Recombinant Interferon Beta and Gamma in the Treatment of Adult T-Cell Leukemia

KAZU TAMURA, MD, SHIGEYOSHI MAKINO, MD, YASUHIKO ARAKI, MD, TAKUHO IMAMURA, MD, AND MASASHI SEITA, MD

Adult T-cell leukemia (ATL) is one of the most difficult diseases to treat because of severe underlying immune deficiency and metabolic disturbance. Interferon has potent antiviral, antiproliferative, and immunomodulating properties, and therefore, this may be a good agent to treat such immune deficient patients with peripheral T-cell leukemia. During a period from April 1984 to August 1985, six patients were treated with interferon-α (IFN-α), and interferon-γ (IFN-γ) was given to five patients. Three patients achieved partial remission by IFN-α administration with a response duration of 1, 1.5, and 12 months respectively, whereas one complete remission and two partial responses were experienced by IFN-γ treatment with 4, 4, and 2 months of response. Side effects of IFN-α were similar to those of IFN-γ including fever, chills, fatigue, mild hematologic depression, and transient hepatic enzyme abnormalities. These promising results warrant further well-designed clinical trials including combination with other agents or modalities of treatment.


Adult T-cell leukemia (ATL) presents a distinct clinicopathologic picture characterized by skin lesions, small peripheral adenopathy, hepatosplenomegaly, hypercalcemia, and a wide range of clinical course. Also, ATL is an endemic disease in the southwestern district of Japan, and closely associated with the first retrovirus isolated from ATL cells, human T-cell leukemia virus I (HTLV-I). Infiltration of the leukemic cells into the vital organs itself causes clinical problems, but patients with ATL are susceptible to and often die of opportunistic infections secondary to the underlying immune deficiency. Since conventional treatments such as combination chemotherapy and radiation therapy are immunosuppressive, treating these patients is very difficult. Other forms of therapy or new antineoplastic agents are required to control this disease.

Interferon is one of the significant biological response modifiers with antitumor activity against a variety of tumors including Acquired Immune Deficiency Syndrome-related Kaposi’s sarcoma, malignant lymphoma, and leukemias.

The development of recombinant techniques has facilitated the production of purified interferon in sufficient quantity for clinical trials. Therapy with recombinant alpha has resulted in clinical benefit with minor toxicity. It was also reported that there were 2 partial responders among 12 patients with chronic lymphocytic leukemia who were treated with a high dose of recombinant alpha interferon. However, interferon-β (IFN-β) and interferon-γ (IFN-γ) have been studied to a limited extent. We report the antitumor effects and toxicity of these two interferons for patients with ATL which have not been previously reported.

Patients and Methods

Interferon-β and IFN-γ were supplied by Kyowa Hakko Kogyo Co. Ltd., (Tokyo, Japan), and prepared from Escherichia coli as previously reported. The molecular weight of IFN-β and IFN-γ was estimated to be 20,040 and 17,100, respectively; the specific activity was $5 \times 10^7$ U and $5 \times 10^6$ Japan Reference Unit (JRU) per milligram of protein, respectively.

Ten patients who were diagnosed as having ATL during a period from April 1984 to August 1985 entered this pilot study. Six patients were treated with IFN-β, and IFN-γ was given to five patients. Patients 1 and 9 were the same patient who was treated with IFN-β first and then treated with IFN-γ upon relapse. The ages ranged from 35 to 71 years with an average performance status of 2 by World Health Organization (WHO) criteria (Table 1).
Adult T-cell leukemia was classified into a low- and high-risk group as previously defined depending on the number of leukemic cells and the presence of hypercalcemia. Patients were evaluated by means of physical and routine laboratory examinations as well as routine lymphoma staging work-ups except for lymphangiography. In addition, purified protein derivative (PPD) skin test, serum immunoglobulin level, serum anti-HTLV-I antibody, and proviral DNA of HTLV-I in the abnormal lymphoid cells were evaluated for immunocompetence and presence of HTLV-I as previously described. All had no prior therapy except Patient 1 (and Patient 9) who had received extensive combination chemotherapy including Adriamycin (doxorubicin), cyclophosphamide, and etoposide, and local radiation therapy to the large bulky skin lesions.

Treatment consisted of $36 \times 10^6$ U IFN-$\beta$ by 1-hour intravenous infusion daily for 5 days followed by 9 days off therapy or $36 \times 10^6$ U three times weekly for 4 weeks or longer. Administration of IFN-$\gamma$ was started daily at a dose of $1 \times 10^6$ JRU intramuscularly or by 1-hour intravenous infusion, and the dose was escalated every 3 days by one to two million units up to $8 \times 10^6$ JRU daily if only expected toxicities are experienced. The interferon was continued until relapse after the patients entered into remission.

Response criteria used in this study strictly adhere to tumor effects, and effects against the hosts such as improvement of immune deficiency, i.e., infections, and metabolic disturbance, i.e., hypercalcemia, are not considered, since there has been no widely accepted response criteria to such factors. A complete response (CR) is defined as complete disappearance of leukemic cells and all lymphomatous lesions, with normalization of bone marrow and peripheral blood pictures. A partial response (PR) is defined as a 50% decrease in leukemic cells and the product of the greatest perpendicular diameters of measurable lesions. This must last at least for 1 month and not be accompanied by increasing or new lesions. No change or stable disease (NC) represents the absence of significant increase (<25%) or decrease (<50%) in the number of leukemic cells or tumor size. Progressive disease (PD) is defined as a significant enlargement of an old lesion, increase in number of leukemic cells or development of new lesions.

### Results

The treatment results are shown in Tables 2 and 3. There are three PR cases in IFN-$\beta$ treatment group. However, the duration of response was rather short; 1, 1.5, and 12 months, respectively. All patients died of infection or hypercalcemia, except Patient 4, who had a PR to interferon and then relapsed in the lymph nodes associated with hypercalcemia. She is now being treated with combination chemotherapy.

One CR and two PRs were obtained in patients treated with IFN-$\gamma$ with a response duration of 4, 4, and 2 months,
respectively. Four patients died of infection and/or hypercalcemia. Patient 5, whose lymph nodes enlarged associated with hypercalcemia after 2 months of a PR, is now being treated with combination chemotherapy.

All patients with a PR relapsed while they were still on IFN-\(\beta\) or IFN-\(\gamma\) therapy, whereas IFN-\(\gamma\) had to be discontinued on one CR patient after 2.5 months of therapy because he underwent thoracotomy for recurrent pneumothorax from multiple bullae and died of respiratory failure associated with fungal pneumonia. Two of the partial responders were high-risk patients, and the remaining four responders including one CR patient fell into low-risk group.

Fever, chills, and fatigue were common side effects of these preparations. Mild hematologic depression and transient hepatic enzyme abnormalities were seen in five and four patients, respectively (Table 4). No cardiac or central nervous toxicity was noted in this study.

**Discussion**

Adult T-cell leukemia is an extremely difficult disease with which to cope. The median survival has been reported to be only 3 to 6 months despite intensive supportive as well as antileukemic treatment.\(^{15,16}\) The main reason why ATL patients die soon after diagnosis is the underlying immune deficiency associated with life-threatening opportunistic infection and uncontrollable hypercalcemia. Interferons were chosen for this study because of their significant biological activity including antiviral and antiproliferative properties and their potential use as an immunomodulator.

This study indicates that IFN-\(\beta\) and IFN-\(\gamma\) possessed antitumor activity against ATL (55% response rate), although the response duration was short. Most of the patients still died of infection and/or hypercalcemia suggesting interferon alone would not be able to control such complications. Two surviving patients relapsed in the lymph nodes after leukemic cells were reduced in number with IFN-\(\beta\) or IFN-\(\gamma\). It is of interest to note that the number of circulating leukemic cells was very few at the time of relapse in the lymph nodes. Two other patients with peripheral T-cell lymphoma not associated with HTLV-I also were treated with IFN-\(\beta\) or IFN-\(\gamma\). Both patients had rapidly enlarging lymph nodes after a complete remission had been obtained with combination chemotherapy. These patients were treated with interferon which had no effect on the rapidly growing tumors. This finding suggests that IFN-\(\beta\) and IFN-\(\gamma\) are active agents for leukemic cells in the peripheral blood and bone marrow, but it may be very difficult for interferon alone to control bulky tumors. It seems that there was not much difference in response to interferons between high- and low-risk patients as long as they were in the leukemic phase of the disease.

For IFN-\(\beta\) and IFN-\(\gamma\), there has been no other study to investigate their activity in ATL. In a large scale trial in Japan, natural alpha interferon (human lymphoblastoid interferon) had reportedly some activity on ATL, in which 16 patients entered the study and 10 patients were evaluable for effects.\(^{6}\) One CR and 2 PRs were reported (30% response rate). Toxicities appeared to be similar to those experienced in this study.

In conclusion, recombinant human interferon gamma and beta appear to play a definite role in treating the patients with ATL as an antiproliferative agent with 55% response rate. However, their immune modulating capabilities remain to be proven. Further basic as well as clinical studies should be designed to explore and assess these agents' ability to control this disease and its causative virus, HTLV-I.

**Table 3. Treatment Results for IFN-\(\gamma\)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total dose ((\times 10^6) JRU)</th>
<th>Response</th>
<th>Duration (mo)</th>
<th>Survival (mo)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>518</td>
<td>CR</td>
<td>4</td>
<td>4.5</td>
<td>Low</td>
</tr>
<tr>
<td>8</td>
<td>218</td>
<td>PR</td>
<td>4</td>
<td>5</td>
<td>High</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>PD</td>
<td>4</td>
<td>4</td>
<td>Low</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>NE</td>
<td>1.5</td>
<td>1.5</td>
<td>High</td>
</tr>
<tr>
<td>11</td>
<td>422</td>
<td>PR</td>
<td>2</td>
<td>2+</td>
<td>Low</td>
</tr>
</tbody>
</table>

CR: complete response; PR: partial response; NE: not evaluable; PD: progressive disease; JRU: Japan Reference Unit; IFN-\(\gamma\): interferon-\(\gamma\).

**Table 4. Side Effects of IFN-\(\beta\) and IFN-\(\gamma\) Treatment**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>IFN-(\beta) (%)</th>
<th>IFN-(\gamma) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>5 (83)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Chills</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (50)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (67)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>2 (33)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (83)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>5 (83)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>4 (67)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

IFN-\(\beta\): interferon-\(\beta\); IFN-\(\gamma\): interferon-\(\gamma\).

**REFERENCES**


AMERICAN CANCER SOCIETY

Research on Psychosocial and Behavioral Aspects of Cancer

The American Cancer Society recognizes the importance of conducting fundamental and applied investigations on the psychosocial and behavioral aspects of cancer and wishes to encourage research in these areas. Support will be provided by means of Research and Clinical Investigation Grants and through Grants in support of Personnel for Research. Applications will be peer-reviewed by the Scientific Advisory Committee on Psychosocial and Behavioral Research and the Council for Research and Clinical Investigation Awards. Support for short-term pilot projects may be obtained through the Society's Research Development Program. Descriptive brochures are available upon request from the Society.

The deadlines for receipt of applications for Research and Clinical Investigation Grants are April, 1 and November, 1. The deadlines for receipt of applications for Grants in Support of Personnel for Research are March, 1 and October, 1. There is no deadline for receipt of applications for Research Development Program Grants. Applications will be accepted for review at any time.

Interested individuals are invited to submit applications to:

American Cancer Society
Research Department
90 Park Avenue
New York, NY 10016

For additional information, please write to the above address or call Dr. John Stevens at (212) 973 8717 or Dr. John Laszlo at (212) 973 8736.