A REPORT TO PHYSICIANS

OncoLog

April–June 1984

THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER
M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

Volume 29, Number 2

Alpha Interferon Induces High Response In Patients with Hairy-Cell Leukemia

by Jorge R. Quesada, MD, Department of Clinical Immunology and Biologic Therapy; James M. Reuben, PhD, Department of Clinical Immunology and Biologic Therapy; John T. Manning, MD, Department of Pathology; Evan M. Hersh, MD, Department of Clinical Immunology and Biologic Therapy; and Jordan U. Gutterman, MD, Department of Clinical Immunology and Biologic Therapy

This article is a summary of a paper that first appeared in The New England Journal of Medicine *310(1): 15-18, January 1984.*

The treatment of patients with hairy-cell leukemia remains controversial, and treatment results have been frequently unsatisfactory. Although splenectomy can occasionally restore hematologic values to normal, a substantial number of patients have no response or only a transient one. Chemotherapy successfully induces remission in only a minority of patients and is often complicated by severe side effects. Recently, other treatments, such as allogeneic mononuclear cell transfusions, nonspecific immunotherapy, and leukapheresis, have improved hematologic values in these patients; these results, however, have been temporary or require the use of cumbersome technology.

Because hairy-cell leukemia is a slow-growing malignancy usually expressing a B-lymphocyte phenotype, we conducted a study to determine whether alpha interferon, which has induced remission in patients with B-cell neoplasms and slow-growing tumors, could control hairy-cell leukemia. Results of the study indicate that alpha interferon may be one of the most effective and least toxic treatments for patients with this disease.

Methods

Six men and 1 woman, aged 26 to 51 years (median, 39), were treated. The diagnosis of hairy-cell leukemia was made on the basis of clinical characteristics and the demonstration of typical hairy cells in peripheral blood, bone marrow, or tissue specimens. A tartrate-resistant acid phosphatase stain of bone marrow was positive in 6 of the 7 patients, and in 3 the diagnosis was further confirmed by electron microscopy. Five of the 7 patients had undergone splenectomy (6 to 48 months before alpha interferon therapy). Two patients had not been treated previously. In all patients, there was evidence of progressive disease at the time of enrollment in the study.

Alpha interferon was obtained from the State Serum Institute, Finnish Red Cross Center, Helsinki, Finland. The material was partially purified to a specific activity of 1×10^6 units/mg of protein. All patients received a daily dose of 3×10^6 units administered by intramuscular injection on an outpatient basis.

A complete remission was defined as: (1) an absence of hairy cells in the bone marrow aspirate and biopsy specimen; (2) a value for bone marrow granulocytes above 35%, defined as the sum of the percentages of myelocytes, metamyelocytes, and

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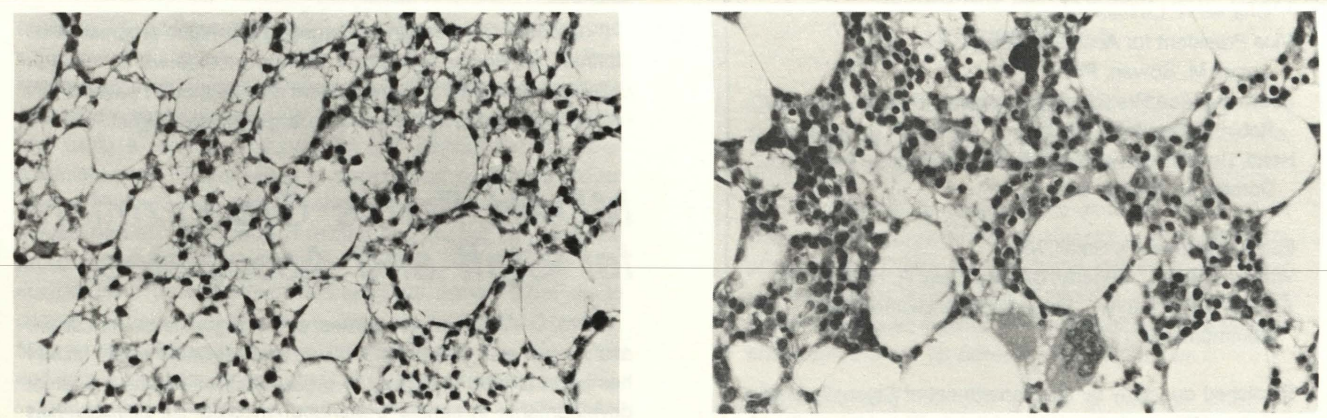

Light photomicrographs illustrate bone marrow biopsy specimens taken from a patient 6 months before alpha interferon treatment (left) (Rx: 1-5-83) and 2 months after treatment (right). Approximately 80% of the cells in the pretreatment specimen photo are hairy cells. (Note the monomorphous leukemic cell population.) After treatment, the bone marrow has recovered its normal polymorphous composition of hematopoietic elements (megakaryocytes and erythroid and myeloid cells) as shown; hairy cells in this specimen comprise no more than 20% of the total cell population. (Both hematoxylin-eosin-stained sections X250.) (Photomicrographs were provided by John T. Manning, MD, Department of Pathology.)

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Research of Magnetic Drug-Delivery Method Underway

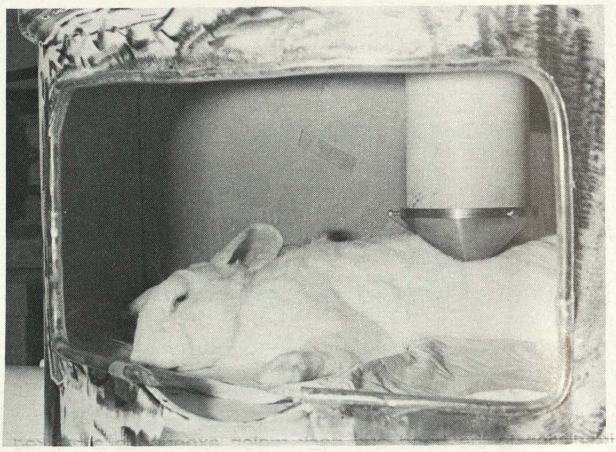
A new method of magnetically targeting high concentrations of cytotoxic drugs to specific tumor sites is currently being investigated at UT MDAH.

According to Arthur W. Boddie, MD, Department of Surgery, who heads this project, the method works by incorporating a cytotoxic drug into magnetized particles or cells and, after intravenous or intra-arterial injection, targeting these drug-laden carriers to the tumor site by the use of a powerful electromagnet.

A research electromagnet, specially designed and built by the J. R. Woodruff Company and the National Electric Coil Company, was acquired by UT MDAH in 1982 for use of this method in animal studies. This electromagnet is designed to produce a 6000- to 8000-G magnetic field over a 4-in pole gap. A small animal can be placed on the ground plane between the magnetic poles and the drug-laden magnetized particles electromagnetically directed to the tumor site.

The primary advantage of the magnetic targeting method is that only the tumor is exposed to maximal concentrations of the cytotoxic drug, thus alleviating the problem of systemic toxicity. According to Dr Boddie, the method may increase concentration of a drug at the tumor site by 30% over that achieved with systemic methods of drug administration.

In the present phase of the project, Dr Boddie is searching for an effective magnetic drug carrier. In other studies of this technique, drugs bound to most types of carriers, such as denatured albumin particles, when injected intravenously, were taken up by the reticuloendothelial system, thus limiting the use of this method. Working with Christopher Poynton, MD, Department of Hematology, and Christopher Reading, PhD, Departments of Tumor Biology and Hematology, Dr Boddie has found ghost red blood cells incorporated with cobalt colloid particles to be possible effective carriers of a cytotoxic drug. "Magnetized ghost red blood cells should be somewhat less susceptible to reticuloendothelial uptake than other types of magnetic particles," Dr Boddie said. Uptake by the reticuloendothelial system will be further diminished by administering compounds that temporarily block the system, such as dextran. This carrier method, if successful, should allow the targeting of drugs to any tumor site.



Use of the electromagnet, built for magnetic drug-targeting experiments in animals, is shown. After the rabbit is injected with cytotoxic-drug-laden magnetized particles, it is placed on the ground plane between the magnetic poles of the electromagnet. With a force of 6000 to 8000 G, the electromagnet directs high concentrations of the drug to the tumor site.

Ultimately, Dr Boddie hopes to combine magnetic targeting with regional hyperthermia. "Hyperthermia is synergistic with a number of chemotherapeutic agents," Dr Boddie explained. "We plan to target drugs magnetically to the tumor site, then focus heat into the region to amplify the effect."

If research of the magnetic targeting technique progresses as planned, Dr Boddie is hopeful that the method will be used in patients within 2 to 3 years. Use of this method in patients will require the construction of a much larger electromagnet.

MDAH Forms Organization for Staff and Associates

UT M. D. Anderson Associates, a new organization for current and former staff members, fellows, and residents of UT MDAH has been formed to convey to organization members the latest developments in cancer treatment; to recognize distinguished achievements of current and former staff members, fellows, and residents; and to provide members with a forum for dialogue.

For more information and an application form, please contact UT M. D. Anderson Associates, HMB Box 223, 6723 Bertner, Houston, Texas 77030, (713) 792-8573.

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Daily Fluoride Routine Prevents Radiation- and Drug-Induced Caries in Cancer Patients

by Terence J. Fleming, DDS, Department of Dental Oncology

This article is a summary of a paper that first appeared in Current Problems in Cancer: Dental Oncology *VII (10): 37-41, April 1983.*

For many years clinicians have observed the damaging effects of cancer therapy on the oral structures. Patients receiving irradiation to the head and neck region experience a marked decrease in salivary secretion. This permanent radiation-induced xerostomia has been found to be significant in producing extreme susceptibility to caries. Salivary secretion is also suppressed temporarily in patients receiving the antiemetic medications often prescribed during chemotherapy.

To alleviate the problem of caries in high-risk patients at UT MDAH, a strict oral hygiene program involving the daily topical application to the teeth of a fluoride gel has been established. This program has proven to be highly effective in patients with radiation- or drug-induced xerostomia.

The need for such a program was made clear after several studies of the effects of radiation on the oral structures of head and neck cancer patients at UT MDAH. In one study a dose of 200 rad per day to all major salivary glands was found to cause a decrease in the salivary flow rate of 57% after five treatments (1 week), a decrease of 76% after 30 treatments (6 weeks), and a continued progressive decrease that resulted (3 years after completion of radiation therapy) in a flow rate of 5% of the pretreatment flow rate. Another UT MDAH study demonstrated a 100-fold increase in the concentration of a caries-associated microbe, *Streptococcus mutans,* 30 months after irradiation.

The same investigation studied the effectiveness of a caries prevention program consisting of daily oral hygiene and topical 1% sodium fluoride (NaF) application. The patients were randomized into three groups: (1) those having oral hygiene and daily topically applied 1% NaF; (2) those on an oral hygiene regime, receiving daily topically applied 1% NaF, and having a restricted sucrose diet; and (3) those on an oral hygiene regime and using a nonfluoride-containing gel. During the first post-treatment year, 81% of cases of caries occurred in patients not receiving the fluoride gel. Essentially no differences were observed between the group receiving fluoride gel only and the group randomized to receive the fluoride plus the restricted sucrose diet. These excellent clinical results, using 1% NaF gel to prevent radiation caries, have been authenticated recently. Meanwhile, continuous fluoride investigations have shown the additional plaque-inhibition benefit of stannous fluoride (SnF_2).

The caries prevention program presently used at UT MDAH involves the daily topical application of a 0.4% SnF_2 gel combined with strict oral hygiene procedures. Patients are encouraged to brush after each meal. Once daily, after a thorough brushing, flossing, and rinsing, patients apply the 0.4% SnF_2 gel to the teeth for a minimum of 5 but preferably 10 minutes by means of custom-fabricated polypropylene fluoride carriers. After fluoride application, the patients swish the accumulated saliva and residue gel for approximately 1 minute and then empty their mouths. The patients do not disturb the applied fluoride film by further rinsing, drinking, or brushing for 30 minutes.

The 0.4% SnF_2 gel, which is available commercially (GelKam, Scherer Laboratories, Inc., Dallas) has a pH of 3.2. Although this

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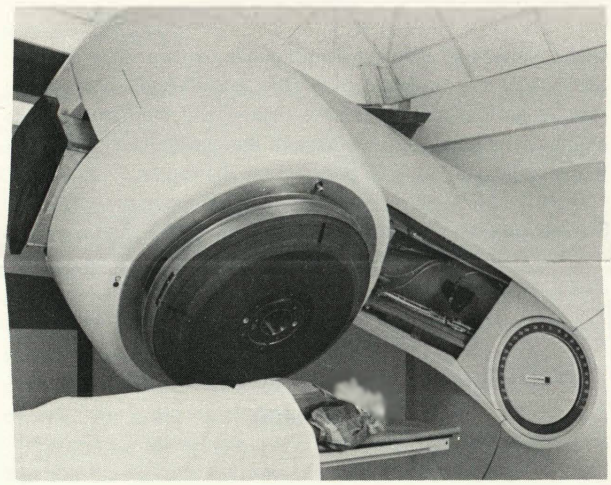
Cyclotron Provides Fast-Neutron Therapy for Patients with Radioresistant Tumors



Use of the cyclotron's isocentric-head delivery system for fast-neutron therapy is demonstrated. The isocentric head, used exclusively for treatment, is able to rotate 200° and thus deliver the fast-neutron beam to almost any site of disease.

UT MDAH is now operating the first U.S. cyclotron specifically designed for cancer therapy and research. The new cyclotron not only provides fast-neutron therapy for patients with tumors resistant to conventional radiotherapy (x-ray or cobalt-60) but also produces radionuclides to aid in cancer diagnosis and research.

According to Lester J. Peters, MD, head of the Division of Radiotherapy, the cyclotron was installed because of the favorable results of a pilot study conducted at Texas A & M University between October 1972 and February 1980. UT MDAH researchers, who used the Texas A & M variable-energy cyclotron for *neutron treatment of cancer patients*, found fast-neutron therapy to be highly effective in controlling disease at various sites.

Encouraged by these results, UT MDAH and The University of Texas Medical Branch at Galveston cooperatively initiated the building of a neutron therapy facility at UT MDAH in 1977. Unlike other cyclotrons in the U.S. designed primarily for research in physics and chemistry, the UT MDAH cyclotron, completed in September of last year, is the first in the nation designed specifically for fast-neutron therapy and isotope production.

The cyclotron is a charged-particle, negative-ion accelerator that produces a high-energy neutron beam by bombarding a beryllium target with 42 MeV protons at a current up to 200 μA. The beam is extracted into one of five beam lines with target areas housed in three rooms; remotely controlled carbon stripping foils are used to direct the beam. A fixed-energy, 26-MeV port is provided for radioactive gas production; a fixed-energy 42-MeV port and a 11- to 42-MeV variable-energy port are provided for liquid and solid radioisotope production. The target area for these ports is housed in an isotope-production room. There are two fixed-energy 42-MeV ports provided for two therapy rooms: one containing an isocentric-head delivery system and the other a horizontal-beam delivery system. The two rooms are encircled by 7-ft-thick reinforced concrete walls that absorb atomic particles.

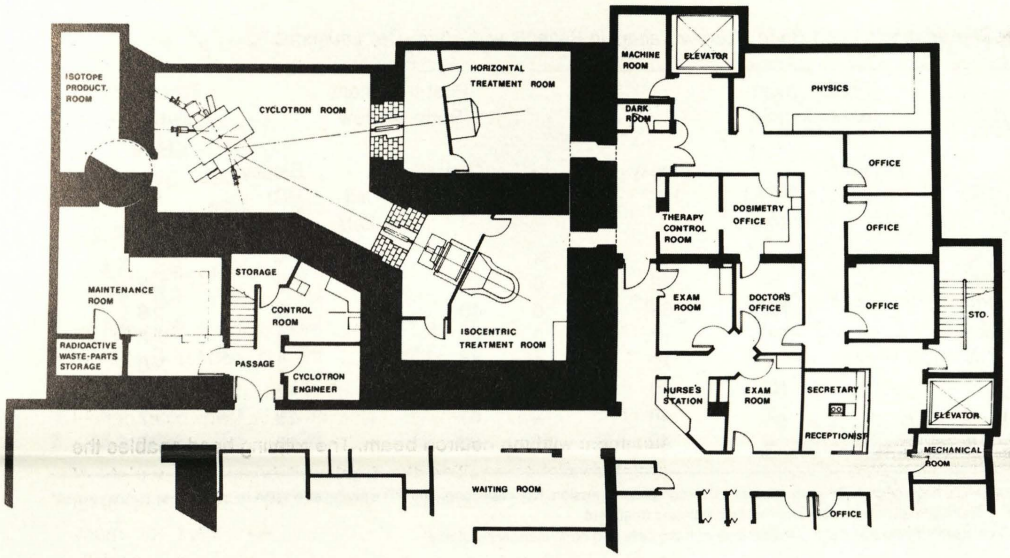
The isocentric-head delivery system, used exclusively for patients, is a special feature of the UT MDAH cyclotron, according to James R. Marbach, PhD, Departments of Physics and Clinical Radiotherapy, a clinical physicist involved in patient treatment with the neutron beam. The rotating head enables the radiotherapist to position the treatment beam at a variety of angles around the patient. "The isocentric head has been available for conventional radiotherapy equipment for many years, but its use with a machine of this power is especially advantageous," he said.

According to Moshe Maor, MD, Department of Clinical Radiotherapy, clinical director of the neutron therapy program, one of the principal reasons for the effectiveness of fast-neutron treatment is that, unlike photons used in conventional radiotherapy, fast neutrons can more easily kill tumor cells that have a poor oxygen supply. These cells, generally found in large solid tumors that have outgrown the blood vessel network, are more radiosensitive to the neutron beam because of its pattern of energy deposition. "The neutron blazes a path of destruction through the tumor cells, whereas the photon has a skip pattern of injury and, therefore, is less effective against dense unoxygenated tumors," Dr Peters explained.

The more powerful neutron beam is also effective because, unlike other forms of radiotherapy, it causes almost irreparable cell damage. In addition, the neutron beam is effective throughout the cell cycle. "It is not as dependent as other forms of radiotherapy on catching the cancer cell at specific, more radiosensitive stages in the cell-division cycle," Dr Maor said.

Nevertheless, neutron therapy is preferable to conventional forms of radiotherapy only in selected patients, according to Dr Peters. Patients with tumors that have good repair capacity, are slow growing, are poorly oxygenated, or are resistant, for any reason, to conventional radiation are most likely to benefit from fast-neutron treatment. Those patients with soft tissue and bone sarcomas, advanced rectal, prostate, bladder, and uterine cancers, pancreatic and stomach cancer, kidney cancer, advanced head and neck cancers (especially of the salivary glands and thyroid), and some lung cancers are currently being accepted for fast-neutron treatment. Fast-neutron treatment, however, cannot be used to control disease at a site that has been previously irradiated by conventional means.

The side effects of neutron therapy are qualitatively similar to those of conventional radiotherapy. Irritation of the skin and mucous membrane or lining of organ tissue may occur soon after treatment. Gradual thickening or fibrosis of deeper tissue may occur months later. Although acute reactions are rare, neutron therapy may cause more severe late effects than x-ray or cobalt-60.



The cyclotron facility floor plan illustrates the cyclotron, its five beam lines, and three target areas (left side), housed in two treatment rooms and an isotope-production room. Offices and laboratories (right side) for personnel involved in cyclotron operations are included in the facility.

The cyclotron also greatly facilitates diagnosis and research with its isotope-producing capability. According to Roy S. Tilbury, PhD, Department of Internal Medicine, who heads the radioisotope production program, the cyclotron makes isotopes of elements naturally occurring in the body, such as carbon, nitrogen, and oxygen, for use in quantitative biochemistry. The cyclotron produces a high-energy proton beam that strikes the nucleus of a common element, transforming the element into an unstable isotope. By labeling naturally occurring elements with their corresponding isotopes and using these isotopes as tracers, more accurate measurements of these elements in the body can be obtained. Isotopes made of elements foreign to the body, such as technetium-99, can never be regarded as true chemical tracers; they are not able to be totally metabolized with the natural element to which they are attached. "With cyclotron-produced isotopes, however, we can label oxygen with oxygen-15, for example, and measure oxygen metabolism in the brain," Dr Tilbury said. "This is important because oxygen and glucose are the only two metabolites the brain uses."

Presently, Dr Tilbury is studying the use of cyclotron-produced isotopes for measuring pH in tissue. "We know that tumor tissue has a lower pH than normal tissue. If we can develop an agent that can measure pH," he explained, "it might give useful diagnostic information and aid in the selection of treatment."

Cyclotron-produced isotopes will eventually be used at UT MDAH to perform receptor-site assays as well. For example, estradiol can be labeled with radioisotopes and measured in vivo to determine whether a breast tumor is or is not estrogen dependent. This assay now must be performed in vitro with a tissue sample.

Finally, cyclotron-produced isotope implants will be used for therapy. At present, the most common radioactive materials implanted in tumors are radioactive "gold seeds," irradiated pieces of gold sealed in platinum tubing, that emit a high-energy radiation to which both the patient and surgeon are exposed. Another isotope used for treatment, iodine-125, has low-energy radiation but a long half-life, which reduces the isotope's therapeutic efficacy. Though experimental, Dr Tilbury has devised a plan to make cesium-131, a low-energy cyclotron-produced isotope with a short half-life, for tumors that can not be surgically removed or treated by other means.

To handle the high levels of radioactivity associated with the isotope program, a "hot" laboratory designed for processing radioactive materials is under construction. Radioactive isotopes will be transported automatically through special tubing between the cyclotron facility and the "hot" laboratory.

According to Dr Peters, the UT MDAH cyclotron is a prototype machine for other research hospitals. Three other U.S. hospitals have obtained grants to build cyclotrons with similar capacities. "Although the cyclotron is not a panacea," Dr Peters said, "its potential for therapy and isotope-producing capability offer exciting possibilities for cancer treatment and research."

(Physicians desiring additional information should write or call Moshe Maor, MD, Department of Clinical Radiotherapy, MDAH Box 276, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030 (713) 792-3410.—ED)

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TABLE 1. *Clinical Characteristics and Bone Marrow Values in Patients with Hairy-Cell Leukemia**

Pt. No. Sex/Age	Prior Splenectomy	Response To IFNα	Pretreatment Bone Marrow				Post-treatment Bone Marrow				Treatment Duration (Mo.)†
			Aspirate			Biopsy	Aspirate			Biopsy	
			HC	GR	B-Cell Markers	HC‡	HC	GR	B-Cell Markers	HC‡	
			%	%		%	%	%		%	
1 M/39	+	CR	38	14	+	28	0	62	–	0	>6
2 M/26	+	CR	17	14	ND	33	0	40	–	0	>8
3 M/34	+	CR	32	15	ND	17	0	64	–	0	>6
4 M/46	+	PR	39	3	+	72	0	46	–	3	>8
5 F/47	–	PR	53	6	ND	30	5	64	–	12	>6
6 M/51	–	PR	Dry		ND	48	4	61	+	19	>7
7 M/31	+	PR	48	10	+	42	18	60	+	10	>10

*Abbreviations are as follows: IFNα = alpha interferon, HC = hairy cells, GR = granulocytes, CR = complete remission, ND = not done, and PR = partial remission.
†Patients were entered into study at different times; response in all patients is sustained by continued treatment.
‡The percentage of hairy cells in biopsy specimens represents the product of the percentage of hairy cells and bone marrow cellularity.

Hairy-Cell Leukemia . . .

Continued from page 1

neutrophils; (3) a normal distribution of cell membrane markers of bone marrow mononuclear cells, as determined by the use of fluorescein-labeled monoclonal antibodies; and (4) restoration of the following values: the hemoglobin level to 12 g/dl or more, the absolute neutrophil count to 1500 or more cells/μl, and the platelet count to 100,000 or more cells/μl.

A partial remission was defined as: (1) a decrease in the hairy-cell leukemia infiltrate of more than 50% from pretreatment values, (2) a value of bone marrow granulocytes above 35%, and (3) restoration of the peripheral-blood values as indicated above.

Results

Table 1 shows the clinical characteristics and bone marrow values of the patients. All patients responded to treatment; 3 had a complete remission, and 4 had a partial remission.

A decrease in the proportion of hairy cells was documented in the bone marrow aspirates from all 7 patients. In 6 patients, the proportion of hairy cells was 5% or less within 8 to 12 weeks after the initiation of treatment. Serial bone marrow biopsies confirmed the absence of hairy cells in the 3 patients who had a complete remission (Table 1). Studies of cell membrane markers in the bone marrow were performed before treatment in 3 patients and after treatment in all patients. Pretreatment specimens showed a predominance of cells with the B phenotype (cells positive for surface immunoglobulins and Ia and B1 antigens). Post-treatment specimens showed a normal phenotypic distribution of mononuclear cells in the 3 patients who had a complete remission and in 2 of the 4 with a partial remission. The other 2 patients continued to have an abnormal number of cells with the B phenotype.

Concurrently, a marked increase in the proportion of bone marrow granulocytes was seen in all patients (Table 1). Before treatment, the proportion of granulocytes in the bone marrow ranged from 3 to 15% (median, 14%). After treatment, the range of the proportion of granulocytes was 40 to 64% (median, 61%). In Patient 6, the pretreatment bone marrow aspirates were repeatedly dry; the bone marrow cellularity increased after treatment, and the proportion of bone marrow granulocytes reached a maximum of 61% by the 20th week of therapy. In addition, bone marrow monocytes (0.5 to 6%) were identified in 5 patients who had previously lacked them. The effects of alpha interferon on the bone marrow differential count were seen within the first 2 to 4 weeks after initiation of treatment.

A rise in the level of hemoglobin occurred in all 6 patients with anemia (Table 2). Pretreatment values ranged from 9.3 to 12.9 g/dl (median, 11.0 g/dl), whereas post-treatment levels ranged from 12.6 to 14.5 g/dl (median, 14.4 g/dl) in the absence of transfused blood products. All patients had an increase in circulating granulocytes, including patients with severe granulocytopenia before treatment. In 3 patients, granulocyte counts of 1500 or more cells/μl were reached within 8 weeks. In all 5 patients with leukopenia, increments in the white cell counts occurred more gradually. In one patient with leukocytosis, alpha interferon reduced the leukocyte count to the normal range and caused an attendant rise in the granulocyte count. Of 4 patients with thrombocytopenia, 2 had normal platelet counts within 3 weeks after the initiation of therapy, and the other 2 within 8 weeks. Alpha interferon did not adversely affect the platelet count in 3 patients with normal pretreatment values.

Remissions were sustained with daily administration of alpha interferon in 4 patients and with doses given 3 times per week in 3 patients who had been treated for longer than 6 months.

Treatment with alpha interferon was well tolerated by the majority of patients. All patients exhibited a transient influenza-like syndrome that has been described in other cancer patients treated with alpha interferon. Six patients reported slight fatigue and anorexia, but all 6 continued their normal activities; no notable weight loss occurred. One patient reported severe fatigue, asthenia, and apathy, symptoms that were reversed by temporary discontinuation of treatment.

TABLE 2. *Peripheral Blood Values in Patients with Hairy-Cell Leukemia**

Pt. No.	Pretreatment Peripheral Blood				Post-treatment Peripheral Blood			
	HG	WC	Neutrophils	Platelets	HG	WC	Neutrophils	Platelets
	g/dl	cells × $10^3/\mu l$			g/dl	cells × $10^3/\mu l$		
1	9.7	2.9	0.2	71	14.4	5.5	4.1	444
2	12.9	8.0	1.4	342	14.5	8.4	2.3	350
3	11.0	2.4	1.2	263	14.5	4.2	2.6	368
4	11.0	3.1	0.2	148	14.4	3.8	2.0	314
5	10.3	1.8	0.5	85	12.6	3.6	2.9	531
6	9.3	1.4	0.4	116	13.3	2.3	1.8	209
7	15.5	29.4	2.0	196	14.9	6.8	5.6	299

*Abbreviations are as follows: HG = hemoglobin, WC = white cells.

Two patients with a history of repeated infections contracted infections within the first 2 weeks after initiation of therapy (lobar pneumonia and soft tissue infection). One other patient had a miliary pulmonary infiltrate of probable fungal origin, which responded to the administration of ketoconazole. No infections occurred in any patient after the first 8 weeks of treatment.

Discussion

In our experience, no other form of treatment has been so consistently effective in achieving remissions in patients with hairy-cell leukemia. When treatment was initiated, all patients had evidence of slowly progressive disease, but none had severe pancytopenia. Whether alpha interferon can induce a similar tumor response in more advanced stages of the disease is not known. Also, the small number of patients in this study and the short time to follow-up preclude statements regarding the long-term efficacy of the treatment or its impact on survival.

The mechanisms responsible for the antitumor activity of alpha interferon and the ensuing benefit in the hematologic values are probably multifactorial. A direct antitumor effect on the malignant cells would allow repopulation of the bone marrow by displaced or inhibited normal blood cell precursors. Alpha interferon has been shown to have a potent antiproliferative effect on lymphoma cell lines in vitro, as well as antitumor effects in patients with B-cell or T-cell neoplasms. In this regard as mentioned above, hairy cells often express a B-lymphocyte phenotype. One other intriguing possibility is that alpha interferon induces differentiation of the malignant cells; it is known to induce differentiation of a leukemic cell line in vitro.

The high sensitivity of hairy-cell leukemia to alpha interferon contrasts with the lower response rate of other B-cell neoplasms, such as nodular lymphocytic lymphoma and multiple myeloma. This high sensitivity may be due to the presence of the Tac antigen, which has been recently described in hairy-cell leukemia and which may indicate a unique stage of B-cell differentiation. The Tac antigen, found in T cells, is associated with the receptor for interleukin 2. A similar rapid tumor response to alpha interferon has been reported in patients with cutaneous T-cell lymphoma. This suggests that the effect of alpha interferon may somehow be related to the interleukin 2 membrane receptors.

Interestingly, the hematologic effect of alpha interferon in patients with other malignant conditions is characterized by a decrement in the peripheral leukocyte and granulocyte counts, as well as a steady decrease in the hematocrit. In vitro test results have shown that alpha interferon blocks granulopoietic differentiation of committed bone marrow colony-forming units. The prompt hematologic effects induced by alpha interferon in patients with hairy-cell leukemia suggest the existence of a functional reserve of cell progenitors, which are influenced to proliferate as a result of treatment. This effect has not been observed in patients receiving other types of treatment.

Numerous biologic effects on the immune system have been ascribed to alpha interferon, some of which may also have influenced the results of our study. For example, alpha interferon is able to activate cytotoxic cells of the immune system; this system is severely impaired in patients with hairy-cell leukemia. Because the synthesis of alpha interferon in the body has been found to be influenced by a chromosome X-linked locus in mice, it is tempting to speculate that patients with hairy-cell leukemia, which occurs predominately in men, have a chromosome X-related deficiency of alpha interferon; this condition may be alleviated by exogenous interferon administration.

In support of this idea, male patients who have Epstein-Barr virus infection with chromosome X-linked immunodeficiency have been found to have a high incidence of B-cell lymphoma. Epstein-Barr virus has been associated with the pathogenesis of hairy-cell leukemia.

Finally, there is increasing evidence that the activation or rearrangement of oncogenes is important in the pathogenesis of B-cell neoplasms and other tumors. Recently, an oncogene coding for a growthlike factor has been described in avian and human B-cell lymphoma. A related gene may also be involved in hairy-cell leukemia. Interferon has been shown to suppress the expression of the protein product of at least one oncogene, suggesting that this mechanism may also have been involved in the antitumor effects observed in our patients.

Regardless of the mechanism, the rapid improvement that occurs in the absence of adverse side effects suggests that interferon is therapeutic in patients with hairy-cell leukemia, including those in whom splenectomy is not desirable. We used a partially pure preparation of alpha interferon that contained numerous interferon subtypes. We hope to confirm our results with purified species of alpha interferon.

Further studies of the mechanisms of action of interferon in hairy-cell leukemia may offer a greater understanding of the disease and increase our knowledge of how interferon works. Hairy-cell leukemia, thus, should provide a disease model for more in-depth study of the diverse biologic effects of interferon, which may have application in the treatment of other malignancies.

(Physicians desiring additional information should write or call Jorge R. Quesada, MD, Department of Clinical Immunology and Biologic Therapy, MDAH Box 55, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030 (713) 792-3527.—ED)

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is more acidic than the 1% NaF, the soft tissue irritations experienced by patients during radiation therapy and sometimes even into the postradiation period have been a problem for less than 2% of our patients.

In evaluating patients and categorizing those who are in the high-risk caries-susceptible group, many clinicians fail to consider the overall contributions of the various salivary glands to the total salivary secretion. Frequently, the decision as to the necessity of placing patients on a fluoride program is based solely on the relative radiation effect on the parotid glands. Investigations have shown this to be incorrect. Under mechanical stimulation (mastication), the contribution of the parotid glands constitutes 58% of the whole saliva; 33% of saliva is supplied by the submandibular glands, 1.5% by the sublingual glands, and 7.5% by the minor accessory salivary glands. The contribution to the total salivary secretion from the parotid glands during the resting state (other than mastication or sleep) is 21.5%; the submandibular glands contribute 71%; the sublingual glands 2.0%; and the minor accessory glands 6.5%. The parotid secretion during sleep is zero; the submandibular gland secretion constitutes 72%; the sublingual glands provide 14%; and the minor accessory glands another 14%.

Clinical observations indicate that patients treated with radiation to the upper neck fields (submaxillary triangle area), such as the postlaryngectomy patient or the patient with a lesion at the base of the tongue or floor of the mouth, have the greatest permanent degree of xerostomia. As expected, such patients who do not comply with the preventive caries program manifest the greatest degree of the typical rampant caries pattern associated with the loss of salivary protection.

Patients undergoing cancer therapy are highly caries susceptible, either temporarily from drug-induced xerostomia or permanently from radiation-induced xerostomia. Clinical experience has shown that fluoride treatments professionally applied at irregular intervals do not provide the necessary degree of protection for these patients. It is essential that this special group of patients follow a continuous daily self-applied topical fluoride program, combined with a high degree of daily oral hygiene and regular professional dental care.

(Physicians desiring additional information should write or call Terence J. Fleming, DDS, Department of Dental Oncology, MDAH Box 9, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030 (713) 792-6945.—ED)

The University of Texas System Cancer Center
M. D. Anderson Hospital and Tumor Institute
at Houston
and
The University of Texas
Health Science Center at Houston

Conference on AIDS: Diagnosis and Management

June 8–10, 1984

Warwick Post Oak Hotel
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Chairpersons: Guy R. Newell, MD, Department of Cancer Prevention, and Peter W. A. Mansell, MB BCH, FRCS, Department of Cancer Prevention

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