Treatment of Hairy Cell Leukemia With Recombinant Alpha<sub>2</sub> Interferon

By Mark J. Ratain, Harvey M. Golomb, James W. Vardiman, Everett E. Vokes, Renee H. Jacobs, and Karen Daly

Nine patients with progressive hairy cell leukemia were treated with subcutaneous injections of recombinant alpha<sub>2</sub> interferon (2 to 10 x 10<sup>6</sup> U/m<sup>2</sup>) three times weekly. Eight patients completed at least eight weeks of treatment and were evaluable; one patient with refractory thrombocytopenia died of an intracerebral hemorrhage after two doses of interferon. Seven of eight patients responded, with responses occurring as early as two weeks. Four patients also had resolution of their monocytopenia. No complete responses were seen with up to 30 weeks of treatment. Bone marrow biopsies demonstrated improvement in all eight patients. No unforeseen toxicity occurred, but most patients had transient myelosuppression during the first few weeks of treatment. Recombinant alpha<sub>2</sub> interferon is effective in the treatment of hairy cell leukemia, with acceptable toxicity.

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MOST PATIENTS with hairy cell leukemia (HCL) require treatment because of cytopenias. Usually, the initial therapy is splenectomy, but one third of the patients require further treatment. Chlorambucil has been used successfully to unpack the bone marrow and improve anemia and thrombocytopenia, but it has little effect on granulocytopenia. Quesada et al recently demonstrated significant responses (including complete remission) in 1 of 16 patients treated with partially purified alpha interferon. In the present paper, we show that recombinant alpha<sub>2</sub> interferon (IFN) is also effective in the treatment of HCL, with responses seen as early as one month after the beginning of therapy.

MATERIALS AND METHODS

In October 1983, we began a study of alpha<sub>2</sub> IFN administered subcutaneously to patients with HCL. Alpha<sub>2</sub> IFN was obtained from the Schering Corporation (Kenilworth, NJ) as the lyophilized powder (10 x 10<sup>6</sup> and 50 x 10<sup>6</sup> IU/vial) and reconstituted with sterile water.

Criteria for inclusion in the study were as follows:

(a) The diagnosis of HCL was confirmed pathologically on the basis of a bone marrow core biopsy performed within one month before entry according to criteria published previously.

(b) Patients had significant anemia (hemoglobin < 10 g/dL or need for transfusions), thrombocytopenia (platelets < 100,000 cells/μL), neutropenia (neutrophils < 1,000 cells/μL), and/or leukemia (white blood cell count > 10,000 cells/μL with more than 50% hairy cells).

(c) Patients had prior splenectomy or refused an operative procedure.

(d) Hepatic and renal function were normal.

(e) Patients must have passed the nadir of toxicity of any previous therapy (chemotherapy and/or radiotherapy); preferably no treatment in the previous four weeks.

(f) Patients had no coagulopathy or active cardiopulmonary disease.

(g) Patients had no prior or concomitant malignant disorder (except for basal cell carcinoma).

The initial dose of IFN in patients 1 through 4 and 6 was 10 x 10<sup>6</sup> U/m<sup>2</sup>. Patients No. 5 and 7 through 9 were initially treated with 2 x 10<sup>6</sup> U/m<sup>2</sup>. This dose was given by self-administered injection three times weekly. The first three injections were administered under direct supervision, with monitoring for six hours. This was usually performed in the hospital, to facilitate teaching of proper injection technique, and mixing of the IFN. Patients were premedicated with acetaminophen 650 mg.

Patients were seen weekly by their referring physicians or at the University of Chicago. Weekly laboratory studies included a complete blood count and differential, a chemistry panel, and a urinalysis. Neutrophil and monocyte counts were calculated by multiplying the percentage of neutrophils (segs and bands) or monocytes times the total white blood cell count. In most patients, the percentage of monocytes was confirmed by the use of the nonspecific esterase reaction.

All patients were seen monthly at the University of Chicago. At this time, bone marrow core biopsies were performed, with assessment of cellularity and percentage of hairy cells. The hairy cell index<sup>(a)</sup> (HCI), defined as (% cellularity x % hairy cells/10,000); and non-hairy cell index (NHCI), defined as (% cellularity/100 - HCI) were calculated.

Patients were evaluated after a minimum of eight weeks after beginning IFN therapy. Criteria for responses were defined as follows:

Complete response (CR): (a) an absence of hairy cells in the bone marrow core biopsy and (b) improvement in the peripheral blood counts to hemoglobin > 12 g/dL, platelets > 100,000 cells/μL, and neutrophils > 1,500 cells/μL.

Partial response (PR): (a) an absence of hairy cells in the peripheral blood and (b) improvement in the peripheral blood counts as indicated above.

Minor response (MR): (a) improvement in hemoglobin to more than 10 g/dL (without transfusions) or (b) improvement in platelets to more than 100,000 cells/μL (without transfusions) or (c) improvement in neutrophils to more than 1,000 cells/μL or (d) decrease in hairy cells (if initially leukemic) to less than 5% of peripheral white cells.
RESULTS

Nine patients were entered on the study between Oct 1, 1983, and March 1, 1984. The characteristics of these patients are seen in Table 1. The initial blood counts and bone marrow results are demonstrated in Tables 2 and 3, respectively. Eight patients were anemic, four patients were thrombocytopenic, and all nine patients were neutropenic. Only patient 8 was leukemic. Most patients had hypercellular marrows, but patient 2 was hypocellular.

Of the nine patients described in this study (Table 1), eight are evaluable, with duration of treatment ranging from nine to 30 weeks (median, 18 weeks). Patient 6 had refractory thrombocytopenia and died during the first week of treatment of an intracerebral hemorrhage. As noted earlier, patients 1 through 4 were given an initial dose of $10 \times 10^6$ U/m$^2$. All four of these patients subsequently had dose reductions to $2 \times 10^6$ U/m$^2$ because of toxicity (described later) or incomplete response.

Tables 2 and 3 demonstrate the changes in blood counts and bone marrow with IFN treatment. Seven of eight (88%) evaluable patients responded to treatment. There were no complete responses, 2 of 8 (25%) partial responses, and 5 of 8 (63%) minor responses. Only patient 7 had no response within nine weeks of treatment, although he had some improvement in his marrow, characterized by a reduction in the HCl and increase in the NHCI.

Three of the eight evaluable patients were severely anemic (hemoglobin < 10 g/dL or requiring transfusion) before IFN therapy. Two of these three patients had improvement in their anemia (hemoglobin > 10 g/dL without transfusion), occurring in eight to nine weeks. Three patients were thrombocytopenic (platelets < 100,000 cells/μL). All three patients had resolution of their thrombocytopenia in two to six weeks (median, four weeks). Six of eight patients had resolution of their neutropenia, occurring in five to nine weeks (median, seven weeks). No patient has had any deterioration in blood counts after achieving a response. The best example of a rapid durable response (patient 4) is seen in Fig 1.

In addition, all eight evaluable patients were severely monocytopenic (<100 cells/μL) before IFN therapy. Four patients (patients 1 through 4) had significant increases in their monocyte counts (250 to 920 cells/μL) with IFN therapy.

Bone marrow changes were also quite dramatic. An example of these changes is seen in Fig 2. Bone marrow changes did not always correlate with improvement in the peripheral blood counts. Six of eight patients had both a reduction in the HCI and increase in the NHCI. Patient 1 had a marked (63%) reduction in the HCI but also a 50% decrease in the NHCI. Patients 2 and 5 remained anemic, despite having the lowest HCI with IFN therapy.

Toxicity occurred in all patients and was similar to previous experiences with recombinant alpha2 IFN.9

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<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response</th>
<th>Duration of Treatment</th>
<th>Hb (g/dL)</th>
<th>Platelets</th>
<th>WBC</th>
<th>Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before Interferon</td>
<td>(cells $\times 10^9$/μL)</td>
<td>With Interferon</td>
<td>(cells $\times 10^9$/μL)</td>
</tr>
<tr>
<td>1</td>
<td>MR</td>
<td>30 + wk</td>
<td>10.5</td>
<td>163</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>MR</td>
<td>26 + wk</td>
<td>9.3†</td>
<td>201</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>PR</td>
<td>22 + wk</td>
<td>11.0</td>
<td>284</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>22 + wk</td>
<td>9.5</td>
<td>40†</td>
<td>3.6</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>MR</td>
<td>13 + wk</td>
<td>10.3</td>
<td>83†</td>
<td>3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>6*</td>
<td>—</td>
<td>1 wk</td>
<td>11.6†</td>
<td>3†</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>NR</td>
<td>9 + wk</td>
<td>14.0</td>
<td>363</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>MR</td>
<td>9 + wk</td>
<td>11.9</td>
<td>185</td>
<td>10.6†</td>
<td>0.7</td>
</tr>
<tr>
<td>9</td>
<td>MR</td>
<td>9 + wk</td>
<td>11.4†</td>
<td>53†</td>
<td>2.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Patient No. 6 was not evaluable owing to intracerebral hemorrhage during first week of treatment.
†Required transfusions.
‡50% Hairy cells.
§8% Hairy cells.
Table 3. Bone Marrow Response to Treatment With Interferon in Patients With Hairy Cell Leukemia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response Before Interferon</th>
<th>Duration of Treatment</th>
<th>With Interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCI</td>
<td>NHCI</td>
<td>HCL</td>
</tr>
<tr>
<td>1</td>
<td>MR</td>
<td>30+ wk</td>
<td>.38</td>
</tr>
<tr>
<td>2</td>
<td>MR</td>
<td>26+ wk</td>
<td>.12</td>
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<tr>
<td>3</td>
<td>PR</td>
<td>22+ wk</td>
<td>.56</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>22+ wk</td>
<td>.83</td>
</tr>
<tr>
<td>5</td>
<td>MR</td>
<td>13+ wk</td>
<td>.23</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>1 wk</td>
<td>.52</td>
</tr>
<tr>
<td>7</td>
<td>NR</td>
<td>9+ wk</td>
<td>.73</td>
</tr>
<tr>
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<td>MR</td>
<td>9+ wk</td>
<td>.70</td>
</tr>
<tr>
<td>9</td>
<td>MR</td>
<td>9+ wk</td>
<td>.57</td>
</tr>
</tbody>
</table>

All eight evaluable patients developed fever, which was partially controlled by acetaminophen. Generally, the fevers abated with further administration of IFN but were more severe at higher doses (patients 1 through 4). Patients 2 and 4 required hospitalization for neutropenic fevers during their first three weeks of IFN. Seven patients (88%) had fatigue, which persisted throughout therapy. Other persistent problems included myalgias in 5 of 8 (63%) patients and dry mouth (63%).

Patients 1 through 4 all had an influenza-like syndrome with their first few doses, which did not occur in the other patients, who received only 2 x 10^6 U/m^2 as the starting dosage. Other toxicity included asymptomatic hepatitis (38%), abnormal taste (25%), paresthesias (25%), and alopecia (13%).

Transient myelosuppression was an important problem during the initial phase of treatment in the seven responding patients. Three of five patients (patients 2 and 9 could not be assessed because of transfusions) had a decrease in hemoglobin of 0.9 to 1.9 (mean, 1.3) g/dL. The nadir of this decrease occurred at one to nine weeks (median, seven weeks) after beginning IFN, with a total duration of six to nine weeks (median, seven weeks). Five patients (patients 4 and 9 received transfusions) had a decrease in platelet count of 40,000 to 180,000 (mean, 80,000) cells/μL. The nadir of this decrease occurred at one to four weeks (median, one week) and lasted for one to 25 weeks (median, four weeks). Five patients had a decrease in neutrophil count of 40 to 400 (mean, 200) cells/μL. The neutrophil nadir occurred at one to three weeks (median, one week), with a duration of one to seven weeks (median, two weeks). No patient required platelet transfusion as a result of IFN, but patient 1 required one transfusion of red blood cells.

**DISCUSSION**

Our results demonstrate that recombinant alpha2 IFN is effective in the therapy of patients with HCL. Of our eight evaluable patients, seven had marked improvement in at least one cytopenia and some improvement in the bone marrow. We have also demonstrated that the severe monocytopenia of HCL can be reversed with IFN therapy. This has not been...
previously described, although Janekila et al\textsuperscript{11} report one patient treated successfully with chlorambucil, who had resolution of his monocytopenia.\textsuperscript{11}

These results are important for two reasons. First, after Quesada et al\textsuperscript{6} had demonstrated that partially purified alpha IFN was effective in the treatment of HCL, we were able to show that recombinant alpha, IFN is also effective. Second, we have demonstrated that IFN is effective in patients with advanced disease, as all nine of our patients required treatment because of marked granulocytopenia (less than 1,000 granulocytes/\(\mu\)L). In addition, three patients had life-threatening thrombocytopenia requiring transfusions. The HCL in our patients was more advanced than that in the patients of Quesada et al\textsuperscript{6}; only four of their seven patients had severe granulocytopenia and none were severely thrombocytopenic. Also, only five of their seven patients had had a prior splenectomy.

Systemic toxicity was minor and similar to that reported previously.\textsuperscript{9} It appeared to be less severe in patients receiving a lower initial dose (2 \(\times\) \(10^6\) U/m\(^2\)) of IFN. Transient myelosuppression was seen in most patients. This may present some difficulty in the use of IFN, especially in patients with moderate thrombocytopenia, who may develop a need for platelet transfusion after beginning IFN. However, all three of our thrombocytopenic patients (excluding patient 6) responded to IFN within two to six weeks. It is also possible that the neutropenic fevers in patients 2 and 4 can be partially attributed to worsening neutropenia due to IFN therapy.

The best treatment for patients with progressive HCL after splenectomy is controversial.\textsuperscript{5} Chlorambucil has been quite effective in reversing persistent anemia and thrombocytopenia, even though six months of treatment is required before a response is obtained.\textsuperscript{4,5} However, in contrast to IFN, granulocytopenia remains a persistent problem. It appears, therefore, that IFN will play an important role in the treatment of HCL, as it acts more rapidly and more effectively than chlorambucil. It may even be appropriate to administer IFN to patients with severe marrow involvement as first-line treatment, because splenectomy is relatively ineffective in patients with an HCL > 0.7.\textsuperscript{4}

Androgens are also sometimes effective in treatment of HCL.\textsuperscript{12} The combination of androgens and IFN may be more effective than IFN alone for two reasons. First of all, androgens may prevent or decrease the transient myelosuppression seen with IFN. Second, some patients (such as patient 2) may have a marked reduction of their hairy cells but persistent severe anemia, which could be improved by the addition of androgens.

The combination of chlorambucil and IFN may also be useful. Even with longer treatment with IFN, the great majority of patients do not have a complete response.\textsuperscript{7} Chlorambucil may be effective in eradicating the remaining hairy cells and could be more safely given to partial responders with normal blood counts. In addition, recombinant alpha, IFN has been reported to enhance subsequent responses to cytotoxic drugs.\textsuperscript{13}

The mechanism of action of IFN in patients with HCL has not yet been defined. Quesada et al\textsuperscript{6} suggest that the effect of IFN may be related to interleukin 2 membrane receptors, associated with the presence of the Tac antigen. It is also possible that IFN acts indirectly through natural killer (NK) cells, as NK cell activity is severely depressed in HCL.\textsuperscript{14} Recombinant leukocyte interferon can stimulate NK activity and inhibit various leukemic cell lines in vitro.\textsuperscript{15}

We still need to determine the optimal dosage, frequency, and route of injections. Doses of 2 \(\times\) \(10^6\) U/m\(^2\) are effective and appear to be less toxic than higher doses. It is possible that even lower doses may be more effective, especially if NK cell activation mediates the therapeutic response.\textsuperscript{16} We have administered IFN injections three times a week, compared with daily injections used by Quesada et al.\textsuperscript{5,7} However, recent animal studies demonstrated that recombinant leukocyte IFN is more effective in L1210 leukemia when given every three days, rather than in more frequent doses.\textsuperscript{17} The route of administration may also be important, as the pharmacokinetics of subcutaneous and intramuscular injections are probably quite different. Finally, the duration of treatment needs to be determined. Is maintenance IFN therapy necessary in patients who have attained a complete remission,\textsuperscript{5,7} or can HCL be “cured” with a single course of IFN?

**NOTE ADDED IN PROOF**

These eight patients have all received 44 to 52 weeks of IFN. Their updated response status is as follows: five PR, three MR.

**ACKNOWLEDGMENT**

We greatly appreciate the participation of the following physicians in the management of four of our patients: Henry Kaplan, (San Jose, Calif.), Ralph Levitt (Fargo, ND), and Robert Kellermeyer (Cleveland). We thank Dr Robert Spiegel of the Schering Corporation for providing the alpha, IFN and Margaret Johnson for coordinating the data management.

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Treatment of hairy cell leukemia with recombinant alpha 2 interferon

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