CONCISE REPORT

Recombinant α-2-Interferon for Hairy Cell Leukemia

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Twenty-two patients with hairy cell leukemia were treated with biosynthetic (recombinant) α-2-interferon in an open-label, single-arm efficacy study. Patients received 2 × 10^6 U/m^2 recombinant α-2-interferon three times weekly. Therapy was well tolerated subjectively with minimal short-term hematologic toxicity. Two patients had bacterial infections during the period of study, and one patient experienced a short-lived readily reversible rejection of a corneal transplant. Statistical comparison of the mean hematologic indices at study entry and after three to six months of therapy with recombinant α-2-interferon indicates a significant improvement in hemoglobin, granulocyte, and platelet counts. Bone marrow biopsies in six of 14 patients after six months of therapy showed a >50% decrease in the infiltration of leukemia cells. We conclude that recombinant α-2-interferon is highly effective therapy for hairy cell leukemia.

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HAIRY CELL LEUKEMIA (HCL) is a well-characterized lymphoid neoplasm in which cells with typical morphology and cytoplasmic projections infiltrate the bone marrow, peripheral blood, spleen, and portal triads of the liver. The disease is often indolent, and the hairy cells rarely invade other tissues. Hairy cell leukemia is usually a neoplasm of B lymphocytes, but T cell variants have been described. Patients typically present with peripheral blood cytopenias, and the major causes of morbidity and mortality are infection and bleeding.

Splenectomy is generally the treatment of choice for HCL; however, patients who fail to respond or progress post splenectomy are often difficult to manage. Chlorambucil, androgens, lithium, leukapheresis, and combination chemotherapy have been reported to be useful in selected patients. Cytotoxic chemotherapy usually produces severe myelosuppression, and there has been no generally effective therapeutic agent with acceptable toxicity.

Quesada and co-workers recently reported that a crude natural α-interferon preparation was useful in the treatment of HCL. It is uncertain whether the responses observed were due to α-interferon itself or another component of the product. Further, natural interferon preparations are not available in sufficient quantity for widespread therapeutic application. We therefore began a prospective study of biosynthetic (recombinant) α-2-interferon in patients with HCL. Our results indicate that α-2-interferon is highly effective therapy for this disorder.

MATERIALS AND METHODS

The diagnosis of HCL was established on the basis of morphologically typical hairy cells in the peripheral blood, bone marrow, or spleen. The hairy cells stained positively for tartrate-resistant acid phosphatase (TRAP) in all patients. Criteria for study entry included persistent cytopenia or lymphocytosis after splenectomy or in patients who refused to undergo splenectomy. Cytopenia was defined as either hemoglobin <9 g/dL or granulocytes <1.0 × 10^9/L or platelets <100 × 10^9/L. Patients with a history of opportunistic infection or other poorly controlled secondary manifestation of HCL such as vasculitis were also eligible. Peripheral blood counts were measured weekly during the first month of therapy and then every two weeks. Bone marrow biopsies were performed at study entry and every three months thereafter. Bone marrow response criteria were (1) complete response, <5% hairy cells on bone marrow biopsy and normal peripheral blood counts; (2) partial response, >50% decrease in the hairy infiltrate on bone marrow biopsy.

The study design was approved by the UCLA Human Subjects Protection Committee. Written informed consent was obtained from all patients. Recombinant α-2-interferon was produced and purified by previously described methods by the Schering Corporation (Kenilworth, NJ). The specific activity of the interferon was 2 × 10^8 U/mg of protein (>98% purity). The patients were medicated before each dose of interferon with 975 mg acetaminophen orally and then every four hours as needed. All patients were taught to self-administer the interferon subcutaneously at a dose of 2 × 10^8 U/m^2 three times per week. Hematologic parameters were statistically analyzed by comparing mean values at study entry and after three and six months of therapy using the paired t test. Hairy cell infiltration of bone marrow biopsy samples was assessed by conventional morphological techniques.

RESULTS

Twenty-two consecutive, unselected patients were treated between March and August 1984. Twenty-one were male and one was female. The median age was 51 years (range, 37 to 84). The median time from diagnosis was 39 months (range, two to 142 months).

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Twenty of the 22 patients had undergone splenectomy two to 120 months (median, 28 months) before study entry. Two patients refused splenectomy. Nine patients were dependent on transfusions of red blood cells before the start of the study, and four others were considered to require them at the time of referral. One patient had lymphocytosis requiring therapy, seven had isolated granulocytopenia, and one had poorly controlled vasculitis. Sixteen patients had a recent history of infection requiring hospitalization and antibiotic therapy. Nine patients had received prior treatment with chlorambucil, one with vincristine and prednisone, two with lithium carbonate, three with androgens, and one with leukapheresis. Five patients had received no prior therapy other than splenectomy. All treatments were discontinued at least one month before starting interferon. Patients receiving at least one dose of interferon were evaluable for toxicity. Patients completing eight weeks of therapy were evaluable for response.

One patient died seven days after study entry from a cerebrovascular accident. He was thrombocytopenic before study entry and remained so during the first week of treatment. The remaining 21 patients are evaluable for response. All patients experienced a fall in granulocyte, erythrocyte, hairy cell, and platelet counts during the first four weeks on treatment. This was followed by a steady increase in granulocytes, erythrocytes, and platelets by eight weeks (Fig 1). The hematologic parameters of all evaluable patients at study entry and after three to six months of treatment with recombinant α-2-interferon are shown in Table 1. Bone marrow aspiration at study entry was successful in one patient only, and bone marrow biopsies demonstrated a hypercellular marrow (70% to 95% cellular) with 40% to 90% replacement of normal marrow cells by HCL. Bone marrow biopsies in all 21 patients after three months of interferon therapy demonstrated a 10% to 60% decrease in the infiltration of hairy cells with regeneration of normal hematopoiesis in all specimens. After three months of therapy, four patients (19%) had a partial response, and after six months of treatment, six evaluable patients (43%) had a partial response; there are no complete responders to date. All patients continue to show a decline in bone marrow hairy cell infiltration and remain on therapy. Bone marrow aspiration was successful in two patients after three months of treatment and was successful in three after six months of therapy.

Nine patients were dependent on red blood cell transfusions before starting interferon therapy. Eight required no further transfusions after three weeks of treatment, and the last became independent of transfusions after six weeks. One patient developed a lobar pneumonia after 17 weeks of interferon treatment and responded promptly to intravenous antibiotics. After 12 weeks of interferon therapy, another patient developed a Staphylococcus aureus infection of the submandibular soft tissue, which responded to a course of intravenous therapy with vancomycin. No other infections were observed.

**Toxicity**

The treatment was well tolerated. All patients experienced fever not exceeding 39 °C. The median time of onset of fever was four hours after the injection, and the median duration was four hours. Myalgia and fatigue were common during the first two weeks of therapy. In most patients, these symptoms were alle-
vitiated by acetaminophen. No patient required discon-
tinuation of therapy due to symptomatic side effects.
No hepatic, renal, CNS, cardiac, or pulmonary toxic-
ity was observed. All patients had a decrease in WBCs
and platelets during the first two weeks of treatment.
By the fourth week of therapy, platelet counts were
greater than prestudy values in all evaluable patients.

One patient showed evidence of rejection of a cor-
neal transplant after two weeks of interferon therapy.
The transplant had been performed ten years previous-
year. Interferon therapy was stopped for one week, and
prednisone ophthalmic drops were given; the rejection
episode ended promptly. Interferon was subsequently
restarted, and the patient has suffered no further visual
disturbance.

DISCUSSION

These data indicate that recombinant α-2-interferon
is a highly active agent in the treatment of patients
with HCL. Prompt responses were seen in the peri-
pheral blood counts, although bone marrow infiltration
regressed more slowly. All patients demonstrated a
reduction in the number of hairy cells in the peripheral
blood and bone marrow. The objective partial bone
marrow response rate of 14 evaluable patients treated
for six months is 43%. No patients have achieved a
complete bone marrow response; however, all continue
to show evidence of improvement and remain on ther-
apy.

α-Interferon has demonstrated antiproliferative,
antiviral, immune-stimulating,
and differentiating
properties. It is uncertain which of these mechanisms
is mainly responsible for the observed response
of patients with HCL, although a direct cytotoxic
effect of interferon on the hairy cells seems likely.

These results with recombinant α-interferon are
encouraging and appear to be superior to those
reported after therapy with androgens,8,9 lithium,9 and
cytotoxic drugs.10,11 In addition, this study demon-
strates that HCL is specifically responsive to α-interfe-
ron rather than other factors contaminating the crude
natural interferon product.

The recombinant α-2-interferon treatment was gen-
erally well tolerated. No patient required discon-
tinuation of therapy because of toxicity. Mild to moderate
symptoms of fever, myalgia, and fatigue were common
but usually improved despite continuing interferon
therapy. Interferon has recently been reported to
increase the incidence of renal allograft graft rejec-
tion.12 The rejection episodes occurred shortly after
transplantation and were not corticosteroid responsive.
The patient in our study who showed evidence of
coneal graft rejection did so ten years after the
transplant and responded to topical corticosteroids.

Interferon was restarted without further evidence of
rejection. The relationship between therapy and the
graft rejection in this patient is therefore uncertain.

Our preliminary data indicate that biosynthetic
(recombinant) α-2-interferon is a highly active agent
in the treatment of HCL and suggest that it is the best
available therapy for patients with progressive disease
postsplenectomy. Prospective controlled studies are
required to determine the optimal dose, schedule, and
duration of therapy.

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