

TREATMENT OF ADULT T-CELL LEUKEMIA-LYMPHOMA WITH A COMBINATION OF INTERFERON ALFA AND ZIDOVUDINE

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Abstract *Background.* Infection with the human T-cell lymphotropic virus type I, a retrovirus, can cause a distinctive cancer, adult T-cell leukemia-lymphoma. The median survival of patients with the acute and lymphomatous forms of the disease is short, despite the use of cytotoxic chemotherapy.

Methods. We treated 19 patients with acute or lymphomatous forms of adult T-cell leukemia-lymphoma with oral zidovudine (200 mg five times daily) and interferon alfa (Intron A, 5 million to 10 million units subcutaneously each day). Seven of these patients had either relapsed after multiagent cytotoxic chemotherapy or failed to respond to that treatment.

Results. Major responses were achieved in 58 percent of the patients (11 of 19), including complete remission in 26 percent (5 of 19). Four patients in whom prior cytotoxic therapy had failed had major responses, two of which were complete remissions. Six patients have survived for more than 12 months, with the longest remission since the discontinuation of treatment lasting more than 59 months.

Conclusions. The combination of zidovudine and interferon alfa has activity against adult T-cell leukemia-lymphoma, even in patients in whom prior cytotoxic therapy has failed. This regimen should be evaluated further for its role in the treatment of adult T-cell leukemia-lymphoma. (N Engl J Med 1995;332:1744-8.)

ADULT T-cell leukemia-lymphoma is etiologically linked to the human T-cell lymphotropic virus type I (HTLV-I).¹⁻³ HTLV-I, a retrovirus, is endemic in southern Japan and the Caribbean basin and occurs sporadically in Africa, Latin America, the Middle East, and the United States.⁴⁻⁸ Adult T-cell leukemia-lymphoma occurs in less than 5 percent of people with HTLV-I infection, with an average latency period of more than 30 years.^{9,10} A cellular immune deficiency in affected patients allows opportunistic infections to develop.^{11,12}

Adult T-cell leukemia-lymphoma is a heterogeneous disease that has been classified into four main categories.¹³ In the relatively indolent smoldering and chronic forms, the median survival is two years or more. In the acute and lymphomatous forms, which resist cytotoxic chemotherapy, the median survival ranges from 3.7 to 6.0 months.¹¹⁻¹⁵ Among the poor prognostic features associated with the acute and lymphomatous forms are hypercalcemia, elevated serum levels of lactate dehydrogenase, poor performance status, age over 40 years, and multiple sites of disease.¹²

Various regimens of cytotoxic chemotherapy have been used to treat patients with the acute and lymphomatous forms of adult T-cell leukemia-lymphoma, but the rates of complete response are below 30 percent and the responses lack durability.¹²⁻¹⁶ Interferon alfa,

beta, and gamma have been evaluated in several small series of patients. They produced complete remission in less than 10 percent, although occasional durable responses have been reported.¹⁷⁻²¹

New treatments are thus needed for the acute and lymphomatous forms of this disease. Cells affected by adult T-cell leukemia-lymphoma express high levels of interleukin-2 receptor α , and treatment with monoclonal antibody to that receptor, alone or conjugated to yttrium, has yielded encouraging results.^{22,23} We found that the combination of zidovudine and interferon alfa induced a rapid and durable response in a patient with adult T-cell leukemia-lymphoma who was coinfecting with both human immunodeficiency virus type 1 (HIV-1) and HTLV-I.²⁴ This observation prompted us to evaluate further the efficacy of zidovudine and interferon alfa in adult T-cell leukemia-lymphoma.

METHODS

Patients

Patients with serologic evidence of HTLV-I infection by an enzyme-linked immunosorbent assay, confirmed by the Western blot assay, and with either the acute or the lymphomatous form of adult T-cell leukemia-lymphoma as defined by Shimoyama¹³ were studied. Acute adult T-cell leukemia-lymphoma was defined on the basis of the morphologic and flow-cytometric identification of circulating leukemic cells of T-cell lineage and the presence of any one of the following: hypercalcemia, lactate dehydrogenase levels more than twice the upper limit of normal, central nervous system disease, malignant ascites, or pleural effusion. Lymphomatous adult T-cell leukemia-lymphoma was defined by the presence of nodal or extranodal lymphomatous masses of tumor cells with a T-cell phenotype and histopathological changes characteristic of the disease. No patient had received cytotoxic chemotherapy for at least two weeks immediately preceding entry into the study.

Extent of Disease

The extent of the disease was established before the start of treatment by physical examination; chest radiography; computed axial tomography, magnetic resonance imaging, or both of the head, chest, abdomen, and pelvis; bone marrow aspiration and biopsy; and the examination of cerebrospinal fluid. Biopsy specimens of cutaneous le-

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sions were obtained for histopathological documentation. Other investigations were performed as clinically indicated. All initial disease sites were reevaluated both at the time of the maximal clinical response and at the conclusion of all therapy.

Treatment

Patients received 200 mg of zidovudine (Burroughs Wellcome, Research Triangle Park, N.C.) orally five times daily (every four hours while awake, 1000 mg per day). Five million units of recombinant interferon alfa (Intron A, Schering-Plough, Kenilworth, N.J.) was given subcutaneously each day, with the dose escalated to 10 million units daily one week later if constitutional symptoms related to treatment with interferon alfa were acceptable. Complete blood counts, serum electrolyte determinations, and renal- and liver-function tests were performed weekly for four weeks and every two weeks thereafter. Both agents were withheld until the resolution of nonhematologic toxic effects of grade 3 or higher, and they were then reinstated at 50 percent of the previous dose. In the event of hematologic toxic effects, the two agents were withheld if the neutrophil count fell below 0.5×10^9 per liter or if the platelet count fell below 25×10^9 per liter, or until the neutrophil count rose to more than 0.75×10^9 per liter, the platelet count to more than 75×10^9 per liter, or both. Therapy was then reinstated at 50 percent of the previous dose. Treatment was continued for at least four weeks after the onset of complete remission or for up to one year in the absence of such a remission. Supportive therapies and treatment for central nervous system involvement were provided at the discretion of the treating physician.

Criteria for Responses

A complete response was defined as the resolution of all malignant disease for four weeks or more. In patients with bone marrow or cutaneous involvement, biopsy was repeated to confirm the response. A partial response was defined as a reduction of 50 percent or more in measurable indexes of disease that lasted four weeks or more, without the development of new lesions or progression of disease at any site, but without the achievement of a complete response. Progressive disease was defined as an increase of 25 percent or more in measurable disease or in the number of circulating leukemic cells. Patients with complete or partial responses that lasted less than four weeks were classified as having had minor responses.

Clonal Integration of HTLV-I in Peripheral-Blood Lymphocytes

Clonal integration of HTLV-I proviral DNA was demonstrated by the Southern blot assay. High-molecular-weight DNA was extracted from peripheral-blood mononuclear cells, and the DNA samples were digested with the restriction enzymes *Bam*HI, *Hind*III, and *Eco*RI (New England Biolabs, Beverly, Mass.) for 16 hours at 37°C and then fractionated according to size on 0.8 percent agarose gel, transferred to nitrocellulose, and hybridized with ³²P-labeled full-length HTLV-I complementary DNA.²⁴

Statistical Analysis

Survival time was defined as the period from the start of treatment to the date of death, with median survival defined as the 50 percent point on the Kaplan-Meier curve.²⁵ Data on patients who were alive or lost to follow-up were censored as of the date the patients were last seen. Various factors were examined by Fisher's exact test²⁶ for possible association with the occurrence of a major response to therapy. These factors included serum lactate dehydrogenase levels more than twice the upper limit of normal, hypercalcemia, Karnofsky score for performance status of less than 30, age over 40 years, prior chemotherapy, and the presence of constitutional symptoms. The effect of these factors and the response to therapy with respect to survival were analyzed by the log-rank test.²⁷

RESULTS

Nineteen patients entered the study. Table 1 summarizes their demographic characteristics and the characteristics of their disease at base line. Four patients had

Table 1. Demographic Variables and Characteristics of Disease in the 19 Patients with Adult T-Cell Leukemia-Lymphoma at Entry into the Study.

VARIABLE*	VALUE
Sex — no.	
Female	12
Male	7
Age — yr	
Median	48
Range	16–88
Karnofsky score for performance status — no. (%)	
≥30	13 (68)
<30	6 (32)
Geographic origin — no. (%)	
Caribbean	7 (37)
Japan	2 (11)
United States	5 (26)
Other†	5 (26)
Features of disease — no. (%)	
Circulating leukemia	15 (79)
Lymphadenopathy	14 (74)
Pleural effusions or ascites	9 (47)
Cutaneous involvement	9 (47)
Hepatosplenomegaly	7 (37)
Central nervous system involvement	5 (26)
Lytic bone lesions	4 (21)
HTLV-I-associated myelopathy	2 (11)
Constitutional symptoms — no. (%)	15 (79)
Concurrent HIV-1 infection — no. (%)	4 (21)
Laboratory values — mean ±SD	
Leukocytes (per mm ³)	63,932 ± 20,112
Serum LDH (units/liter)	1,398 ± 330
Serum calcium (mg/dl)‡	11.7 ± 0.76

*HTLV-I denotes human T-cell lymphotropic virus type I, HIV-1 human immunodeficiency virus type 1, and LDH lactate dehydrogenase.

†These patients came from Liberia, Egypt, Iran, Mexico, and Peru.

‡To convert values for calcium to millimoles per liter, multiply by 0.25.

concurrent HIV-1 infection without a previous illness that defined their condition as being the acquired immunodeficiency syndrome, and none had ever received zidovudine therapy. Seven patients either had not responded or had relapsed after combination cytotoxic chemotherapy for adult T-cell leukemia-lymphoma; two had had major responses lasting three and six months. All the patients had widely disseminated disease; 17 had adult T-cell leukemia-lymphoma in its acute form, and 2 had the lymphomatous form. The Karnofsky scores of six patients (32 percent) were below 30. The serum lactate dehydrogenase level was more than twice the upper limit of normal in 13 patients (68 percent), and the serum calcium level was elevated in 11 (58 percent).

Immunophenotypic studies of blood or marrow showed that the malignant cells were CD4+ in all cases. Clonal integration of HTLV-I was found in the peripheral-blood mononuclear cells of 10 patients among 13 studied.

Response to Treatment

Eleven of the 19 patients (58 percent) had major responses to zidovudine and interferon alfa (Table 2). There were complete responses in five patients (26 percent) and partial responses in six (32 percent). Of the seven patients in whom prior chemotherapy had failed, four had major responses, two of which were complete

remissions, after treatment with zidovudine and interferon alfa. The median time that elapsed before the start of a complete or partial response was 33 days (range, 5 to 168) (Fig. 1). Decreases in the number of circulating leukemic cells were observed in all patients with leukemic involvement and were associated with the normalization of hypercalcemia and with a decline in serum lactate dehydrogenase levels.

Two of the five patients who had complete responses had concurrent HIV-1 infection; one died of HIV-related wasting syndrome, and the other died of bacterial pneumonia, 22 and 29 months, respectively, after the start of therapy with zidovudine and interferon alfa. The three remaining patients with complete responses remained alive after more than 15, 16, and 63 months had elapsed since the start of therapy; at this writing, the last two of these patients had received no therapy for more than 10 and 59 months. Among the six patients with partial responses, one whose previous chemotherapy had failed lived for 13 months after the start of treatment with zidovudine and interferon alfa. Another continued to receive therapy after more than five months. The other four had responses of short duration, lasting from one to five months. Six of the 11 patients (55 percent) who had either complete or partial responses lived more than one year.

It is noteworthy that in seven of the eight patients who did not have major responses there was a rapid decline in the number of circulating leukemic cells, with decreases ranging from 53 to 100 percent. Two of these seven patients died without evidence of disease, but within less than four weeks of entering remission, at days 28 and 45. The remaining five died of leukemia or related complications. In the only patient who had no objective evidence of tumor regression, hypercalcemia nevertheless resolved. This patient's clinical course was complicated by pulmonary aspergillosis and an intraocular lymphoma; he died of progressive disease 10 months after starting therapy.

None of the following factors were significantly correlated with the response to therapy: a serum lactate dehydrogenase level more than twice the upper limit of normal, hypercalcemia, age over 40 years, prior chemotherapy, and the presence of constitutional symptoms. In the analysis of Karnofsky scores for performance

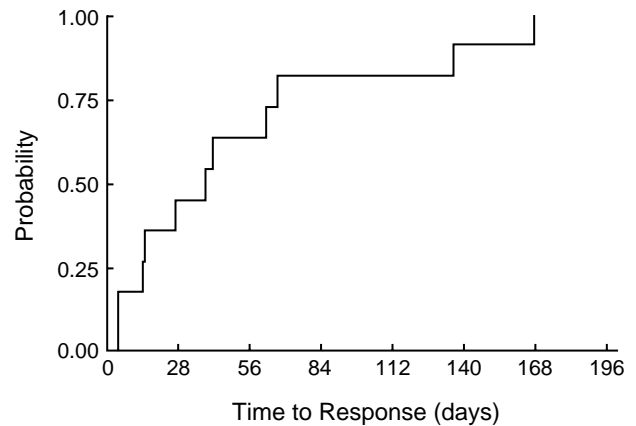


Figure 1. Time to the Start of the Response in 11 Patients with Complete or Partial Responses.

status, the patients with complete responses all had scores of 30 or above. Nine of the 13 patients with Karnofsky performance scores of 30 or above (69 percent) had complete or partial responses, as compared with 2 of the 6 patients with scores below 30 (33 percent). These results show strong trends, but the differences were not statistically significant.

The same factors were analyzed for their effect on survival. The median overall survival in all 19 patients was 3.0 months. The median survival in patients with complete or partial responses to the therapy was 13.0 months, whereas in patients with minor responses and patients who did not respond, it was 1.3 months ($P < 0.001$ by the log-rank test). Karnofsky performance scores of 30 or above were predictive of prolonged survival (median survival, 13 months, vs. 1.6 months in patients with scores of < 30 ; $P = 0.003$). No other factors had a significant effect on survival. Furthermore, there was no significant difference in survival between the patients who had received prior chemotherapy and those who had not ($P = 0.88$) (Fig. 2).

Toxicity and Adverse Events

Table 3 summarizes the toxic effects of treatment. Five patients had grade 4 neutropenia, and four of them also had grade 4 thrombocytopenia. Therapy was delayed for up to four weeks in these five patients; they all received granulocyte colony-stimulating factor, and four received transfusions of platelets. Because of anemia, eight patients required transfusions of red cells during therapy; two others were given recombinant erythropoietin. Ten patients had transient elevations in liver enzymes.

Other toxic effects included low-grade fever in eight patients, fatigue with weakness in seven, and diarrhea in two. Three patients had nausea and vomiting or abdominal discomfort. One patient had mild peripheral neuropathy and reported anorexia two weeks after the start of therapy. There were infectious complications in eight patients: bacterial infections occurred in six, and opportunistic infections (aspergillosis and *Pneumocystis carinii* pneumonia) in two others. One patient with a

Table 2. Treatment Outcomes.

GROUP AND RESPONSE*	No. (%)	MEDIAN SURVIVAL (MO)†
Previously untreated patients (n = 12)		
Complete or partial	7 (58)	16.0
Minor or none	5 (42)	1.7
Patients with prior chemotherapy that failed (n = 7)		
Complete or partial	4 (57)	17.5
Minor or none	3 (43)	1.2
All patients (n = 19)		
Complete or partial	11 (58)	13.0
Minor or none	8 (42)	1.3

*Patients with no response had progressive disease.

†Median survival was calculated by the Kaplan-Meier method.

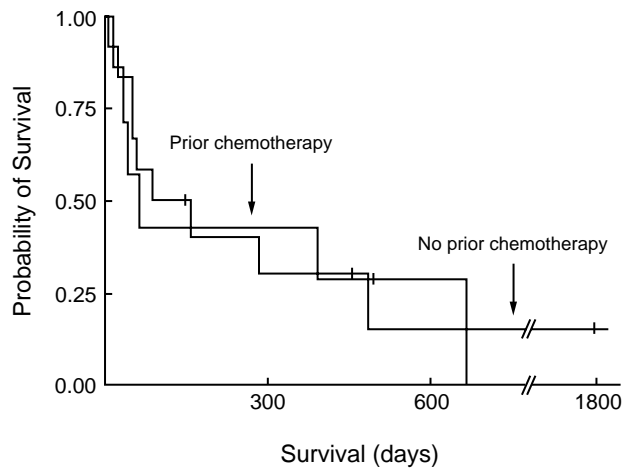


Figure 2. Comparison of Survival between Patients Who Received Prior Chemotherapy and Those with No Prior Chemotherapy.

When survival in the 7 patients whose prior chemotherapy failed was compared with that in the 12 patients with newly diagnosed disease, no significant differences were noted ($P=0.88$ by the log-rank test). Four patients remained alive as of December 30, 1994.

complete response had transient episodes of syncope after four weeks of therapy that recurred on rechallenge with zidovudine and interferon alfa; therapy was discontinued.

DISCUSSION

The combination of zidovudine and interferon alfa produced complete or partial responses in 58 percent of 19 patients with acute or lymphomatous forms of adult T-cell leukemia-lymphoma. Five patients had complete responses. The median survival among the 11 patients who had complete or partial responses was 13.0 months. The results in seven patients who had had treatment failures or relapses after prior cytotoxic chemotherapy are noteworthy. Four of these patients had complete or partial responses, and three of them remained alive one year or more after the start of treatment with zidovudine and interferon alfa. The median survival of 17.5 months in these patients was thus similar to that in the patients who had not had prior chemotherapy. It is also noteworthy that seven of the eight patients who did not have complete or partial responses nonetheless had reductions of 53 to 100 percent in the number of circulating leukemic cells. Thus, the regimen of zidovudine and interferon alfa has potent antileukemic effects in adult T-cell leukemia-lymphoma and does not appear to be cross-resistant with cytotoxic chemotherapy.

No alternative therapy has been available for patients with adult T-cell leukemia-lymphoma who do not respond to cytotoxic chemotherapy. In one study of seven such patients, only one patient responded to subsequent multiagent chemotherapy.¹⁵ Among six patients in whom prior chemotherapy failed, only one partial response to pentostatin was documented.¹⁶ In a more re-

cent study, 14 patients with acute or lymphomatous adult T-cell leukemia-lymphoma whose prior therapy failed were treated with irinotecan. Partial responses were documented in four, and a complete response in one.²⁹ None of the three patients with acute adult T-cell leukemia-lymphoma had responses. Moreover, none of the responses were durable; relapse appeared after a median of 31 days in the patients with responses.²⁹ In contrast with these results, our study suggests that a combination of zidovudine and interferon alfa can be efficacious in relapsed or refractory adult T-cell leukemia-lymphoma.

It is not possible to conclude that treatment with zidovudine and interferon alfa is superior to cytotoxic chemotherapy in untreated patients with this disease. Only one prospective clinical trial in patients with newly diagnosed adult T-cell leukemia-lymphoma has been reported; a combination of vincristine, cyclophosphamide, prednisolone, and doxorubicin, with or without methotrexate, was used in 54 patients. There were complete remissions in 28 percent, and the median survival in all 54 patients was approximately six months.¹¹ Our series is smaller, but the complete-remission rate of 26 percent is similar. The shorter median survival in our series may be explained by the fact that 32 percent of the patients we studied had Karnofsky performance scores below 30; all six of these patients survived less than two months. Randomized trials comparing zidovudine and interferon alfa with the best available regimen of cytotoxic chemotherapy thus appear warranted.

The mechanism of the antileukemic activity of zidovudine and interferon alfa is unknown. Zidovudine can exert cytostatic effects by terminating DNA replication,³⁰ and this effect may be enhanced by interferon alfa. Zidovudine was recently shown to block the transformation of normal peripheral-blood lymphocytes that were cocultured with HTLV-I-transformed cell lines. Furthermore, zidovudine prevented a disease similar to adult T-cell leukemia-lymphoma from being produced by the propagation of HTLV-I-transformed cell lines in rabbits.³¹ One clinical report demonstrated an apparently direct antitumor effect of zidovudine in a patient with adult T-cell leukemia-lymphoma who had pulmonary infiltration.³² Interferon alfa has multiple biologic effects, such as the inhibition of protein synthesis and cell growth³³ and the induction of expression

Table 3. Hematologic and Hepatic Toxic Effects.*

VARIABLE AFFECTED	TOXIC EFFECTS		
	GRADE 2	GRADE 3	GRADE 4
	<i>no. (%) of patients</i>		
Absolute neutrophil count	5 (26)	5 (26)	5 (26)
Hemoglobin	5 (26)	11 (58)	0
Platelets	3 (16)	3 (16)	4 (21)
Liver enzymes [†]	5 (26)	5 (26)	0

*The Common Cancer Toxicity Criteria²⁸ were used in the grading of toxicity.

[†]Denotes the serum levels of alanine aminotransferase and aspartate aminotransferase.

of major histocompatibility complex I and II molecules.^{34,35} Interferon alfa has also occasionally induced therapeutic responses in patients with adult T-cell leukemia-lymphoma.¹⁷⁻²¹ Its effect in this disease may therefore result from enhanced immunologic recognition of cells affected by adult T-cell leukemia-lymphoma, direct antiproliferative effects, and synergism with zidovudine.

We conclude that zidovudine and interferon alfa are a highly active combination in patients with advanced adult T-cell leukemia-lymphoma, including those in whom multiagent chemotherapy has failed. The optimal uses for this combination and its precise mechanism or mechanisms of action remain to be determined.

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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.
- Reitz MS Jr, Poiesz BJ, Ruscetti FW, Gallo RC. Characterization and distribution of nucleic acid sequences of novel type C retrovirus isolated from neoplastic human T lymphocytes. *Proc Natl Acad Sci U S A* 1981;78:1887-91.
- Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood* 1977;50:481-92.
- Blattner WA, Kalyanaraman VS, Robert-Guroff M, et al. The human type-C retrovirus, HTLV, in blacks from the Caribbean region, and the relationship to adult T-cell leukemia/lymphoma. *Int J Cancer* 1982;30:257-64.
- Hinuma Y, Komoda H, Chosa T, et al. Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. *Int J Cancer* 1982;29:631-5.
- Saxinger W, Blattner WA, Levine PH, et al. Human T-cell leukemia virus (HTLV-I) antibodies in Africa. *Science* 1984;225:1473-6.
- Meytes D, Schochat B, Lee H, et al. Serological and molecular survey for HTLV-I infection in a high-risk Middle Eastern group. *Lancet* 1990;336:1533-5.
- Robert-Guroff M, Weiss SH, Giron JA, et al. Prevalence of antibodies to HTLV-I, -II, and -III in intravenous drug abusers from an AIDS endemic region. *JAMA* 1986;255:3133-7.
- Tajima K, Ito S-I, Tsushima ATL Study Group. Prospective studies of HTLV-I and associated diseases in Japan. In: Blattner WA, ed. *Human retrovirology: HTLV*. New York: Raven Press, 1990:267-79.
- Murphy EL, Hanchard B, Figueroa JP, et al. Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. *Int J Cancer* 1989;43:250-3.
- Shimoyama M, Ota K, Kikuchi M, et al. Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA or VEPA-M. *J Clin Oncol* 1988;6:128-41.
- Lymphoma Study Group. Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study. *Leuk Res* 1991;15:81-90.
- Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma: a report from the Lymphoma Study Group (1984-87). *Br J Haematol* 1991;79:428-37.
- Hanchard B, Gibbs WN, Lofters W, et al. Adult T-cell leukemia/lymphoma (ATL) in Jamaica. In: Blattner WA, ed. *Human retrovirology: HTLV*. New York: Raven Press, 1990:173-83.
- 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.
- Lofters W, Campbell M, Gibbs WN, Cheson BD. 2'-Deoxycytosine therapy in adult T-cell leukemia/lymphoma. *Cancer* 1987;60:2605-8.
- Ichimaru M, Kamihira S, Moriuchi Y, et al. Clinical study on the effect of natural α -interferon (HLBI) in the treatment of adult T-cell leukemia. *Jpn J Cancer Chemother* 1988;15:2975-81. (In Japanese.)
- Kamihira S, Soda H, Kinoshita K, Ichimaru M. Effect of human lymphoblast interferon in adult T-cell leukemia and non-Hodgkin's lymphoma. *Jpn J Cancer Chemother* 1983;10:2188-93. (In Japanese.)
- Kimura K, Cooperative Study Group of Ro 22-8181 in Japan. Phase II study of recombinant leukocyte A interferon (Ro 22-8181) in hematological malignancies. *Jpn J Cancer Chemother* 1985;12:928-35. (In Japanese.)
- Matsushima M, Yoneyama AW, 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.
- Waldmann TA, Goldman CK, Bongiovanni KF, et al. Therapy of patients with human T-cell lymphotropic virus I-induced adult T-cell leukemia with anti-Tac, a monoclonal antibody to the receptor for interleukin-2. *Blood* 1988;72:1805-16.
- Waldmann TA, Goldman CK, Top L, et al. The treatment of HTLV-I-associated adult T-cell leukemia (ATL) with genetically engineered monoclonal antibodies armed with radionuclides. *J Acquir Immune Defic Syndr* 1993;6:671. abstract.
- Shibata D, Brynes RK, Rabinowitz A, et al. Human T-cell lymphotropic virus type I (HTLV-I)-associated adult T-cell leukemia-lymphoma in a patient infected with human immunodeficiency virus type 1 (HIV-1). *Ann Intern Med* 1989;111:871-5.
- Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley, 1980.
- Mehta CR, Patel NR. A network algorithm for performing Fisher's exact test in $R \times C$ contingency tables. *J Am Stat Assoc* 1983;78:427-34.
- Tarone RE, Ware J. On distribution-free tests for equality of survival distributions. *Biometrika* 1977;64:156-60.
- Investigator's handbook: a manual for participants in clinical trials of investigational agents sponsored by the Division of Cancer Treatment, National Cancer Institute. Rev. ed. Washington, D.C.: Government Printing Office, 1993. (NIH publication no. 93-2770.)
- Tsuda H, Takatsuki K, Ohno R, et al. Treatment of adult T-cell leukemia-lymphoma with irinotecan hydrochloride (CPT-11). *Br J Cancer* 1994;70:771-4.
- Furman PA, Fyfe JA, St Clair MH, et al. Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. *Proc Natl Acad Sci U S A* 1986;83:8333-7.
- Isono T, Ogawa K, Seto A. Antiviral effect of zidovudine in the experimental model of adult T cell leukemia in rabbits. *Leuk Res* 1990;14:841-7.
- Saito N, Takemori N, Hirai K, Onodera R, Watanabe S, Namiki M. Suppression of HTLV-I-induced human leukemia cell infiltration by zidovudine. *Am J Hematol* 1994;47:246-7.
- Gendelman HE, Baca L, Turpin J, et al. Regulation of HIV replication in infected monocytes by IFN- α : mechanisms for viral restriction. *J Immunol* 1990;145:2669-76.
- Friedman RL, Manley SP, McMahon M, Kerr IM, Stark GR. Transcriptional and posttranscriptional regulation of interferon-induced gene expression in human cells. *Cell* 1984;38:745-55.
- Morris A, Tomkins PT, Maudsley DJ, Blackman M. Infection of cultured murine brain cells by Semliki Forest virus: effects of interferon-alpha beta on viral replication, viral antigen display, major histocompatibility complex antigen display and lysis by cytotoxic T lymphocytes. *J Gen Virol* 1987;68:99-106.