PAN AMERICAN ALLERGY SOCIETY

The 1989 training course and seminar will be held in San Antonio, Tex., March 8–12.

Contact Betty Kahler at the Society, 411 E. College, Fredericksburg, TX 78624; or call (409) 297-5636.

CHICAGO SCHOOL OF MEDICINE

The following programs will be held: "The Psychiatric Interview" (Chicago, March 10–12); "New Techniques in ENT" (Vail, Colo., March 19–25); and "Advances in Gynecology" (Chicago, March 31–April 2).

Contact Univ. of Chicago, Ctr. for Cont. Medical Educ., 5841 S. Maryland, Box 139, Chicago, IL 60637; or call (312) 702-1056.

MIDWEST CENTER FOR OCCUPATIONAL HEALTH AND SAFETY

The following courses will be offered in St. Paul, Minn.: "10th Annual Occupational Medicine Update" (March 10) and "Comprehensive Industrial Hygiene Review" (March 13–17, April 10–14, and Aug. 14–18).

Contact Ruth K. McIntyre, MCOHS, St. Paul–Ramsey Medical Ctr., 640 Jackson St., St. Paul, MN 55101; or call (612) 221-3992.

ARIZONA CANCER CENTER

The 7th winter symposium will take place in Snowbird, Utah, March 11–17.

Contact Mary Humphrey, Arizona Cancer Ctr., Tucson, AZ 85724; or call (602) 626-2276.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION

The 15th annual marketing section meeting, entitled "The Changing Landscape of American Medicine," will be held in Laguna Niguel, Calif., March 12–15.

Contact PMA, 1100 15th St., NW, Washington, DC 20005; or call (202) 835-3400.

JOHNS HOPKINS MEDICAL INSTITUTIONS

The following courses will be offered in Baltimore, unless otherwise noted: "Spectrum of Developmental Disabilities XI–Dyslexia: Clinical and Research Issues" (March 13–15); "PET: Imaging of Brain Chemistry with Special Emphasis on PET as a Clinical Tool in Neurology, Psychiatry, and Neurosurgery" (March 16–18); "6th Annual Wilmer Institute Current Concepts in Ophthalmology" (Vail, Colo., March 18–25); "Retinal Vascular Center 19th Anniversary Meeting–Macula" (June 30); and "Diabetic Retinopathy in 1989" (Oct. 13).

Contact Program Coordinator, Office of Cont. Educ., Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Ave., Baltimore, MD 21205; or call (301) 955-2959.

UNIVERSITY OF UTAH

The following courses will be offered: "Practices and Procedures in Asbestos Abatement for Contractors, Supervisors, Project Designers, and Workers" (Salt Lake City, March 13–16 and May 16–19; Denver, June 12–15; Aspen, Colo., Aug. 21–24; and Las Vegas, Oct. 9–12); "Asbestos Refresher Course for Contractors, Supervisors, Project Designers, and Workers" (Salt Lake City, March 17, June 23, and Oct. 20, and Aspen, Colo., Aug. 25); and "Comprehensive Review of Industrial Hygiene" (Maui, Hawaii, March 20–24).

Contact RMCOEH/Cont. Educ., Univ. of Utah, Bldg. 512, Salt Lake City, UT 84112; or call (801) 581-5710.

NEUROLOGY IN THE 1990's

The continuing education and board review course will be offered in Cambridge, Mass., March 13–18.

Contact Dr. Neil W. Kowall, Neurology Service, Massachusetts General Hosp., Fruit St., Boston, MA 02114; or call (617) 726-3786.

INTERNATIONAL CLINICAL HYPERTHERMIA SOCIETY

The 12th international symposium will take place in Rome, April 27–30.

SPECIAL REPORT

USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

A Preliminary Report

STEVEN A. ROSENBERG, M.D., PH.D., BEVERLY S. PACKARD, PH.D., PAUL M. AEBERSOLD, PH.D., DIANE SOLOMON, M.D., SUZANNE L. TOPALIAN, M.D., STEPHEN T. TOY, PH.D., PAUL SIMON, PH.D., MICHAEL T. LOTZE, M.D., JAMES C. YANG, M.D., CLAUDIA A. SEIPP, R.N., COLLEEN SIMPSON, R.N., CHARLES CARTER, STEVEN BOCK, M.D., DOUGLAS SCHWARTZENTRUBER, M.D., JOHN P. WEI, M.D., AND DONALD E. WHITE, M.S.

Abstract Lymphocytes extracted from freshly resected melanomas can be expanded in vitro and can often mediate specific lysis of autologous tumor cells but not allogeneic tumor or autologous normal cells. We treated 20 patients with metastatic melanoma by means of adoptive transfer of these tumor-infiltrating lymphocytes and interleukin-2, after the patients had received a single intravenous dose of cyclophosphamide. Objective regression of the cancer was observed in 9 of 15 patients (60 percent) who had not previously been treated with interleukin-2 and in 2 of 5 patients (40 percent) in whom previous therapy with interleukin-2 had failed. Regression of cancer occurred in the lungs, liver, bone, skin, and subcutaneous sites and lasted from 2 to more than 13 months. Toxic effects of interleukin-2 occurred, although the treatment course was short (five days); these side effects were reversible.

It appears that in patients with metastatic melanoma, this experimental treatment regimen can produce higher response rates than those achieved with interleukin-2 administered alone or with lymphokine-activated killer cells. It is too early to determine whether this new form of immunotherapy can improve survival, but further trials seem warranted.

We have previously reported that adoptive immunotherapy using lymphokine-activated killer (LAK) cells plus interleukin-2 or high-dose interleukin-2 alone can result in the regression of cancer in a variety of murine models[1-4] and in selected patients with advanced metastatic cancer.[5-7] The LAK cells used in this therapy were non-T, non-B, "null" lymphocytes capable of recognizing and lysing a wide variety of fresh tumor cells but not normal target cells.[1,8,9] The ability of LAK cells to mediate tumor

From the Surgery Branch (S.A.R., B.S.P., P.M.A., S.L.T., M.T.L., J.C.Y., C.A.S., C.S., S.B., D.S., J.P.W., D.E.W.) and the Laboratory of Pathology (D. Solomon), National Cancer Institute, and the Department of Transfusion Medicine (C.C.), Clinical Center, National Institutes of Health, Bethesda, Md.; and E.I. DuPont and Company (S.T.T., P.S.), Glenolden Laboratories, Wil-

regression led us to search for other subpopulations of lymphocytes that might be effective in cancer treatment.

We previously described a technique for the isolation and in vitro expansion of lymphocytes infiltrating into solid tumor masses.[10] The adoptive transfer of these tumor-infiltrating lymphocytes (TIL) was from 50 to 100 times more potent than that of LAK cells in mediating the regression of established cancer in several murine tumor models.[11,12] Successful therapy with TIL depended on pretreatment of the tumor-bearing host with either cyclophosphamide or total-body irradiation and on the simultaneous administration of interleukin-2.[11] TIL can be grown from a variety of human cancers.[13-19] In a Phase I study of 12 patients treated either without cyclophosphamide or with escalating doses of the drug, with escalating doses of interleukin-2, and with low numbers of TIL, we demonstrated the safety of the administration of this combination therapy.[20] In another pilot study, treatment with low numbers of TIL without cyclophosphamide or interleukin-2 was also safe, although no objective antitumor responses were seen.[21] We present our preliminary results of the treatment of a series of patients with metastatic melanoma by means of a regimen of cyclophosphamide in conjunction with the adoptive transfer of large numbers of autologous TIL and interleukin-2.

Methods

Patients

All the patients had a diagnosis of metastatic malignant melanoma, which could be evaluated by physical or radiographic examination. Of the 20 patients in this study, 18 had undergone surgical excision, 5 had received chemotherapy that had failed, 3 had received radiotherapy, 5 had received therapy with interleukin-2, and 1 had received therapy with alfa-interferon. None had undergone any other form of therapy for their disease for 30 days before treatment according to our protocol, and none received treatment during the follow-up period. Patients with central nervous system metastases were excluded; however, metastases to the brain developed in three patients (not included in this study) between the time of tumor resection and the growth of the TIL and were treated with reduced doses of interleukin-2.

Protocol

Tumor deposits were resected, usually under local anesthesia; most resected tumors weighed between 10 and 30 g. TIL were expanded in culture for four to eight weeks, according to techniques similar to those previously described.[18] When the TIL were ready for infusion, patients first received a single intravenous dose of cyclophosphamide (25 mg per kilogram of body weight) and 36 hours later the first intravenous infusion of TIL in an intensive care unit; a maximum of 2×10^{11} cells were administered in 200 to 250 ml over a period of 30 to 60 minutes. Each patient received a total of one to seven infusions over one to two days, depending on the number of cells to be administered and the time required to harvest the cells. After the first infusion of TIL, the patients began receiving recombinant interleukin-2 (kindly supplied by the Cetus Corporation, Emeryville, Calif.) (100,000 units per kilogram, given intravenously every eight hours in 50 ml of 0.9 percent saline with 5 percent albumin).[22] Interleukin-2 was administered kin-2 administration were treated with acetaminophen, indomethacin, ranitidine, and meperidine as previously described.[7]

Assessment of Response to Treatment

A response was considered to be complete if all measurable tumor disappeared, and to be partial if the sum of the products of the longest perpendicular diameters of all lesions decreased by at least 50 percent and if no tumor had any increase and no new tumor appeared. The term "objective responses" refers to the sum of complete and partial responses.

Results

Studies in murine tumor models have indicated that successful therapy with TIL depended on prior administration of cyclophosphamide.[11] Thus, to determine the degree of tolerance and response to cyclophosphamide plus interleukin-2 without administration of TIL, we began these clinical studies by treating a series of 13 patients with metastatic melanoma with various doses of cyclophosphamide (4 patients with 50 mg per kilogram, 6 with 25 mg per kilogram, and 3 with 10 mg per kilogram) followed 36 hours later by infusion of interleukin-2 (100,000 units per kilogram every eight hours). On the basis of this preliminary evaluation, a dose of 25 mg per kilogram was selected for the TIL therapy because it was the highest dose that resulted in acceptable levels of hematologic suppression when given with interleukin-2. Partial responses were observed in 2 of the 13 patients (1 patient who received 50 mg per kilogram and 1 who received 10 mg per kilogram) — results similar to those expected using treatment with interleukin-2 alone.

The characteristics of the 20 patients with metastatic melanoma treated with cyclophosphamide, TIL, and interleukin-2 and the characteristics of their treatment and response are shown in Table 1. The number of TIL infused ranged from 3×10^{10} to 75×10^{10} cells (median, 20.5×10^{10}; 25th percentile, 12.8×10^{10}; 75th percentile, 29.8×10^{10}). Of the 15 patients who had never before been treated with interleukin-2, 9 (60 percent) had objective evidence of cancer regression. Of the five patients in whom interleukin-2–based therapies had previously failed, two (40 percent) had objective responses. Regression of cancer was observed at a variety of sites, including the lungs (Fig. 1), liver, spleen, lymph node, bone, and subcutaneous tissue. Two of these responding patients (Patients 8 and 9) received a second course of therapy with cyclophosphamide, TIL, and interleukin-2, and four (Patients 3 through 6) received a second course of interleukin-2 alone approximately two months after the first course of cyclophosphamide, TIL, and interleukin-2. All these patients, however, had objective responses after the first course of treatment. The duration of the responses ranged from 2 to more than 13 months.

The toxicity of the treatment is summarized in Table 2. Chills were the only toxic effect associated with TIL infusion and were easily controlled with meperi-

Table 1. Characteristics of Therapy in 20 Patients Treated with TIL.*

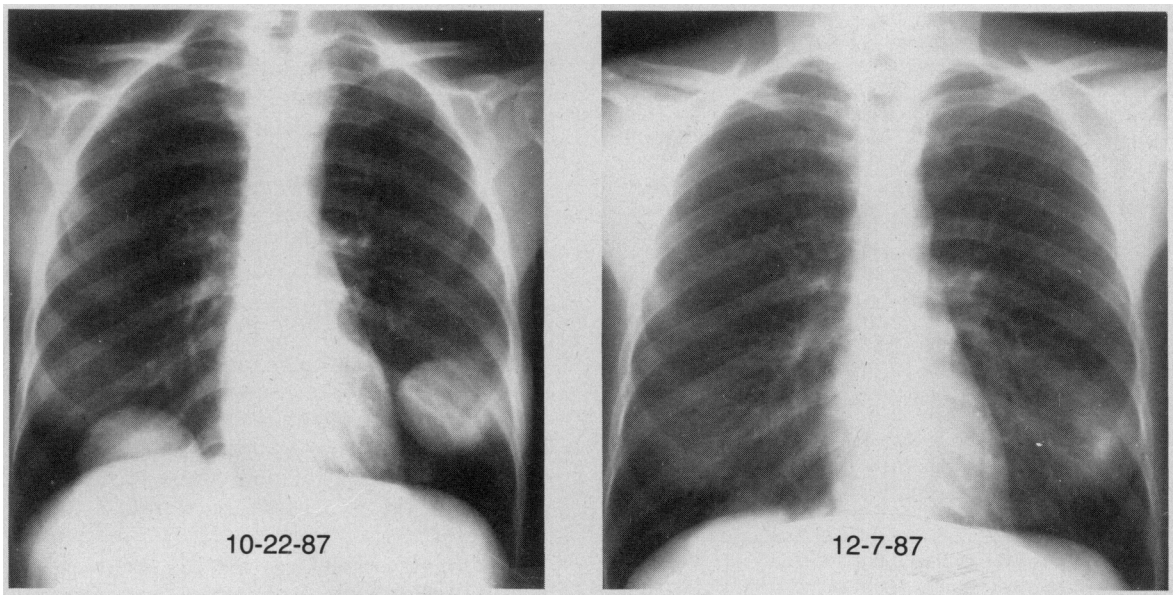
Patient No.	Sex/Age	Tumor Harvest	Tumor-Infiltrating Lymphocytes*					Doses of IL-2†	Response		
		Site	% Lympho-cytes	Days in Culture	Lymphocyte Expansion Index	Cells Infused ($\times 10^{-10}$)	CD3/CD4/CD8 (%)		Type	Site	Duration (mo)
1	F/46	Subcutaneous	15	27	330	23	95/6/93	11	Partial	Lung	3
2	M/56	Subcutaneous	70	29	300	3	74/4/64	12	Complete	Subcutaneous	>13
3	F/42	Subcutaneous	6	27	4,633	25	97/83/12	7	Partial	Lung, subcutaneous, nodal	3
4	F/38	Subcutaneous	6	24, 38	27,100	30	98/82/20	7	Partial	Lung, subcutaneous	4
5	M/37	Lymph node	16	29	585	9	98/81/7	7	Partial	Subcutaneous	7
6	M/21	Subcutaneous	28	34	2,423	23	83/93/10	13	Partial	Liver, spleen, nodal, subcutaneous	7
7	M/58	Lymph node	41	39	588	1.3	99/98/<3	12	None	—	—
8	M/25	Lymph node	4	42	44,450	19	97/19/>90	13	Partial	Lung, liver, nodal, subcutaneous	9 4
9	M/58	Liver	24	26	2,317	75	98/88/<3	7	Partial	Lung, liver	—
10	F/45	Lymph node	50	56	1,802	12	93/87/3	10	Mixed	Liver responded (brain metastases)	—
11	F/28	Subcutaneous	6	29	4,867	35	99/93/3	14	None	—	—
12	M/59	Soft tissue	6	53	2,623	17	96/67/2	9	None	—	—
13	M/50	Soft tissue	7	44	2,443	43	76/73/11	6	None	—	—
14	M/35	Bone and soft tissue	6	33	32,017	29	95/80/14	10	Partial	Lung, bone, subcutaneous	4
15	F/50	Lymph node	84	30	17,544	22	100/50/50	7	None	—	—
16‡	M/32	Lymph node	15	49	45,597,875	10	95/20/70	4	None	—	—
17‡	M/41	Subcutaneous	58	37	7,062	15	95/2/80	3	None	—	—
18‡	F/39	Subcutaneous	10	39	39,827	19	100/15/85	11	Partial	Subcutaneous	2
19‡	F/35	Lung	15	36	8,938	34	98/72/16	8	None	—	—
20‡	F/58	Lymph node	21	31	45,670	17	100/98/4	3	Partial	Nodal	6

*Before treatment with TIL, all patients received 25 mg of cyclophosphamide per kilogram.

†Doses of 100,000 units per kilogram every eight hours. Patient 16 received three of the four doses at 30,000 units per kilogram; Patient 17 received all three doses at 30,000 units per kilogram.

‡Previous treatment with interleukin-2 alone or interleukin-2 plus LAK cells had failed.

leukin-2 infusions and appeared to be related to an increased vascular permeability that led to loss of intravascular volume and accumulation of fluid in visceral organs and soft tissues.[23] No patient died of treatment. The side effects all resolved after interleukin-2 was discontinued, and the median time from the end of treatment to hospital discharge was four days (25th percentile, three days; 75th percentile, seven days). Toxicity was lower in this regimen than in others using this dose of interleukin-2, because the treatment time was shorter (median, 5 days; 25th percentile, 4 days; 75th percentile, 6 days) than the 15 days required for a course of therapy with LAK cells plus interleukin-2.



Tumor cells were obtained from 17 patients (other than the 20 patients listed in Table 1), but no treatment was given to them — 7 patients because of debilitation caused by the progression of their disease, 8 because of poor lymphocyte growth, and 2 because of contamination of cultures by bacteria. Three other patients not listed in Table 1 had brain metastases that developed between the time of tumor harvest and the time of final TIL growth; they received TIL, but because of their poor performance status at the time of treatment their doses of interleukin-2 were reduced. One of these patients died 13 days after infusion of TIL, with metastases involving the brain and virtually all visceral organs. Another patient had a decrease in cutaneous metastases and a decrease in brain metastases on CT scans obtained one month after treatment. This patient died at home one month later of what appeared to be an intracerebral event, although no autopsy was performed.

Discussion

Conventional chemotherapy is relatively ineffective in the treatment of patients with metastatic melanoma, and approximately 6000 patients die of this disease in the United States each year. We have sought new immunotherapeutic approaches to the treatment of patients with melanoma and have reported that regression of metastatic melanoma could be achieved in some patients treated with high doses of interleukin-2 alone or in combination with the adoptive transfer of LAK cells.[5-7] A recent analysis of our experience (as of May 1988) has revealed that objective evidence of cancer remission was observed in 10 of 48 patients (21 percent; 4 with complete and 6 with partial regressions) in whom melanoma was treated with LAK cells plus interleukin-2 and in 9 of 37 patients (24 percent; all 9 with partial regressions) treated with high doses of interleukin-2 alone.

Studies of the adoptive transfer of TIL in murine tumor models have shown that these cells are 50 to 100 times more effective than LAK cells in mediating tumor regression.[11,12] In contrast to LAK cells, TIL obtained from mice and patients are predominantly T lymphocytes, and those from patients are often capable of lysing autologous melanoma in a fashion that is highly specific and restricted by the major histocompatibility complex.[13-19] As with other forms of experimental adoptive therapy with T cells, immunosuppression of the tumor-bearing host with either cyclophosphamide or total-body irradiation is required for treatment to be successful.[24-26] This pretreatment is thought to eliminate suppressor cells or to facilitate lymphocyte "homing." Cyclophosphamide administration or total-body irradiation does not affect treatment with LAK cells in murine models.

We therefore first treated 13 patients with the combined administration of cyclophosphamide and interleukin-2, and observed only two objective responses with the use of interleukin-2 alone. However, the addition of TIL to the combination of cyclophosphamide and interleukin-2 resulted in responses in 9 of 15 patients (60 percent) who had not previously been treated with interleukin-2 and in 2 of 5 patients (40 percent) in whom treatment with interleukin-2 had previously failed (both patients had previously received a different preparation of recombinant interleukin-2). It thus appears that treatment with TIL increased response rates among patients with metastatic melanoma, as compared with therapy with LAK cells and interleukin-2, cyclophosphamide and interleukin-2, or interleukin-2 alone. It should be emphasized, however, that the duration of response was often short, and it is too early to determine the effect of treatment on survival. The results reported here reflect primarily the results of a single cycle of treatment with TIL. Since only 1 of the 11 responding

Table 2. Toxicity of Treatment with TIL, Interleukin-2, and Cyclophosphamide.

Toxic Effect	No. of Patients (N = 20)
Chills	10
Nausea and vomiting	11
Diarrhea	9
Mucositis	1
Hyperbilirubinemia (peak value)*	
2.1–6.0 mg/dl	10
6.1–10.0 mg/dl	10
≥10.0 mg/dl	0
Hypotension (requiring pressors)	13
Arrhythmias	1
Oliguria	
<80 ml/8 hr	10
<240 ml/24 hr	0
Elevated creatinine (peak value)†	
2.1–6.0 mg/dl	8
6.1–10.0 mg/dl	2
≥10.0 mg/dl	0
Weight gain (% body weight)	
5.1–10.0	5
10.1–15.0	2
≥15.1	2
Respiratory distress	
No intubation	1
Intubation	1
Anemia requiring transfusion (units transfused)	
1–5	14
6–10	2
≥11	0
Thrombocytopenia (minimum/mm^3)	
≤20,000	4
21,000–60,000	7
61,000–100,000	6
Neutropenia (minimum/mm^3)	
≤500	1
501–1000	3
Disorientation	4
Coma	1
Somnolence	1
Death	0

*Bilirubin levels returned to normal in all patients over a median of 4.5 days.

patients had a complete response, perhaps more intensive or repeated therapy might improve the quality of response.

The shorter course of treatment with TIL and interleukin-2 (5 days as compared with 15 days for therapy with LAK cells and interleukin-2) was better tolerated by the patients. There were no treatment-related deaths among the 20 patients described here, although 1 of 3 patients with brain metastases treated with lower doses of interleukin-2 died 13 days after therapy, with extensive intracranial, visceral, and cutaneous disease. All side effects occurring in these 20 patients resolved after the completion of therapy.

Extensive immunologic studies have been performed on the initial suspensions of tumor cells and on the infused TIL to determine the requirements for successful therapy. The great majority of the infused TIL were CD3+, though the relative number of CD4+ and CD8+ cells varied among the patients (Table 1). Cultures of TIL exhibited varying patterns of cytotoxicity, proliferation, and lymphokine production, though no pattern has yet emerged to predict the TIL populations that will mediate cancer regression in vivo. Interestingly, a study of TIL traffic in six patients with melanoma who each received a small aliquot of indium-111–labeled TIL revealed substantial homing of TIL to cancer deposits.[27]

This study represents a further development of the approach of adoptive immunotherapy to the treatment of patients with advanced cancer. Higher response rates have been achieved using TIL in patients with metastatic melanoma than have previously been achieved with treatment with LAK cells, and patients with other types of cancer should be studied. Although the treatment can cause regression of cancer, it is not yet known whether regression will affect survival. In addition, the methods required to generate TIL are complex and laborious, and simplification of the culture techniques is required. This treatment should be considered highly experimental and should be pursued in centers where the immunologic factors required for successful treatment can be assessed. The present study does demonstrate, however, that the adoptive transfer of immune autologous cells can be effective in mediating cancer regression in selected patients, and further emphasizes the need to pursue the development of this biologic approach to cancer therapy.

We are indebted to Deborah Shulman, Carolyn Buresh, Linda Paczkowski, Cornelia Hyatt, Susan Johnson, and Kathryn Ottaway, who generated the TIL cells; to data managers Melissa Corbitt and Allison McMullen; and to the dedicated nurses of the 2 East Surgical Unit and the 2J Surgical Intensive Care Unit of the Clinical Center, National Institutes of Health, who provided the patients with excellent and compassionate care.

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