Follow-up Observations on the Effect of Human Leukocyte Interferon in Non-Hodgkin’s Lymphoma

By Arthur C. Louie, James G. Gallagher, Karol Sikora, Ronald Levy, Saul A. Rosenberg, and Thomas C. Merigan

Follow-up data for 11 patients with non-Hodgkin’s lymphoma treated with partially purified human leukocyte interferon is presented. The interferon preparation used was 0.1% pure and treatment consisted of $5 \times 10^6$ U given intramuscularly twice daily for 60 injections. One complete, three partial, and three minimal responses were observed in five of seven evaluable patients with nodular non-Hodgkin’s lymphoma. Duration of response appears to be from 6 to 12 mo. One patient achieved a second partial response on retreatment with interferon in spite of having received chemotherapy in the interval between interferon treatments. No responses were seen in three patients with rapidly progressive diffuse histiocytic lymphoma. Dose-limiting toxicity is leukopenia, which necessitated modification or cessation of treatment in three patients. Nonhematologic toxicities consisted of fever, malaise, arthralgia, and loss of appetite. In conclusion, interferon has activity against non-Hodgkin’s lymphoma, and prior treatment with chemotherapy does not preclude a response to interferon.

THE INTERFERONS are a group of glycoproteins first described by Isaacs and Lindenmann in 1957, which are excreted by cells in minute quantities following exposure to a variety of biologic and chemical stimuli. In nature, interferons appear to be a major component of host defense against viral infection. This protection against viral infection extends to those viruses capable of inducing tumor formation. In addition, interferon treatment inhibits tumor formation and dissemination following exposure to tumor-inducing viruses. Subsequent observations in a wide variety of animal tumor systems show antitumor effects for interferon against chemical carcinogen-induced tumors and spontaneously occurring tumors as well.

Attempts to extend these observations to the treatment of human tumors have given rise to a number of reports suggesting clinical activity for human leukocyte interferon in osteogenic sarcoma, breast cancer, multiple myeloma, acute lymphocytic leukemia, Hodgkin’s disease, and the non-Hodgkin’s lymphomas. In a previous communication we described objective response in 3 of 6 patients with non-Hodgkin’s lymphoma treated with human leukocyte interferon. We have followed this original group of patients for an additional 22 mo and have treated an additional 5 patients, all with non-Hodgkin’s lymphoma. This article describes the fate of the original group of patients and expands upon our observations of the effect of partially purified human leukocyte interferon on the course of non-Hodgkin’s lymphoma.

MATERIALS AND METHODS

Human Leukocyte Interferon (IF)

IF was prepared by Dr. Kari Cantell using methods already described. The interferon preparation used had a specific activity of $10^6$ reference U/mg protein and a titer of $4 \times 10^6$ U/ml. The purity of this preparation was estimated to be 0.1% and was free of endotoxin by either the rabbit or limulus assays. Routine bacterial and fungal cultures established the sterility of the preparation.

Patient Selection

Patient characteristics are shown on Tables 1 and 2. Eleven patients with non-Hodgkin’s lymphoma were treated with human leukocyte interferon. The first three patients had rapidly progressive diffuse histiocytic lymphoma (DHL) and the remaining eight patients had nodular non-Hodgkin’s lymphoma; seven with nodular lymphocytic poorly differentiated lymphoma (NLPD) and one with nodular mixed lymphoma (NML). The median age for the entire group was 52, with a range of 27–68. There were six males and five females. All patients had Karnofsky performance status of 80% or greater.

The three patients with DHL were distinctly different in age, sex, prior therapy, and aggressiveness of their tumors when compared with the eight patients having nodular non-Hodgkin’s lymphoma. The DHL patients were all males, and two of the three patients were considerably younger than the group median age. All three had received prior radiation therapy and chemotherapy and all had become refractory to conventional treatment. The nodular lymphoma group by comparison was generally older, had more females than males, and six of the eight patients had received prior therapy. Two patients had prior chemotherapy and one patient (patient 4) had received two courses of interferon, the first course preceded by no prior therapy and the second preceded by both interferon and six cycles of CVP chemotherapy. All patients had measurable peripheral adenopathy and 10 patients, in addition, had measurable lesions on lymphogram or chest x-ray.

Patient Evaluation

Pretreatment evaluation included a complete history and physical examination, pathologic review of all specimens by the Stanford Surgical Pathology Department, CBC with differential count, platelet count, chemical screening battery (SMA-12), chest x-ray, and

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INTERFERON AND NON-HODGKIN’S LYMPHOMA

Table 1. Characteristics of 11 Patients With Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Age</th>
<th>Median 52</th>
<th>Range 27-68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 6</td>
<td>Female 5</td>
</tr>
<tr>
<td>Performance status</td>
<td>90+ 7</td>
<td>80-90 4</td>
</tr>
<tr>
<td>Histologic type</td>
<td>DHL 3</td>
<td>NLPD 7</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>None 6</td>
<td>Radiotherapy 0</td>
</tr>
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</table>

bipedal lymphogram. The lymphogram was omitted if sufficient dye from earlier studies was present.

During interferon treatment patients were monitored with twice weekly CBCs, differential counts, and platelet counts and weekly SMA-12 screening. Blood counts were monitored more often if the granulocyte count fell below 2500/cumm or platelet count below 75,000/cumm.

Patient evaluation by physical examination and x-ray studies were performed at intervals no greater than every 2 wk during the time of treatment and at 2-4-wk intervals during the subsequent 60 days. Thereafter, patients were followed at 1-3-mo intervals. Duration of follow-up for the entire group is now 14-36 mo.

Interferon Treatment

No phase I study has been performed for human leukocyte interferon because of the extremely limited supplies of interferon available. As a consequence, both the dose and the schedule of treatment were arbitrary. (See Table 3 for summarization of the treatment of 11 patients.) The first six patients (three with DHL and three with NLPD) were given single intramuscular injections of 2.5 x 10^6 U of interferon on the first day, followed by 5.0 x 10^6 U twice daily if major acute reactions were not observed. The planned course of treatment was to be 60 injections. Only minimal acute effects were seen among the first six patients, and consequently, the remaining five patients had treatment started at full dose.

Two patients were given weekly courses of interferon in an attempt to see if short courses of treatment could be as effective as more prolonged treatment. Patient 7 was given a single 1-wk course of interferon (14 injections) followed 3 mo later by a second 1-wk treatment. Six months later, this patient received a full 30-day course of treatment. Patient 8 received 1 wk of treatment followed 6 wk later by a full 30-day course.

Table 2. Clinical Features of 11 Patients With Non-Hodgkin’s Lymphoma Treated With Interferon

<table>
<thead>
<tr>
<th>Patient Age/Sex</th>
<th>Histologic Type</th>
<th>Sites of Measurable Disease</th>
<th>Prior Therapy</th>
<th>Time From Prior Therapy to Start of IF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—66/M</td>
<td>DHL</td>
<td>+</td>
<td>-</td>
<td>EF-XRT, CAT x 2, CHOP x 3, Bleo x 3</td>
</tr>
<tr>
<td>2—29/M</td>
<td>DHL</td>
<td>+</td>
<td>-</td>
<td>TNI, CAT x 11, CVP x 8</td>
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<tr>
<td>3—27/M</td>
<td>DHL</td>
<td>-</td>
<td>+</td>
<td>TNI, CAT x 7, CVP ± Bleo x 2, MOPP x 1</td>
</tr>
<tr>
<td>4—65/M</td>
<td>NLPD</td>
<td>+</td>
<td>+</td>
<td>None/CVP x 6</td>
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<tr>
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<td>NLPD</td>
<td>+</td>
<td>+</td>
<td>None</td>
</tr>
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<td>6—56/F</td>
<td>NLPD</td>
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<td>-</td>
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<td>+</td>
<td>None</td>
</tr>
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<td>NML</td>
<td>+</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>10—66/F</td>
<td>NLPD</td>
<td>+</td>
<td>-</td>
<td>CVP x 11</td>
</tr>
<tr>
<td>11—68/M</td>
<td>NLPD</td>
<td>+</td>
<td>-</td>
<td>CVP x 2, MVP x 11, chlorambucil + vinblasteine, AVP x 2, Bleo x procarbazine, vinblasteine, Adria x 2, VP-16 x 1, HIIM x 1 vinblasteine + prednisone</td>
</tr>
</tbody>
</table>

LAG, lymphogram; CXR, chest x ray.
had to be present for at least 1 mo to be counted. Progressive disease was defined by the appearance of any new lesions or a greater than 25% increase in the sum of the products of the longest perpendicular diameters of measurable lesions.

Response duration is calculated from the time objective response is noted to the time progressive disease is first diagnosed. Time to subsequent treatment is calculated from the completion of interferon to the time of onset of the subsequent chemotherapy or radiotherapy.

RESULTS

The treatment and clinical course of 11 patients with non-Hodgkin's lymphoma are presented in Table 3. Responses occurring in opacified lymph nodes on lymphogram were also reflected in reduced peripheral adenopathy.

The three patients with DHL did not respond to interferon and in each case disease progression was documented within 1 mo of completion of interferon therapy. All three patients eventually died of refractory lymphoma.

Eight patients with nodular non-Hodgkin's lymphoma were subsequently treated with 12 courses of interferon: 3 1-wk courses and 9 attempts at 30-day treatment. As already noted, one patient (patient 11) is considered nonevaluable for response because treatment was stopped on the eighth day due to profound granulocytopenia, with an absolute granulocyte count of only 78.

Two patients received 3 1-wk courses of treatment. Patient 7 achieved a 28% reduction in nodal size after a 7-day treatment. Three months later an additional 1-wk course was given with no significant effect (<15% regression). Patient 8 demonstrated no response to 1 wk of treatment.

Seven patients were given 8 full courses of interferon (60 injections) and objective response was seen in 3 patients. Patient 5 had disappearance of peripheral adenopathy, reduction of all opacified retroperitoneal lymph nodes to normal size, and the disappearance of small numbers of circulating monoclonal B cells following treatment. This patient is considered to be a complete responder. His response lasted for 12 mo, at which time a single 0.5 cm left epitrochlear node was discovered. Biopsy of this node confirmed recurrence of NLPD. No other evidence of recurrent NLPD was discovered until another 17 mo elapsed, when enlargement of iliac lymph nodes were observed. This patient remains alive with slowly progressive lymphoma and has been followed off treatment for 29 mo after completion of interferon therapy.

Partial response was achieved in patient 4 (see Fig. 1), who had regression of palpable diffuse peripheral
adenopathy and reduction of abnormal nodes on lymphogram. Tumor regression persisted for 6 mo when peripheral and retroperitoneal lymph nodes began to regrow at a moderate rate. The appearance of hepatosplenomegaly, thrombocytopenia, and the appearance of circulating abnormal lymphocytes led to the start of CVP chemotherapy 6.5 mo after the completion of interferon therapy. Six cycles of low-dose CVP were given with little change in lymph node size but with improvement in the peripheral blood picture and in hepatosplenomegaly. Five months after cessation of CVP chemotherapy, lymph nodes began to grow again and circulating abnormal lymphocytes reappeared. Testing of these lymphocytes showed them to be monoclonal B cells. The patient was retreated with another 30-day course of interferon. Within 2 wk regression in all parameters of disease was again noted. Maximal regression occurred 2 mo after completion of treatment. This second response lasted 5 mo before relapse again occurred in lymph nodes. He is currently alive with stable disease on chemotherapy. Patient 6 had an objective partial regression of both palpable peripheral lymph nodes and measurable nodes on lymphogram. This response lasted for 12 mo before progression was documented. An additional 6 mo elapsed before progressive disease led to treatment with chemotherapy. This patient is currently alive with stable disease on cytotoxic therapy.

Minimal responses were seen in two patients following full courses of interferon. Patient 7 had a 17% regression lasting 10 mo before signs of progression were observed. This patient has now been followed for an additional 4 mo off all therapy with slowly progressive lymphoma. Patient 10 had an 18% regression for only 2 mo before progression necessitated treatment with chemotherapy. This patient is currently alive with stable disease on cytotoxic therapy.

Patient 8 is a nonresponder who was followed for 15 mo off all therapy after treatment with interferon. CVP was eventually started, and this patient is alive with good response to chemotherapy. No response was seen in patient 9 who remains alive off all therapy with slowly progressive lymphoma 13 mo after interferon. A summary of treatment results for the entire group is presented on Table 4.

Toxicity

The main goal of this pilot study was to demonstrate activity for interferon in patients with non-Hodgkin's lymphoma. Because of severe limitations in drug supply, no attempt was made to perform a phase I dose escalation and toxicity study. Although the doses and schedules used were arbitrary, some toxic effects were seen in every patient.

Table 5 illustrates the toxic effects seen in our group of 11 patients. Leukopenia developed in nearly all the patients and was relatively more severe than thrombocytopenia. Reduced blood counts could be observed as early as 2–5 days following the start of interferon therapy. Continued treatment with interferon produced progressively lower white blood counts until days 6–10, when the counts stabilized even though treatment was continued. In three patients, leukocyte and platelet counts fell during the first week, but later fluctuations produced nadir counts during the third and fourth weeks, although no clear trend toward lower counts could be observed. The three patients with DHL had more marked hematologic toxicity probably reflecting limited marrow reserve following extensive prior therapy.

Among the group of patients with nodular non-Hodgkin's lymphoma, patient 9 had severe leukopenia. Surprisingly, this patient had no history of prior therapy. The lowest white blood count in this patient was 1200/cumm and the platelet count fell to 99,000/cumm. No cumulative toxicity was observed in spite of prolonged exposure to interferon at $5 \times 10^6$ U daily.

Patient 11 had received extensive prior therapy before treatment with interferon. Six days of interferon treatment produced only a moderate leukopenia, but a marked decrease in the percentage of granulocytes led to a profound absolute granulocytopenia. Treatment was withheld on the seventh day and resumed at half dose on the eighth day. Blood counts...
from the morning of the eighth day showed an absolute granulocyte count of only 78. Treatment was discontinued at this point. Subsequent development of cellulitis in the patient's left leg prevented resumption of therapy.

The major nonhematologic toxicities are listed in Table 5. These toxicities were generally mild to moderate in severity and were well tolerated by the majority of patients. Malaise during the course of treatment was almost universal. Myalgias and arthralgias were common and were reported as being mild to moderate, except for one patient who experienced severe myalgias. The majority of patients had decreased appetite and moderate (2–4 kg) weight loss. Hair loss was observed in four patients. Mild hair loss was seen in two patients and moderate loss in two others. Loss of hair was confined to the scalp and consisted of low grade but persistent shedding. Two patients observed shedding of hair continuing 2–3 mo after the completion of interferon treatment.

Table 5. Treatment Toxicity of Human Leukocyte Interferon in 11 Patients With Non-Hodgkin's Lymphoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>WBC (x 10^3)</th>
<th>Platelet (x 10^3)</th>
<th>WBC (x 10^3)</th>
<th>Platelet (x 10^3)</th>
<th>Fever</th>
<th>Malaise</th>
<th>Joint Pains</th>
<th>Muscle Aches</th>
<th>Loss of Appetite</th>
<th>Weight Loss</th>
<th>Alopecia</th>
<th>Fatigue</th>
<th>Nausea</th>
<th>Mental Depression</th>
<th>Cellulitis</th>
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<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5.6</td>
<td>245</td>
<td>1.4</td>
<td>130</td>
<td>+</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<td>+</td>
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<tr>
<td>3</td>
<td>7.0</td>
<td>580</td>
<td>4.4</td>
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<td>+</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Tissue abscess</td>
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<td>4</td>
<td>9.0</td>
<td>195</td>
<td>3.1</td>
<td>140</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Skin bx</td>
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<td>7.0</td>
<td>126</td>
<td>2.3</td>
<td>74</td>
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<td>0</td>
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<tr>
<td>6</td>
<td>6.3</td>
<td>270</td>
<td>2.4</td>
<td>155</td>
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<tr>
<td>7</td>
<td>6.4</td>
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<td>2.5</td>
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<td>+</td>
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<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

We have attempted to characterize the quality and duration of the response to human leukocyte interferon treatment in a well defined group of patients with non-Hodgkin's lymphoma. Quantitative data on the activity of interferon await treatment of larger numbers of patients with more highly purified forms of interferon.

Four objective responses (CR and PR) were seen in three patients with nodular non-Hodgkin's lymphoma. The duration of unmaintained response appears to be from 6 to 12 mo. In addition, 3 minimal (15%–49%) regressions were noted. Among the 7 evaluable patients not achieving an objective response, two have remained clinically stable off all treatment for 11 and 15 mo after interferon.

Five of 11 patients did not receive full dose, 30-day courses of treatment either because of progressive disease (2 patients) or treatment toxicity (3 patients). The remaining six patients completed 7–30-day

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DISCUSSION

We have attempted to characterize the quality and duration of the response to human leukocyte interferon treatment in a well defined group of patients with non-Hodgkin's lymphoma. Quantitative data on the activity of interferon await treatment of larger numbers of patients with more highly purified forms of interferon.

Four objective responses (CR and PR) were seen in three patients with nodular non-Hodgkin's lymphoma. The duration of unmaintained response appears to be from 6 to 12 mo. In addition, 3 minimal (15%–49%) regressions were noted. Among the 7 evaluable patients not achieving an objective response, two have remained clinically stable off all treatment for 11 and 15 mo after interferon.

Five of 11 patients did not receive full dose, 30-day courses of treatment either because of progressive disease (2 patients) or treatment toxicity (3 patients). The remaining six patients completed 7–30-day
courses of interferon treatment, and in this group we observed one complete response, three partial responses, and two minimal responses.

Two patients completed 3 1-wk courses of treatment and only a single minimal response was achieved. Although our experience with 1-wk courses of treatment is very limited, it appears that longer duration of treatment enhances the likelihood of response.

No activity was demonstrated for interferon in three patients with rapidly progressive diffuse histiocytic lymphoma. All three of these patients had received extensive prior treatment. It is unknown whether this resistance is due to an inherent insensitivity of DHL for interferon, the effect of prior therapy on selection of resistant clones of tumor cells, or to the poorer general condition of this group of patients.

Treatment toxicity was tolerable and, in general, our observations confirm those presented by others.10-13 Dose-limiting toxicity is leukopenia, and this was encountered in four patients: three with marked leukopenia and one with marked granulocytopenia in the presence of moderate leukopenia. All of the patients with diffuse histiocytic lymphoma had extensive prior therapy and seven of eight patients with nodular non-Hodgkin’s lymphoma had marrow involvement. Consequently, diminished bone marrow reserve was present in the majority of our patients and may account for the surprisingly high incidence of leukopenia. The pattern of hematologic toxicity is distinctly different from that observed with cytotoxic agents. White blood cell and platelet counts fall rapidly during the first week and then level off by day 10 even with continued treatment. No clear trend toward progressive leukopenia or thrombocytopenia was observed during the last 20 days of treatment. At the completion of treatment we routinely observed prompt hematologic recovery, with return to baseline levels in several patients occurring within 1 wk.

A variety of nonhematologic toxicities were encountered, consisting mainly of fever, malaise, arthralgias and myalgias. These complaints were well controlled with acetaminophen. Loss of appetite and weight loss were common. Mild to moderate hair loss was seen in four patients and listlessness, loss of mental sharpness, and difficulty coping with normal stresses were also observed. Four patients had transient elevations of liver transaminase levels.

Many important questions remain before the role of interferon in the treatment of lymphomas can be suggested. The interferon preparation used in this group of patients was only 0.1% pure. As preparations of increasing purity become available, it will be possible to establish that antitumor activity is indeed due to interferon rather than to some unknown impurity. The optimal dose and schedule of interferon is still unknown, and when adequate quantities of drug become available, phase I studies will still be necessary. The usefulness of maintenance therapy and intermittent “booster” courses of IF also needs to be investigated. Pertinent to this is our observation that the only patient to be retreated with interferon following relapse had a second meaningful response. This second response occurred after six cycles of CVP chemotherapy and indicates that prior chemotherapy does not preclude a response to interferon.

In transplantable animal tumor systems, interferon appears most active under conditions of minimal tumor load.1 If activity for interferon can be confirmed in patients with lymphomas or solid tumors, the experimental use of interferon in the adjuvant setting will be justified. Interferon has manageable toxicity and the degree of prior therapy appears to correlate with the degree of hematologic toxicity. Further investigations will include evaluating interferon therapy in other histologic types of lymphomas and selected solid tumors.

REFERENCES


Follow-up observations on the effect of human leukocyte interferon in non-Hodgkin's lymphoma

AC Louie, JG Gallagher, K Sikora, R Levy, SA Rosenberg and TC Merigan