumor was diagnosed after a few doses of IFN and 2 patients in whom non-small-cell lung cancer developed. The other deaths were cardiovascular; 1 patient died of congestive heart failure, 1 of acute myocardial infarction, and 1 of superior mesenteric venous thrombosis. The last occurred in one of the patients who developed erythrocytosis and is the only death possibly related to long-term rIFN-α2a treatment.

**DISCUSSION**

Since the development of rIFN-α, HCL patients have been treated at several institutions with various regimens that differ in the type of IFN used and in dose, schedule, and duration of treatment. Although these studies clearly show that 3 million units of IFN administered in a variety of schedules can cause clinically significant improvement in PB counts and reduce hairy cell infiltrate in BM, the optimum duration of treatment has not been defined.

The unique aspect of our study is the uninterrupted administration schedule, with patients receiving IFN-α until unacceptably toxicity or progressive disease occurs. In other studies, IFN-α treatment was discontinued routinely after 3 months,7,10 7 months,12 12 months,18,19 18 months,19 or 24 months.11 After cessation of treatment in these studies, some patients had deterioration of PB counts and required further treatment. Quesada et al19 reported that 14% of patients (3 of 21) treated for 2 years with partially purified natural IFN required retreatment 10, 12, and 14 months after discontinuation of treatment. Of 25 patients treated with IFN-α2a for only 1 year at the same institution, 8 (32%) required reinitiation of therapy within 3 to 10 months of discontinuation of therapy.14 A follow-up report showed that the number of patients requiring retreatment had increased to 9 of 21 patients (43%) who received 24 months of natural IFN and 10 of 21 patients (48%) who received 1 year of rIFN-α2a.25 In a recent long-term follow-up report, Ratain et al26 noted that 27 of 60 (45%) responding HCL patients whose IFN treatment was discontinued after 12 or 18 months required further therapy, with a median actuarial failure-free survival (time to require additional treatment) of 25.4 months.24 Thus, most responding patients in whom IFN-α is discontinued apparently will eventually require retreatment. Fourteen of the relapsing patients were evaluable for response to a second course of IFN. Seven patients achieved a PR and four achieved an MR, indicating that many, but not all, relapsing patients retain sensitivity to IFN.

Our study demonstrates that prolonged IFN therapy is well tolerated and is not associated with any toxicities not previously described in other studies, except possibly erythrocytosis in two patients.27 The chronic fatigue syndrome described by other investigators as significantly affecting the quality of life of many patients28 was not observed in our trial.

One potential concern about chronic administration of IFN in patients with HCL was that neutralizing antibodies would develop.29 One might anticipate that the proportion of patients in whom such antibodies developed and who would acquire IFN resistance would increase over time with prolonged therapy. As described elsewhere,31 however, with long-term follow-up, neutralizing interferon antibodies have not developed in any new patients, and antibodies to IFN are no longer detectable in most of our patients who previously had antibody despite continued exposure to IFN-α2a. Therefore, with continuous prolonged IFN therapy, development of antibody-mediated IFN interferon resistance in increasing numbers of patients apparently will not occur. Figure 2 shows that median platelet and absolute granulocyte counts steadily increased with time on treatment while median serum sIL-2R decreased. This marker correlates well with clinical assessments of tumor response.32 Together these data show that long-term treatment (>18 months) results in continuing hematologic improvement. Although continued hematologic improvement observed in the entire group may have resulted from the disappearance of anti-IFN antibodies in the subset of patients who had them, statistical analysis showed this was not true because steady improvement was noted equally in patients in whom antibodies never developed (Fig 2B and C). In addition, in 9 patients, prolonged treatment resulted in continued reduction of hairy cell infiltrate in BM beyond that achieved at 18 months of therapy. Five of these patients had neutralizing anti–rIFN-α2a antibodies, 2 had nonneutralizing antibodies, and 2 never had antibodies to rIFN-α2a. Only 1 of these 9 patients has persisting presence of anti-IFN antibodies (nonneutralizing).

The definition of response in the different IFN trials varies but responses (MR + PR + CR) have been noted in 70% to 100% of patients.30,32 The overall response rate of the present study, 82%, is consistent with that observed by other investigators. In comparison with the largest multiinstitutional study of IFN treatment in HCL,28 a higher percentage of our patients (76% v 22%) attained a pathologic PR or CR (>50% decrease in the percentage of hairy cells in BM), although the overall response rate in that multinstitutional study (hematologic PR + pathologic PR + CR [81%]) was similar to our results. In addition, 20 of our patients (38%) cleared their BM biopsies to less than 5% hairy cell infiltrate, which meets the criteria for a CR used in some studies.32 The pathologic CR + PR rates in the present study are similar to another single-institution study of rIFN-α2a administered by the same schedule we used. Berman et al37 reported a 69% PR rate in 35 patients treated for 24 months. Their definition of response was identical to ours.

Because current data suggest that few if any HCL patients are cured with IFN-α treatment and because many patients will relapse within 2 years of stopping therapy, not all of whom will respond to reinstitution of therapy, we contend that another rational approach to treatment of these patients is chronic uninterrupted therapy, which could be administered at the same dose used to induce a remission or at a reduced dose. A Swedish-Danish study will test both methods by randomizing responsive patients after 2 years of IFN-α2b therapy to either the same induction dose (2 × 10^6 U/m² three times weekly) or to half
this dose. An alternate approach would be the use of even a smaller IFN maintenance dose that may have even greater, such as 2 x 10^7 U/m^2 three times weekly. The cost of prolonged treatment with IFN-α would be significantly higher than shorter term treatments such as dCF or 2-chlorodeoxyadenosine.

Our study of long-term continuous rIFN-α treatment of HCL patients demonstrates acceptable toxicities and continued hematologic improvement with time on treatment. Whether survival will be improved over that observed in patients treated intermittently cannot now be assessed. Our results suggest that continuous therapy is capable of maintaining and improving initial responses to IFN without unexpected long-term side effects or an increasing incidence of anti-IFN antibodies and does not expose patients to the potential risks that may attend intermittent disease exacerbations.

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