

BRIEF REPORT: TREATMENT OF ADULT T-CELL LEUKEMIA-LYMPHOMA WITH ZIDOVUDINE AND INTERFERON ALFA

OLIVIER HERMINE, M.D., DIDIER BOUSCARY, M.D.,
ANTOINE GESSAIN, M.D., PH.D.,
PASCAL TURLURE, M.D.,
VERONIQUE LEBLOND, M.D.,
NATHALIE FRANCK, M.D.,
AGNES BUZYN-VEIL, M.D.,
BERNARD RIO, M.D.,
ELISABETH MACINTYRE, M.D., PH.D.,
FRANÇOIS DREYFUS, M.D.,
AND ALI BAZARBACHI, M.D.

HUMAN T-cell lymphotropic virus type I (HTLV-I)¹ is the etiologic agent of adult T-cell leukemia-lymphoma.² The serum of patients with this disease contains antibodies to HTLV-I,³ and there is monoclonal integration of HTLV-I proviruses in the malignant cells.⁴ The principal clinical features of adult T-cell leukemia-lymphoma⁵ are lymphadenopathy, hepatosplenomegaly, skin lesions, and hypercalcemia. Compromise of the immune system can allow opportunistic infection. The blood contains abnormal lymphocytes with characteristic indented or convoluted nuclei ("flower cells"). These malignant lymphocytes are activated CD4-positive T cells with increased expression of the alpha chain of the interleukin-2 receptor.

Four different clinical subtypes of adult T-cell leukemia-lymphoma have been defined: smoldering, chronic, acute, and lymphomatous.⁶ These subtypes usually, but not necessarily, appear in sequence. The outcome of treatment of the acute and lymphomatous subtypes is disappointing.^{7,8} Combination chemotherapy,⁸ novel chemotherapeutic drugs,⁸ the interferons,⁹⁻¹¹ and monoclonal antibodies against the interleukin-2 receptor¹² can all induce long-term disease-free survival in a few patients, but overall survival is only 50 percent at five months.^{8,13} In contrast, the chronic and smoldering types of adult T-cell leukemia-lymphoma have a longer course, regardless of treatment, and aggressive chemotherapy may be more harmful than beneficial.

How HTLV-I induces adult T-cell leukemia-lymphoma is not well understood. HTLV-I infection may be the first event in an oncogenic process whose later steps are unknown. A cooperative effect between HTLV-I proteins or replicating virus and the mutation of cellular genes is possible.¹⁴ Antiretroviral therapy may therefore have the ability to control the proliferation of HTLV-I-infected cells. A preliminary report suggested that a combination of interferon alfa and zidovudine could induce a rapid and durable response in

patients with adult T-cell leukemia-lymphoma.¹⁵ In this paper we report the efficacy of this combination in one patient with smoldering disease and four patients with acute adult T-cell leukemia-lymphoma.

CASE REPORTS

Table 1 summarizes the main characteristics of the five patients. They were all found to have antibodies to HTLV-I by enzyme-linked immunosorbent assay and Western blotting. None of them had antibodies against human immunodeficiency virus type 1 or type 2. The diagnosis of adult T-cell leukemia-lymphoma and the classification of subtypes followed the criteria of Shimoyama.⁶ Patients 1, 2, 3, and 5 had acute disease; Patient 4 had the smoldering subtype. Clonal integration of the HTLV-I provirus was demonstrated in all patients by Southern blotting of DNA extracted from ether peripheral-blood mononuclear cells or biopsy material from involved skin, and hybridization with an HTLV-I-specific probe.¹⁶ Informed consent was obtained from each patient. The schedule and doses of zidovudine and interferon alfa for each patient are given. The doses of the two agents were reduced by half when there were hematologic toxic effects.

Responses to treatment were defined as follows. Complete remission and 95 percent remission corresponded to a normalization of the white-cell count, with no leukemic cells (i.e., cells affected by adult T-cell leukemia-lymphoma) and less than 5 percent leukemic cells on the blood smear, respectively, and the disappearance of all tumor masses, as determined on clinical and radiologic examination, and the normalization of serum levels of lactate dehydrogenase (to <290 IU per liter) and calcium (to <10 mg per deciliter [2.5 mmol per liter]). All these criteria had to be met for more than one month. Remissions of 75 percent and 50 percent corresponded to decreases by more than 75 percent and 50 percent, respectively, in tumor size, white-cell count, number of leukemic cells, and level of lactate dehydrogenase. Normalization of the serum calcium level was required. Leukemic cells were defined according to cytologic and immunophenotypic criteria. Table 2 gives the responses to treatment and follow-up.

Patient 1

Patient 1 was a 30-year-old Bulgarian woman who was hospitalized because of lymphadenopathy, leg pain, and infiltration of the skin of the ears and eyelids. She had received a blood transfusion four years earlier. The leukocyte count was 3.3×10^9 per liter, with 30 percent leukemic cells. The lactate dehydrogenase level was 400 IU per liter. X-ray films and a technetium-99m bone scan showed lytic bone lesions, but the serum calcium level was normal. Biopsy specimens of lymph node, bone marrow, and skin showed lymphomatous infiltration, with flower cells typical of adult T-cell leukemia-lymphoma, which were positive for CD2, CD3, and CD4 but negative for CD25. HTLV-I infection was confirmed by sequencing the viral genome.¹⁷

The woman received 250 mg of oral zidovudine every 12 hours and 5 million units of interferon alfa subcutaneously once a day, five days a week. No major side effects of this treatment were noticed. Four months after diagnosis she was in complete remission. The blood smear, bone marrow-biopsy specimen, x-ray film of bone, and technetium-99m bone scan were normal. The total duration of treatment was eight months. Four months after stopping treatment, she relapsed with diffuse skin infiltration and 80 percent leukemic cells in the blood. Lactate dehydrogenase and calcium levels were elevated. After one month of therapy with higher doses of zidovudine (250 mg every six hours) and interferon alfa (9 million units per day), the skin lesions disappeared and the calcium and lactate dehydrogenase levels returned to normal, but leukocytosis persisted (at 12×10^9 cells per liter), with 60 percent leukemic cells. Four months after relapse she was in complete remission. She continued to receive zidovudine and interferon alfa until she relapsed again, 20 months after diagnosis, with reappearing skin tumors and circulating leukemic cells. She was then given combination chemotherapy containing an anthracycline and was in a third complete remission 27 months after diagnosis.

Patient 2

Patient 2 was a 37-year-old Jamaican man who was hospitalized with small skin tumors on the chest and head and generalized lymphadenopathy. Laboratory examination revealed leukocytosis (30×10^9 cells per liter) with 72 percent leukemic flower cells. The lactate dehydrogenase level was 600 IU per liter. He received oral zido-

From the Departments of Clinical Hematology (O.H., A.B.-V.) and Biologic Hematology (E.M.), Hôpital Necker, Paris; the Departments of Clinical Hematology (D.B., F.D.) and Dermatology (N.F.), Hôpital Cochin, Paris; the Department of Retroviruses, Institut Pasteur, Paris (A.G.); the Department of Clinical Hematology, Hôpital Beaujon, Clichy (P.T.); the Department of Clinical Hematology, Hôpital de la Pitié, Paris (V.L.); and the Department of Clinical Hematology, Hôtel-Dieu, Paris (B.R., A.B.) — all in France. Address reprint requests to Dr. Hermine at the Service d'Hématologie Adulte, Hôpital Necker, 149 rue de Sevres, 75743 Paris CEDEX 15, France.

Table 1. Characteristics of HTLV-I-Positive Patients with Adult T-Cell Leukemia-Lymphoma Treated with Zidovudine and Interferon Alfa.

PATIENT NO.	AGE (YR)/SEX	DISEASE SUBTYPE*	SITE TESTED FOR HTLV-I CLONAL INTEGRATION†
1	30/F	Acute	Blood
2	37/M	Acute	Blood, skin
3	39/M	Acute	Blood
4	23/F	Smoldering	Blood
5	75/F	Acute	Blood

*According to the classification system of Shimoyama.⁶

†HTLV-I serologic testing was performed by the enzyme-linked immunosorbent assay, and the results were confirmed by the Western blot assay. Clonal integration of the HTLV-I provirus was determined by Southern blotting of DNA from peripheral-blood mononuclear cells or a biopsy specimen of involved skin.

zidovudine (1000 mg per day) and subcutaneous interferon alfa (9 million units per day). His skin lesions disappeared after one month of treatment. The lactate dehydrogenase level returned to normal, but leukocytosis persisted (25×10^9 cells per liter), with 90 percent lymphocytes but only 5 percent typical leukemic cells. The maximal response (75 percent remission) was obtained six months after diagnosis, with a normal white-cell count but 5 percent abnormal lymphocytes. Twelve months after diagnosis, he remained under treatment, with half-doses of zidovudine and interferon alfa, and in 75 percent remission.

Patient 3

Patient 3 was a 39-year-old man from the French West Indies who was hospitalized for nausea, vomiting, night sweats, and weight loss. He had splenomegaly and diffuse lymphadenopathy. Laboratory examination revealed hypercalcemia (serum calcium level, 18 mg per deciliter [4.5 mmol per liter]) and an elevated lactate dehydrogenase level (3000 IU per liter). The white-cell count was 10.5×10^9 per liter, with 40 percent leukemic cells that were positive for CD3, CD4, and CD25. The computed tomographic (CT) scan showed many enlarged abdominal lymph nodes. A lymph-node aspirate revealed many leukemic cells. Treatment with oral zidovudine (500 mg per day) and subcutaneous interferon alfa (4.5 million units per day) was started. Five days later, progression of tumor masses was observed, with the appearance of skin infiltration. The doses of interferon alfa and zidovudine were increased to 9 million units per day and 1 g (250 mg every six hours), respectively. Two weeks later, the peripheral and abdominal lymphadenopathy had disappeared, and the spleen was no longer palpable. The white-cell count was 1.5×10^9 per liter, with 33 percent neutrophils and 13 percent leukemic cells. The lactate dehydrogenase level decreased to 725 IU per liter.

One month after diagnosis, the patient had a partial response (75

percent remission); all tumor masses had disappeared, the white-cell count was 1.8×10^9 per liter, and there were 10 percent leukemic cells. Three months later, the patient discontinued his treatment. He was readmitted five months after diagnosis for severe hypercalcemia that was resistant to treatment with diphosphonates. The white-cell count was normal and the number of circulating atypical cells stable (6 percent), but the appearance of these cells was that of large-cell lymphoma rather than adult T-cell leukemia-lymphoma. Therefore, two courses of an anthracycline-containing regimen were administered. Clinical remission and a normal white-cell count with 1 to 6 percent leukemic cells were obtained after the first course. However, a relapse occurred three weeks after the second course of chemotherapy. Twelve months after the diagnosis, after a complex clinical course, the patient died of severe pseudomonas septicemia due to chemotherapy-induced neutropenia.

Patient 4

Patient 4 was a 23-year-old woman from French Guiana who was hospitalized for dyspnea. Her physical examination was normal, without lymphadenopathy, splenomegaly, or skin abnormalities. The white-cell count was 7.1×10^9 per liter, with 2×10^9 lymphocytes and 5 percent leukemic cells. A bone marrow aspirate showed occasional leukemic cells (5 percent). The immunophenotype of peripheral-blood cells was that of a CD4-positive, CD7-negative T-cell population of which 10 percent were CD25-positive cells. The serum calcium, hepatic-enzyme, and lactate dehydrogenase levels were normal. An abdominal CT scan was normal. A CT scan of the lung showed multiple nodular masses about 2 cm in diameter. Bronchoalveolar lavage and lung biopsy showed that the masses resembled those caused by cryptococcus. Treatment with amphotericin B (1 mg per kilogram of body weight per day for one month) led to improvement of the pulmonary lesions. Treatment with oral zidovudine (250 mg every six hours) and subcutaneous interferon alfa (9 million units per day) was started. Two months later, the patient's general condition was good, and the white-cell count had decreased to 2.1×10^9 per liter with 0.5×10^9 neutrophils, 1×10^9 lymphocytes, and 20 percent leukemic cells. Because of the patient's neutropenia, the doses of zidovudine and interferon alfa were reduced by half. Immune skin tests became weakly positive. Treatment was stopped six months after diagnosis. Six months later, the patient remained in 50 percent remission with 10 percent leukemic cells in the blood.

Patient 5

Patient 5 was a 75-year-old woman from the French West Indies who was hospitalized with generalized lymphadenopathy, hepatomegaly, splenomegaly, skin tumors, and low-grade fever. The white-cell count was 56.4×10^9 per liter, and 60 percent of the lymphocytes were characteristic of adult T-cell leukemia-lymphoma. A bone marrow aspirate showed massive infiltration of leukemic cells positive for CD2, CD3, CD4, CD5, and CD25 and negative for CD7. Biopsy specimens of skin and lymph node showed a T-cell lymphoma of the pleomorphic type. The lactate dehydrogenase level was 1100

Table 2. Responses of Five Patients to Treatment with the Study Drugs (Zidovudine and Interferon Alfa), with Salvage Therapy as Needed.

VARIABLE	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Response to study drugs	Complete	75%	75%	50%	Complete
Time to maximal response (mo)	4	6	1	6	6
Duration of treatment (mo)	8	9	4	6	12
Time from maximal response to disease progression (mo)	8	No progression	3	No progression	No progression
First salvage therapy	Study drugs	—	Study drugs	—	—
Second response	Complete	—	None	—	—
Time to progression (mo)	8	—	—	—	—
Second salvage therapy	Chemotherapy	—	Chemotherapy	—	—
Third response	Complete	—	75%	—	—
Time to progression (mo)	No progression	—	1	—	—
Third salvage therapy	—	—	Study drugs	—	—
Fourth response	—	—	75%	—	—
Time to progression (mo)	—	—	1	—	—
Total follow-up after diagnosis (mo)	27	12	12	12	12
Status at end of study	3rd Complete remission	75% Remission	Dead	50% Remission	1st Complete remission

IU per liter, and the serum calcium concentration 13 mg per deciliter (3.29 mmol per liter).

The hypercalcemia resolved rapidly after treatment with fluids and diphosphonates. Treatment with oral zidovudine (250 mg every six hours) and subcutaneous interferon alfa (9 million units per day) was started. Three weeks later the patient was afebrile, and the physical examination showed a decrease of approximately 70 percent in the lymphadenopathy and the skin tumors. The liver and spleen were no longer palpable. The white-cell count was 6.8×10^9 per liter with 4×10^9 lymphocytes and 6 percent leukemic cells. The hemoglobin level was 9 g per deciliter, and the platelet count 80×10^9 per liter. Levels of calcium and lactate dehydrogenase were normal. Treatment was tapered to 500 mg of zidovudine per day and 4.5 million units of interferon alfa per day. Six months after diagnosis, the patient had 95 percent remission and all tumor masses had disappeared, as assessed by clinical examination and abdominal CT; the calcium and lactate dehydrogenase levels were normal, as was the white-cell count, with 1 to 3 percent atypical flower cells. Twelve months after diagnosis and still in therapy, the patient continued in complete remission, with no detectable leukemic cells in the peripheral blood or the bone marrow aspirate.

DISCUSSION

Adult T-cell leukemia-lymphoma is an aggressive cancer of mature, activated T cells. Its poor prognosis is mainly due to resistance to chemotherapy.^{7,8} The median survival is 5 months in patients with the acute type and 10 months in patients with the lymphomatous type.^{8,13} Although the smoldering and chronic types have a better prognosis, no treatment has halted their progression to the acute type.⁷

In the present study, five previously untreated patients with adult T-cell leukemia-lymphoma received the combination of zidovudine and interferon alfa described in the preliminary report by Gill et al.¹⁵ Complete or partial remissions were obtained in all five. The patients had rapid responses, with reduced numbers of circulating leukemic cells, shrinkage of tumor masses, and a return of the serum calcium and lactate dehydrogenase levels to normal. Of four patients with acute adult T-cell leukemia-lymphoma, three were alive 27, 12, and 12 months after diagnosis (Patients 1, 2, and 5, respectively), which suggests that treatment with zidovudine and interferon alfa may prolong the survival of such patients. However, the salvage polychemotherapy administered to Patients 1 and 3 probably contributed to their relatively prolonged survival times.

Two patients (Patients 1 and 3) relapsed 12 and 4 months after diagnosis, while they were not receiving treatment. Maintenance therapy may be needed to prolong remission, because these two patients responded to retreatment with zidovudine and interferon alfa. Toxic effects in our patients were mild and mainly hematologic. Only one patient required red-cell transfusions. Profound pancytopenia was observed only when high doses of both zidovudine and interferon alfa were used. In Patient 4, the treatment and cure of an opportunistic infection were not hampered by treatment with interferon alfa and zidovudine. Although the role of HTLV-I replication in adult T-cell leukemia-lymphoma has not been fully elucidated,¹⁸⁻²¹ zidovudine and interferon alfa may block production of the virus. Alternatively, these drugs may act as cytotoxic drugs.²² The two mechanisms may not be mutually exclusive.

In conclusion, the combination of zidovudine and in-

terferon alfa had a beneficial effect in five patients with adult T-cell leukemia-lymphoma. Our experience with these patients suggests that treatment should begin with high doses of zidovudine (1000 mg per day) and interferon alfa (9 million units per day), with subsequent adjustment depending on the toxic effects. Further studies are needed to define the optimal doses and duration of treatment.

We are indebted to Erard Gilles, M.D. (Laboratoires Roche, Paris), who kindly provided recombinant interferon alfa (Roferon); and to Professors Bruno Varet, Robert Zittoun, and Georges Flandrin for helpful criticisms and suggestions.

REFERENCES

- Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A* 1980;77:7415-9.
- Wong-Staal F, Gallo RC. Human T-lymphotropic retroviruses. *Nature* 1985;317:395-403.
- Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukaemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci U S A* 1981;78:6476-80.
- Seiki M, Eddy R, Shows TB, Yoshida M. Nonspecific integration of the HTLV provirus genome into adult T-cell leukemia cells. *Nature* 1984;309:640-2.
- Takatsuki F, Yamaguchi K, Hattori T. Adult T-cell leukemia/lymphoma. In: Gallo RC, Wong-Staal F, eds. *Retrovirus biology and human disease*. New York: Marcel Dekker, 1990:147-59.
- Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: a report from the Lymphoma Study Group (1984-87). *Br J Haematol* 1991;79:428-37.
- Bunn PA Jr, Schechter GP, Jaffe E, et al. Clinical course of retrovirus-associated adult T-cell lymphoma in the United States. *N Engl J Med* 1983;309:257-64.
- Shimoyama M. Treatment of patients with adult T-cell leukemia-lymphoma: an overview. *Gann Monogr Cancer Res* 1992;39:43-56.
- Waldmann TA, White JD, Goldmann CK, et al. The interleukin-2 receptor: a target for monoclonal antibody treatment of human T-cell lymphotropic virus I-induced adult T-cell leukemia. *Blood* 1993;82:1701-12.
- Matsumura M, Yoneyama A, Nakamura T, et al. A first case of complete remission of beta-interferon sensitive adult T-cell leukemia. *Eur J Haematol* 1987;39:282-7.
- Tamura K, Makino S, Araki Y, Imamura T, Seita M. Recombinant interferon beta and gamma in the treatment of adult T-cell leukemia. *Cancer* 1987;59:1059-62.
- Ezaki K, Hirano M, Ohno R, et al. A combination trial of human lymphoblastoid interferon and bestabucil (KM2210) for adult T-cell leukemia-lymphoma. *Cancer* 1991;68:695-8.
- Kawano F, Yamaguchi K, Nishimura H, Tsuda H, Takatsuki K. Variation in the clinical courses of adult T-cell leukemia. *Cancer* 1985;55:851-6.
- Hölsberg R, Hafler DA. Pathogenesis of diseases induced by human lymphotropic virus type I infection. *N Engl J Med* 1993;328:1173-82.
- Gill P, Masood R, Cai J, et al. Novel antiviral therapy for adult T-cell leukemia secondary to HTLV-I infection. *Blood* 1992;80:Suppl 1:74a. abstract.
- Gabarre J, Gessain A, Raphael M, et al. Adult T-cell leukemia/lymphoma revealed by a surgically cured cardiac valve lymphomatous involvement in an Iranian woman: clinical, immunopathological, and viromolecular studies. *Leukemia* 1993;7:1904-9.
- Picard F, Dreyfus F, Le Guern M, et al. Acute T-cell leukemia/lymphoma mimicking Hodgkin's disease with secondary HTLV I seroconversion. *Cancer* 1990;66:1524-8.
- Popovic M, Lange-Wantzin G, Sarin PS, Mann D, Gallo RC. Transformation of human umbilical cord blood T cells by human T-cell leukemia/lymphoma virus. *Proc Natl Acad Sci U S A* 1983;80:5402-6.
- Franchini G, Wong-Staal F, Gallo RC. Human T-cell leukemia virus type (HTLV-I) transcripts in fresh and cultured cells of patients with adult T-cell leukemia. *Proc Natl Acad Sci U S A* 1984;81:6207-11.
- Berneman ZN, Gartenhaus RB, Reitz MS Jr, et al. Expression of alternatively spliced human T-lymphotropic virus type I pX mRNA in infected cell lines and in primary uncultured cells from patients with adult T-cell leukemia/lymphoma and healthy carriers. *Proc Natl Acad Sci U S A* 1992;89:3005-9.
- Bazarbachi A, Saal F, Lasneret J, et al. Unintegrated HTLV-I proviral DNA in cell lines and uncultured peripheral blood mononuclear cells from tropical spastic paraparesis (TSP/HAM) and adult T-cell leukemia (ATL) patients. *C R Acad Sci III* 1994;317:264-9.
- Tosi P, Visani T, Ottaviani G, Gamberi E, Cenacchi B, Tura S. Synergistic cytotoxicity of AZT plus alpha and gamma interferon in chronic myeloid leukemia cell line K562. *Eur J Haematol* 1993;51:209-13.