CONCISE REPORT

Recombinant α-2-Interferon for Hairy Cell Leukemia

By Andrew D. Jacobs, Richard E. Champlin, and David W. Golde

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 $2 \times 10^6$ U/m² 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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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 been treated with chlorambucil, one with vincristine and prednisone, two with lithium carbonate, three with androgens, and one with leupheresis. 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. 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 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-

Table 1. Hematologic Values of Patients at Study Entry and After Three to Six Months of Treatment With Recombinant α-2-Interferon

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Time (mo)</th>
<th>Median</th>
<th>Range</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>21</td>
<td>0</td>
<td>9.9</td>
<td>5.1-14.1</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>3</td>
<td>12.1</td>
<td>8.9-13.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>6</td>
<td>13.5</td>
<td>10.6-16.3</td>
<td></td>
</tr>
<tr>
<td>Granulocytes (10^9/L)</td>
<td>21</td>
<td>0</td>
<td>0.7</td>
<td>0.1-2.3</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>3</td>
<td>1.2</td>
<td>0.4-4.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>6</td>
<td>1.5</td>
<td>0.4-3.5</td>
<td></td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>21</td>
<td>0</td>
<td>91</td>
<td>18-283</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>3</td>
<td>240</td>
<td>65-358</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>6</td>
<td>253</td>
<td>133-345</td>
<td></td>
</tr>
</tbody>
</table>

*Results of a paired t test.
viated by acetaminophen. No patient required discontinuation of therapy due to symptomatic side effects. No hepatic, renal, CNS, cardiac, or pulmonary toxicity 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 corneal transplant after two weeks of interferon therapy. The transplant had been performed ten years previously. 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 peripheral 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 therapy.

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, lithium, and cytotoxic drugs. In addition, this study demonstrates that HCL is specifically responsive to α-interferon rather than other factors contaminating the crude natural interferon product.

The recombinant α-2-interferon treatment was generally well tolerated. No patient required discontinuation 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 rejection. The rejection episodes occurred shortly after transplantation and were not corticosteroid responsive. The patient in our study who showed evidence of corneal 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.

**ACKNOWLEDGMENT**

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**REFERENCES**

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