A Phase I Toxicity, Pharmacology, and Dosimetry Trial of Monoclonal Antibody OKB7 in Patients With Non-Hodgkin's Lymphoma: Effects of Tumor Burden and Antigen Expression

By David A. Scheinberg, David J. Straus, Samuel D. Yeh, Chaitanya Divgi, Pilar Garin-Chesa, Martin Graham, Keith Pentlow, Daniel Coit, Herbert F. Oettgen, and Lloyd J. Old

Eighteen patients with relapsed non-Hodgkin's lymphoma (NHL) were infused with escalating doses of monoclonal antibody (mAb) OKB7, trace-labeled with iodine-131 (^{131}I), in order to study toxicity, pharmacology, antibody localization, and dosimetry of radioiodine. OKB7 is a noncytotoxic mouse immunoglobulin G2b (IgG2b) mAb reactive with B cells and most B-cell NHL. Three patients each were treated at six dose levels ranging from 0.1 mg to 40 mg. All patients had radionuclide imaging and counting daily, had serial blood sampling to study pharmacokinetics, human antimouse antibody (HAMA), and circulating antigen, and had a biopsy of accessible lymphoma to determine delivery of isotope to tumors and assess the effect of tumor antigen expression on mAb delivery. Bone marrow biopsies were also done in the majority of patients. There was no toxicity. Serum clearance showed a median early phase half-life of 1.9 hours and a later phase half-life of 21.7 hours. Median total body clearance half-life was 22 hours. Pharmacokinetics were not dose-related. HAMA was detected in five patients. Circulating blocking antigen was detected in the serum of four patients, but at levels that were of pharmacologic consequence only in one. Biopsied tumor tissue from five patients did not express OKB7 antigen. No significant uptake of antibody was seen in these tumor sites. Mean total uptake of isotope into lymphoma measured in biopsies correlated linearly over the 400-fold increase in injected mAb dose. However, the percent of injected dose found per gram of tumor was unrelated to dose, but correlated inversely with tumor burden. In two patients with minimal tumor burden, 1.0 mg and 5.0 mg doses of OKB7 resulted in tumor to body radioisotope dose ratios of 22 and 7, which would theoretically permit tolerable delivery of 4,400 and 1,400 rads to these tumors, respectively, if OKB7 were conjugated with higher doses of ^{131}I.

J Clin Oncol 8:792-803.

HEMATOPOIETIC neoplasms have long been considered potential targets for monoclonal antibody (mAb) therapy because of their accessibility to the blood, their well-defined cell surface antigens, and their sensitivity to mAb-delivered radiation.[1] Early trials with unmodified mAbs in acute and chronic leukemias and cutaneous T-cell lymphomas demonstrated some of the problems associated with antibody therapy including acute toxicities associated with mouse mAb infusions, development of human antimouse antibody (HAMA) responses, and modulation of the antigen from the target cell surface.[2-7] Although major tumor regressions were seen in these pilot trials, they were almost always transient, in part due to the problems noted above, and also because the mAbs did not activate cytotoxic effector mechanisms. More recent pilot studies have focused on using cytotoxic, complement-fixing mAbs or mAbs labeled with therapeutic doses of radioisotopes.[2,8-13] These strategies have resulted in consistently higher percentages of major tumor regressions.

B-cell non-Hodgkin's lymphomas (NHL) were chosen as targets for our studies with mAbs for several reasons. They express clearly defined lineage and maturation-specific cell-surface antigens that may be used as targets,[14] and the incidence of HAMA responses appears to be low in patients with B-cell neoplasms.[2] Moreover, they are a common adult hematopoietic cancer for which no effective curative treatments exist for the majority of patients.[15,16] In patients with diffuse and nodular poorly differentiated lymphomas (DPDL and NPDL), diffuse well-differenti-

From the Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted July 28, 1989; accepted December 1, 1989.

Supported in part by the Lucille P. Markey Charitable Trust, an American Society of Clinical Oncology Young Investigator Award to Dr Scheinberg, The Westvaco Fund, The Lymphoma Research Fund, and the Jennie R. and Oliver S. Donaldson Charitable Trust.

Dr Scheinberg is a Lucille P. Markey Scholar.

Address reprint requests to David A. Scheinberg, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

0732-183X/90/0805-0013$3.00/0

ated lymphocytic lymphomas (DWDL), and chronic lymphocytic leukemias (CLL), a consistent pattern of inevitable relapse is seen despite chemotherapy-induced remissions.[16-18]

Small numbers of patients with B-cell lymphomas have been treated in several pilot studies of mAb including the use of the pan-B reactive mAb IF5,[19] mAb directed to the specific cell-surface immunoglobulin (Ig) (idiotype) of nodular lymphomas,[20-22] and several mAbs to the pan-lymphoid antigen CAMPATH-1.[11,12] Infusions of radioiodinated Lym-1 and MB-1, both broadly reactive with B-cell lymphomas, have resulted in high rates of tumor regression, including complete responses.[8,13] The success of these pilot trials of mAb in B-cell lymphomas argue for more detailed studies of mAb toxicity, pharmacology, dosimetry, and HAMA responses to optimize mAb use. Because of the complexities in the interaction of the mAb with the host, the small numbers of patients involved in early trials and the lack of biopsy data in some of these trials, many of the factors controlling antibody targeting to tumors are still poorly understood.

For the study presented here we have used mAb OKB7, a mouse IgG2b reactive with the Epstein-Barr virus receptor, CR2.[23-26] The antigen is restricted to a subset of peripheral blood B cells, lymph node and spleen follicular B cells, and most NHL and CLL; it is not found in normal adult tissues.[27] OKB7 was earlier reported to cause B-cell activation and differentiation in vitro after binding to cell-surface CR2.[28] However, later preparations of the material lacked the activity except when used concurrently with phorbol esters.[29] The highly purified material used in our clinical trial lacked activating activity in vitro. OKB7 does not fix complement or mediate target cell killing via cell-mediated mechanisms, but it does induce modulation of the antigen with some internalization of antibody. The highly restricted expression of OKB7 permitted us to study factors affecting mAb delivery and assess the potential of this antibody as a carrier of cytotoxic radionuclides in future therapeutic trials in patients with B-cell lymphomas.

METHODS

mAb

Mouse hybridomas producing OKB7 were provided by Ortho Diagnostics (Raritan, NJ). The OKB7 hybridoma was grown as an ascites tumor in (CA) F1 mice, which had been primed with pristane and sublethally irradiated. High titer ascites fluid was pooled and clarified by ultracentrifugation. Igs were concentrated and partially purified using 50% neutral ammonium sulfate and then equilibrated to pH 8.6 by Sephadex (Pharmacia, Piscataway, NJ) G50 chromatography. OKB7 was purified from the crude Ig fraction by sequential pH elutions using protein-A affinity chromatography followed by cation exchange fast-performance liquid chromatography (FPLC) on a Mono S column (Pharmacia). A major contaminating peak of Ig produced by the OKB7 hybridoma was removed by the cation exchange step. Immunopathologic analysis of pure OKB7 showed enhanced specificity for B cells as compared with the original hybridoma product. Purity was assessed on silver-stained sodium-dodecyl sulfate polyacrylamide gels, and antibody titers were verified after each step in the purification. All procedures were done aseptically with pyrogen-free materials.

Safety Testing and Quality Control

All batches of ascites were screened for murine viruses before pooling. Low titer batches were discarded to reduce the amount of nonspecific mouse Igs. The final OKB7 clinical product was tested by FPLC, high-performance liquid chromatography (HPLC), and gel electrophoresis for purity. Pyrogenicity was tested in rabbits. Assays were done for contaminating viruses. Endotoxin was assayed by the limulus test. Microbiologic cultures were done at the microbiology laboratories at Memorial Hospital. General safety testing was performed in small animals.

Radiolabeling of OKB7

One milligram of OKB7 was radiolabeled with 3 to 4 mCi iodine-131 (^{131}I) (Amersham, Arlington Heights, IL) using chloramine-T. The reaction was terminated with sodium metabisulfite, and the labeled antibody was purified by size exclusion chromatography on Sephadex G25. Immunoreactivity of the labeled product was determined by binding to an excess of antigen (live RAJI cells). Purity was determined by HPLC on a 7.5 × 600 mm TSK-250 column (Biorad, Richmond, CA). For doses of 5, 15, and 40 mg of OKB7, the radiolabeled OKB7 was mixed with unlabeled OKB7 to adjust the doses upwards and passed through a 0.20 μm filter. For doses of 0.1 and 0.5 mg OKB7, only these amounts of OKB7 were labeled. Injected doses contained approximately 2 mCi ^{131}I; specific activities of the injected material ranged from 20 mCi/mg to 0.5 mCi/mg (0.1 to 40 mg OKB7 doses).

Patients

All patients had histologically proven NHL who had progressed on, or relapsed after, chemotherapy or chemotherapy and additional radiotherapy or immunotherapy. Criteria for eligibility included a Karnofsky performance status of at least 70, no chemotherapeutic treatment, immunotherapy, or radiation therapy within 4 weeks (6 weeks for nitrosoureas), serum creatinine under 2 mg/100 mL, serum bilirubin under 2 mg/100 mL, granulocytes greater than 1,500/mm^3, platelets greater than 10^5/mm^3, and prothrombin time less than 1.3 × control. Patients with serious cardiac disease (New

York State Heart Association class III-IV), pulmonary or infectious diseases, known infection with human immunodeficiency virus (HIV), prior treatment with mouse mAbs, pregnancy or lactation, or with an expected survival of less than 6 weeks, were excluded. All patients had lymphoma nodes or masses, easily accessible for biopsy. All patients signed informed consent.

Treatment Plan

Three patients each were entered at six ascending dose levels: 0.1 mg, 0.5 mg, 1.0 mg, 5.0 mg, 15.0 mg, and 40.0 mg OKB7. Two millicuries of ^{131}I attached to OKB7 were administered at each level. A single infusion of ^{131}I-OKB7 in 100 mL of saline containing 5% human serum albumin was administered over 60 minutes. Patients were given Lugol's solution 1 day before treatment and thereafter for 4 days. A skin test for wheal and flare reaction to 0.1 μg OKB7 was done 1 hour before beginning the OKB7 infusion.

Patient Evaluations

The following evaluation was done on patients before treatment: physical examination including measurement of nodes, masses, liver size and spleen size; complete blood count including platelet counts, ECG, chest x-ray, urinalysis, Ig levels, HIV antibody titer, serum biochemistry studies and electrolytes, prothrombin and partial thromboplastin times, serum C3 and CH50, and cell-surface markers on peripheral blood lymphocytes (and bone marrow if involved). Serum was drawn before treatment, at 7 to 10 days after treatment and monthly thereafter for measurement of HAMA responses. Other diagnostic imaging procedures (computed tomography, ^{99}Tc-liver-spleen scans, gallium scans) were used to measure the extent of disease when indicated.

Evaluations of the extent of disease were performed along with serum chemistries and complete blood counts, at least monthly as long as patients remained on study. Patients were removed from the study when tumor progression occurred or when chemotherapy or radiotherapy was reinstated.

Biopsies

A biopsy of a peripheral lymph node or tumor mass was performed in all patients on days 3 to 5 after infusion of OKB7. In patients with possible bone marrow involvement, a bone marrow biopsy and aspirate were also performed. The tumor biopsy was evaluated for pathology, immunopathology, and radioactivity.

^{131}I-OKB7 Imaging

Patients underwent anterior and posterior whole body imaging using a Gemini Imager (General Electric, Madison, WI) at 2 to 4 hours, and then daily until biopsy.

Pharmacologic Studies and Dosimetry

Blood was collected at 5, 15, 30, 45, 60, 120, 240, 360, and 480 minutes and then every 12 hours until biopsy for determination of OKB7 levels and radioactivity. Because acid precipitable counts per minute (cpm) were similar to total cpm in patients selected for study, the latter were used for pharmacologic studies. Cumulative urine radioactivity was obtained over 48 to 72 hours. Whole body radioactivity was measured at 3 m. Rad per millicurie doses to tumor, whole body, blood, marrow and spleen were calculated using biologic half-life data and MIRD S factors.[30]

HAMA

HAMA was measured in serum by enzyme-linked immunosorbent assay (ELISA) on OKB7 dried onto 60-well Teraski titration plates. Fifty nanograms of OKB7 was dried into each well and then blocked with phosphate-buffered saline (PBS) containing bovine albumin and gamma-globulin-free fetal calf serum. Human serum (including known positive controls) was added in dilutions beginning at $^1/_{10}$ and washed off with PBS at 60 minutes. Alkaline phosphatase conjugated goat antipolyvalent human Ig (Zymed) was added for 60 minutes and then washed off. Sodium p-nitrophenyl phosphate (Sigma) in diethanolamine buffer was added for 10 minutes and the assay was read in an Artek ELISA plate reader. Background optical density was approximately 5% of the maximum; positive wells were scored when the optical density was at least twice the background. The titer was scored as the last positive well.

Pathology and Immunopathology

Tumor or lymph node specimens obtained after treatment were examined in frozen and fixed sections for presence of lymphoma, normal tissue, and inflammatory infiltrates. Indirect immunoperoxidase assays were done to determine the presence of OKB7 antigen and OKB7 antibody, as well as the immunophenotype of the cells present.[31]

Toxicity Criteria

Toxicity was scored according to the National Cancer Institute common toxicity scale.

Serum Blocking Antigen

The presence of antigen capable of blocking the binding of OKB7 IgG to target cells was measured using ^{125}I-OKB7 in a competition direct radioimmunoassay with live RAJI cells. This was done using pretreatment serum samples essentially as described for another antibody.[32]

RESULTS

Eighteen patients were entered into the trial between April 1988 and April 1989. Important features of these patients are shown in Tables 1 and 2. All patients had a history of relapsed NHL and had been diagnosed from 1 to 15 years (median, 5 years) before entry onto this study. All patients underwent a biopsy of accessible lymphoma as part of this trial; most of the patients required the biopsy as part of an ongoing restaging and diagnostic reevaluation. Karnofsky performance status ranged from 70 to 90 (median, 90). The extent of disease ranged from single nodes to widespread disease involving the blood, marrow, liver, and spleen.

Table 1. Patient Characteristics

No./Age/Sex	Diagnosis	Extent of Lymphoma Involvement	Prior Therapy
1/54/M	NPDL	Cervical, submental, axillary, inguinal nodes; spleen	Chemotherapy
2/47/F	LPCL	Cervical, supraclavicular, inguinal nodes; liver; spleen	Chemotherapy, immunotherapy
3/66/M	NML	Retroperitoneal node/pelvic mass with ureteral compression.	Chemotherapy
4/26/M	NPDL	Retroperitoneal, inguinal, cervical, axillary, supraclavicular nodes; spleen	Chemotherapy, immunotherapy
5/39/M	NPDL	Axillary, cervical, retroperitoneal nodes, spleen	Chemotherapy, radiotherapy
6/37/F	DHL	Subcutaneous in buttocks and back	Chemotherapy
7/73/F	DHL	Left submandibular node	Chemotherapy, radiotherapy
8/73/F	DHL	Pelvic, rib, and lung parenchymal masses	Chemotherapy, radiotherapy
9/63/F	NPDL	Cervical, supraclavicular, axillary retroperitoneal nodes; pulmonary effusions; ascites; liver; marrow	Chemotherapy
10/64/M	DPDL	Cervical, supraclavicular nodes; thigh and colonic masses	Chemotherapy, radiotherapy
11/69/M	LPCL	Right inguinal; small cervical nodes	Chemotherapy
12/55/M	NPDL	Right axillary node	Chemotherapy, radiotherapy
13/53/F	DPDL	Cervical, supraclavicular, axillary nodes, abdominal masses	Chemotherapy, immunotherapy
14/48/M	DML	Pelvic, axillary, abdominal, pancreatic and subcutaneous masses	Chemotherapy, radiotherapy
15/63/M	DPDL	Cervical and auricular nodes; bone marrow and blood	Chemotherapy
16/63/M	DHL	Supraclavicular, mediastinal, cervical nodes	Chemotherapy
17/31/M	NPDL	Spleen; retroperitoneal, inguinal, axillary, cervical, nodes; pleural effusions	Chemotherapy
18/61/M	NPDL	Cervical, mediastinal, mesenteric nodes	Chemotherapy

Abbreviations: DHL, diffuse histiocytic lymphoma; DML, diffuse-mixed lymphoma; DPDL, diffuse poorly differentiated lymphocytic lymphoma; LPCL, lymphoplasmacytoid lymphoma; NML, nodular-mixed lymphoma; NPDL, nodular poorly differentiated lymphoma.

All patients were evaluable for toxicity, pharmacology, dosimetry, and HAMA. Ten patients were not evaluable for tumor response: seven required chemotherapy within 1 month after OKB7 infusion, and three patients had no measurable disease following surgical-excisional biopsy. One patient was not evaluable for immunopathology because of technical problems with the specimen.

OKB7 Labeling and Quality Control

Following radiolabeling with ^{131}I the OKB7 was analyzed for purity and immunoreactivity. Trichloroacetic acid precipitation of the labeled

Table 2. Initial Laboratory Values for Patients Studied

	Hematology*					Chemistry†			
Patient No.	WBC	Platelets	Hgb	Abs. No. of Lymphs	OKB7+‡ Lymphs	LDH	Creat	IgG	IgM
1	4.6	100	12.9	1,053	168	224	1.2	985	75
2	4.1	257	12.2	1,119	ND	184	0.8	1,230	386
3	6.7	250	15.7	938	131	193	1.6	ND	ND
4	4.9	154	14.3	1,078	22	158	0.9	595	28
5	5.0	195	12.9	1,050	28	157	1.0	644	61
6	5.9	240	13.4	1,829	237	204	0.7	715	57
7	11.2	285	13.8	3,203	208	198	0.9	602	227
8	4.4	204	12.0	445	0	225	0.9	1,355	134
9	10.8	306	12.1	334	7	1,125	1.4	ND	ND
10	3.7	150	12.0	473	28	139	1.4	1,119	36
11	6.8	238	11.8	1,890	189	129	1.0	855	68
12	6.6	205	16.5	1,775	142	217	0.9	1,026	24
13	5.8	322	11.8	1,426	182	168	0.7	490	33
14	5.5	669	8.1	281	34	162	0.9	1,415	52
15	30.9	116	12.5	19,776	14,824	220	1.1	272	22
16	5.2	231	13.5	1,742	157	373	1.0	1,081	20
17	5.0	90	10.3	3,650	2,113	201	0.9	281	17
18	8.5	264	13.9	1,680	165	209	1.0	495	80

Abbreviations: Abs no. of lymphs, the absolute number of lymphocytes per mm^3; ND; not done; Hgb, hemoglobin; Creat, serum creatinine; LDH, lactate dehydrogenase.

*All hematologic data, except Hgb, are per mm^3: WBC ($\times 10^{-3}$); platelets ($\times 10^{-3}$); Hgb is g/100 mL.

†LDH and alkaline phosphatase are U/L. Creat is mg/100 mL. IgG and IgM are mg/L.

‡Lymphocytes bearing OKB7 antigen on their surfaces were calculated from the percentage of OKB7+ cells by flow cytometry.

product showed that greater than 95% of the ^{131}I was precipitable. HPLC analysis of 12 samples showed that in 11, more than 98% of the radionuclide was associated with Ig at a molecular weight of 150,000 d. In one dose (no. 2), high molecular weight aggregates of Ig accounted for about 50% of the labeled IgG. Immunoreactivity assays of the ^{131}I-OKB7 from all 17 doses tested consistently showed that approximately 60% of the labeled antibody bound to excess live target cells in 1 hour.

Initial Laboratory Data

Initial WBC counts ranged from 3,700 to 30,900/mm^3 (median, 5,800); platelets from 90,000 to 669,000/mm^3 (median, 239,000); hemoglobin from 8.1 g to 16.5 g/100 mL (median, 12.7). With one exception, patient no. 15, no patient had significant numbers of OKB7-positive circulating cells. Patient no. 15 was in a leukemic phase of DPDL, and 73% of his circulating cells bound OKB7.

Relevent serum chemistry values are shown in Table 2. All patients were HIV-antibody negative. Baseline serum Ig levels were variable: patients no. 4 to 7, 13, 15, and 17 had reduced IgG; patients no. 4, 10, and 12 to 17 had reduced IgM; patient no. 2 had elevated IgM.

Toxicity

There were no adverse reactions unequivocally attributable to OKB7. All pretreatment skin tests for immediate hypersensitivity to OKB7 were negative. One patient (no. 14) who had a history of recurrent disease-related fevers developed a brief fever of 38.5°C during the OKB7 infusion, which resolved within several hours. No symptoms attributable to the treatment were noted. There were no significant changes in the measured hematologic or biochemical parameters. Serum complement (C_3 and CH_{50}) levels, measured on day 0 and day 3, did not change as a result of OKB7 infusion.

OKB7 binds to a subset of peripheral blood B cells.[23] In 16 of the patients the number of OKB7-positive peripheral blood cells was so small that reliable changes were not detected (Table 2). In patient no. 15, treated during a leukemic phase of his DPDL, with 73% OKB7-positive cells, WBC counts continued to rise despite the OKB7 infusion.

Pharmacology

Computer regression analysis of the data fit a two-slope model of the serum clearance with a rapid early phase (alpha) (median, 1.9 hours) and a slower later phase (beta) (median, 21.7 hours) (Table 3). Because the OKB7 was infused over 1 hour, the initial clearances within minutes cannot be determined. With one exception, serum half-life (T½) beta ranged from 10.0 hours to 69.3 hours: patient no. 3 had a significantly prolonged serum T½ of ^{131}I, probably due to ureteral obstruction resulting in an increased

Table 3. OKB7 Pharmacology

Patient No.	Dose Level (mg)	Serum T½		Total Body T½	% Urinary Excretion (^{131}I at 48 hours)
		T½ Alpha	T½ Beta		
1	0.1	0.7	21.7	30	49
2	0.1	2.8	17.3	16	70
3	0.1	3.9	115.5	48	38
4	0.5	0.9	23.9	27	61
5	0.5	0.5	14.4	18	53
6	0.5	0.7	39.7	33	44
7	1	1.8	25.7	25	79
8	1	1.0	19.2	35	59
9	1	9.0	37.9	227	11
10	5	3.6	20.8	22	57
11	5	1.4	22.4	29	40
12	5	2.9	69.3	30	58
13	15	1.9	10.0	15	87
14	15	2.7	52.5	17	67
15	15	1.2	21.7	25	52
16	40	2.2	19.5	22	34
17	40	1.0	15.5	21	73
18	40	4.0*	—	14	81

*The error in fitting a two-slope model was too large. A better fit was obtained with a single phase of clearance.

serum creatinine (1.6 mg/dL), and a reduced creatinine clearance. We did not distinguish free from acid-precipitable ^{131}I, so the prolonged T ½ may be due to decreased ^{131}I clearance. The unusual pharmacokinetics seen in patient no. 18 may be related to high levels of circulating blocking antigen (see following). There were no clear changes in serum clearance related to dose level.

Total body T½ ranged from 14 to 33 hours (median, 22 hours) with two exceptions. Patient no. 3 had a prolonged T½ (48 hours) probably due to reduced clearance as discussed above. Patient no. 9 had a markedly prolonged T½ (227 hours). This patient had extremely widespread lymphoma involving multiple nodal areas, liver, spleen, bone marrow, pleural effusions and ascites. Her images showed radiolabel retained diffusely in her entire body, probably due either to vascular leakage or lymphoma.

Urinary excretion of radiolabel accounted for approximately 50% to 70% of the injected dose within 48 hours except in patient no. 9 who had minimal urine output, and only 11% of the radiolabel cleared via her kidneys in 48 hours. No major variations in pharmacokinetics resulted from the 400-fold increase in doses administered.

Serum blocking antigen. Pretreatment sera from four of 18 patients (no. 4, 13, 14, and 18) were able to partially block OKB7 binding to target lymphoma cells in vitro at a concentration of 0.1 μg/mL. Blocking disappeared as OKB7 concentrations were raised to 0.5 μg/mL in patient no. 14 and to 2 μg/mL in patients no. 4 and 13. In patient no. 18, serum was still able to partially block OKB7 binding at 2 μg/mL. The circulating antigen in this patient may be responsible for the marked change in pharmacology seen in serum clearance and the shortened total body clearance. As 2 μg/mL levels of OKB7 can be achieved with doses of 10 mg or greater, the 10 mg dose may be the lower limit for overcoming competition of circulating antigen for antibody binding.

Imaging

All patients had whole body gamma camera images within 3 to 4 hours after injection and then daily for at least 2 more days. At all time points, the spleen was clearly seen in 17 of 18 patients. Patient no. 2 did not show spleen

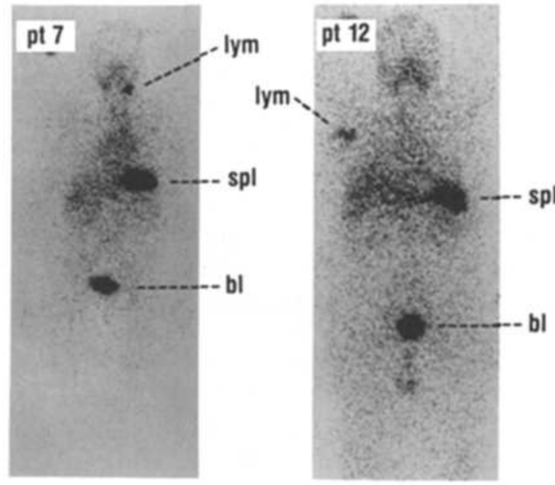

Fig 1. Anterior whole body gamma camera images at 2 days after injection of ^{131}I-OKB7. Left: patient no. 7 with left submandibular node, spleen, and bladder indicated. Right: patient no. 12 with right axillary nodes, spleen, and bladder indicated.

visualization. This may be attributable to aggregation of the labeled antibody at this dose as detected by HPLC analysis (see OKB7 Labeling and Quality Control above). The blood pool, including major vessels such as the vena cava and iliac veins, were visible in most patients at the higher dose levels, but only at the initial time points.

Tumors were visualized in a minority of patients. Patients no. 7, 12, 16, and 18 had clear images of involved lymph nodes (Fig 1). Tumor to serum ratios of radioactivity measured by biopsy in patients no. 7, 12, 18 were 12:1, 4:1, and 1:1, respectively. A different tumor than the one that imaged was biopsied in patient no. 16. Patients no. 4, 13, and 15 had borderline positive images of nodes. Five patients were found to have tumors that poorly expressed or did not express antigen. None of these nodes or masses gave positive images. In the case of patient no. 14, whose tumor did not image, antigen expression could not be assessed. High expression of the OKB7 antigen on a target tumor was therefore a necessary but not in itself sufficient condition for imaging. Splenic images were presumed to be "specific" for OKB7-positive B cells residing there; however, deposition of OKB7 antigen-antibody complexes cannot be ruled out. Since antigen-negative masses did not take up significant ^{131}I-OKB7, the targeting in vivo could be assumed to be specific. The two patients with the highest uptake of OKB7 into their lymphoma (no. 7 and 12) had strongly positive images and minimal tumor burden, no splenomegaly, and no significant OKB7-positive circulating cells. Patient no. 11 showed high OKB7 uptake into a node but did not have a positive image, probably due to the small size of the node (1 cm). This patient also had minimal tumor burden.

Organs involved in metabolism of free ^{131}I imaged in all patients by the second day. This included the thyroid, stomach, and bladder. Such catabolism and excretion was predicted by animal models.[33] Besides these organs, no other normal organs imaged suggesting that there was no significant antigen present at sites accessible to OKB7. This specificity was predicted based on immunopathology data showing the presence of OKB7 antigen only in areas of the spleen and lymph nodes containing B cells. Nonspecific uptake in the liver was not seen in any patient suggesting that the high uptake seen in several other imaging trials using radiometal chelate-labeled mAb may be due to the labeling methods.[33-36]

Pathology and Immunopathology

All patients entered on trial had a tumor biopsy following OKB7 infusion. Patients no. 1, 2, and 4 to 6 had biopsies on day 5; all others had biopsies on day 3. Immunopathologic analysis included histopathologic diagnosis, indirect immunoperoxidase assay for the presence of target antigen (gp140), and direct immunoperoxidase analysis using goat antimouse antibody for the presence of OKB7 IgG at the tumor site (Table 4). The biopsy from patient no. 14 could not be examined due to technical problems. Five patients had either minimal or no staining for the presence of OKB7 antigen. None of these tumors imaged or showed high uptake ratios of ^{131}I in the tumors (Table 4). One patient (no. 6) had a lipoma and a normal node which was positive for OKB7 antigen in the normal follicles only. Two patients had large hyperplastic nodes: the lymph node removed from patient no. 12 was morphologically atypical and showed a t(14; 18) translocation consistent with NPDL. The node from patient no. 11 was read as "normal." OKB7 uptake was seen in both of these nodes as determined by counting radioactivity (see following). The node in patient no. 12 also gave an especially clear image (Fig 1).

All lymphomas were of B-cell origin. No tumor showed the presence of OKB7 IgG in the biopsy by immunoperoxidase. This is not surpris-

Table 4. Pathologic Findings and Immunopathology at Biopsy: Effects of Dose and Antigen Expression on ^{131}I Delivery

Patient No.	% Injected Dose Per g of Tumor	Dose (mg)	IgG Per G of Tumor ($\times 10^{-9}$)	Biopsy*	OKB7 Antigen†	OKB7 IgG‡	Immunophenotype
1	.00020	0.1	< 1	NPDL	2+	–	B Cell
2	.00003	0.1	< 1	DPDL	2+	–	B Cell
3	.00144	0.1	6	DML	2+	–	B Cell
4	.00008	0.5	2	NPDL	3+	–	B Cell
5	.00100	0.5	20	NPDL	3+	–	B Cell
6	.00070	0.5	14	Normal node, lipoma	(B cell+)	–	B Cell
7	.01900	1	800	NML	3+	–	B Cell
8	.00020	1	8	DHL	–	–	B Cell
9	.00060	1	24	DHL	–	–	B Cell
10	.00020	5	40	DPDL	3+	–	B Cell
11	.00200	5	400	Hyperplastic normal node	2+	–	B Cell
12	.00500	5	1,000	Atypical hyperplastic t(14;18)	3+	–	B Cell
13	.00070	15	420	DPDL	2+	–	B Cell
14	.00050	15	300	DML	NE	NE	NE
15	.00010	15	60	DPDL	–/+	–	B Cell
16	.00090	40	1,460	DHL	–/+	–	B Cell
17	.00020	40	320	NPDL	3+	–	B Cell
18	.00127	40	2,032	NPDL	3+	–	B Cell

Abbreviation: NE, not examined due to technical problems.

*The histopathologic diagnosis of the tumor biopsied on study.

†Scored for the presence of OKB7 target antigen (gp140) by indirect immunopathology: –, no positive cells; –/+, < 10% positive cells; 2+, 50% to 70% positive cells; 3+, > 70% positive cells.

‡Scored for the presence of OKB7 IgG in the tumor biopsy.

ing since the amount of OKB7 IgG per gram of tumor in all of the biopsies was extremely low, and about 1 billion lymphocytes might be contained in 1 g of tissue (Table 4).

Tumor Uptake of OKB7 and Radioisotope Dosimetry

The amount of ^{131}I-OKB7 in the tumor was determined by weighing the biopsy specimen and counting the radioactivity in a gamma counter. The percentage of the injected dose of OKB7 per gram of tumor tissue was calculated (Table 4).

The mean amount of IgG delivered per gram of tumor varied directly with the injected dose (Table 4). The average number of molecules of OKB7 per cell ranged 400-fold, from 2 to 3 IgG to 1,270 IgG, exactly the same 400-fold range as that of the doses injected (0.1 to 40 mg). In contrast, the percentage of injected dose per gram of tumor was unrelated to the injected dose. Two features that were critical in determining what percentage of the injected dose was found in tumor tissue were the strength of OKB7 antigen expression in the tumor and the size of the tumor burden. Antigen-negative tumors did not take up OKB7 and the intensity of targeting to antigen-positive tumors was related inversely to the amount of tumor (Fig 2).

Radiation doses delivered to the whole body and blood were calculated by MIRD S factors and the effective T½s of ^{131}I in the various parts of the body (Table 5). In 17 of the patients rad per millicurie doses to the whole body were low, ranging from 0.2 to 0.7 rad/mCi. Nonpenetrating blood doses were somewhat higher. Patient no. 9 received a higher rad per millicurie dose due to a longer antibody T½ as discussed above. Patient no. 3 had a large blood dose due to increased serum T½. If 200 rad to the whole body were considered a tolerable limit of radiation dose,[37] between 300 and 1,000 mCi total dose of ^{131}I could be injected safely, depending on the particular patient's pharmacokinetics, without expecting severe myelosuppression.

Tumor doses were calculated in patients no. 7 and 12 using the exact dose delivered to the tumor from the biopsy and the effective T½ of the iodine at the tumor based on cpm in areas of interest from the images. The tumor to blood, marrow, and body ratios for rad per millicurie doses to these tissues suggested that therapeutic doses might be delivered to these tumors with significant dose escalation without compromising marrow function. Assuming a 200 rad cumulative dose to the bone marrow, then isotope dose escalation to this upper limit would deliver 4,400 rad to the tumor in patient no. 7 and 1,400 rad to the tumor in patient no. 12.

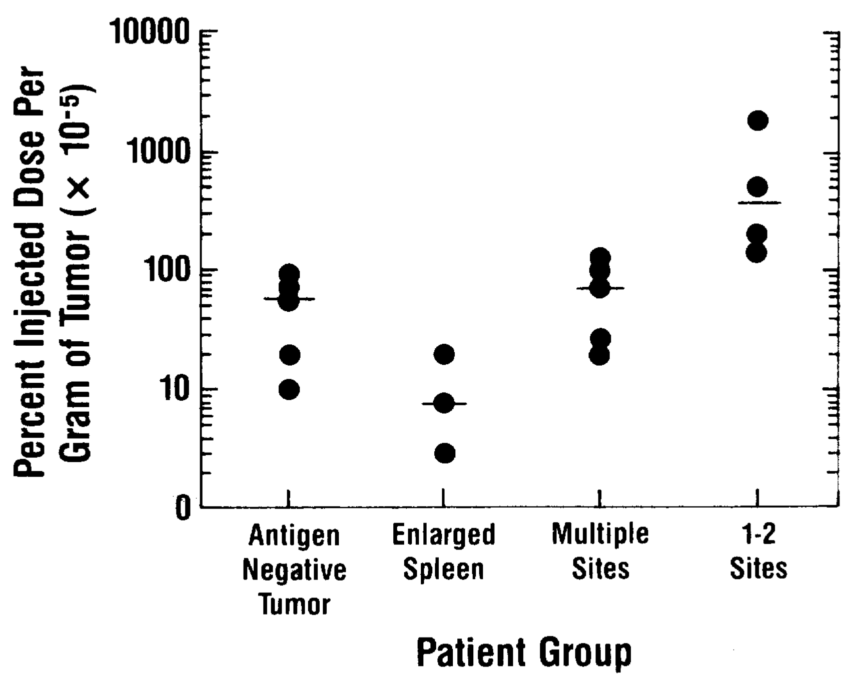

Fig 2. Patient characteristics v the percentage of injected dose of ^{131}I-OKB7 per gram of tumor at biopsy. The percentage of injected dose is expressed on a log scale. Individual values are shown in Table 4. Full description of the patients appears in the text.

HAMA Responses

Serum was collected from all patients to determine the presence, duration, and strength of the HAMA response. Five patients developed HAMA (patients no. 5, 7, 10, 11, 12). The antibodies disappeared at 7, 9, and 11 months in three patients and were still detectable at 9 months in two. These responses were not OKB7-specific (antiidiotypic). The appearance of HAMA did not appear to correlate with pretreatment IgG or IgM levels. Of interest is that three of the five HAMA-positive patients had a small burden (no. 7, 11, 12) and are still without evidence of disease. The two other patients had moderate tumor burden.

Tumor Responses

No lymphoma regression could be attributed to the OKB7 infusions. In two patients all measurable disease was removed by the surgical biopsy (patients no. 7 and 12). Two patients (no. 6 and 11) had normal nodes at biopsy. Three of these four patients (no. 7, 11, and 12) have remained in remission at 12+, 11+, and 11+ months, respectively. These three patients had the highest percentage of uptake of OKB7 per dose in their nodes (Table 5).

DISCUSSION

This phase I trial was designed to examine OKB7 toxicity and pharmacology, the development of HAMA responses to OKB7, and the relationships of antibody dose, tumor antigen expression, and tumor burden on the delivery of mAb to the tumors. The study included a large escalating dose range and a variety of patients with relapsed NHL, differing in extent of disease and degree of antigen expression in tumor tissue. Accurate determination of tumor uptake was made by biopsy in all patients. Other trials examining some of these issues have been limited either by small size, lack of biopsy data, no dose escalation, or no immunopathologic correlation.[8,9,13,35] The information offered in this study will now be used to design a therapeutic trial that will optimize ^{131}I-OKB7 delivery to lymphomas.

The mAb doses showed reproducible labeling characteristics and immunoreactivity. No toxicity and no tumor response could be attributed to the mAb infusion. Since these patients generally did not have significant numbers of OKB7-positive cells in their circulation, antigen modulation was not studied.

Development of HAMA was observed in five of 18 patients. The incidence of HAMA is

Table 5. Dosimetry Calculations for ^{131}I-OKB7

Patient No.	Dose (mg)	Doses Delivered (rad/mCi) Body	Serum*	Tumor†	(Rad/mCi) Ratio of Tumor to Body	^{131}I Ratios Tumor to Marrow‡	Tumor to Serum
1	0.1	0.43	1.94			—	0.2
2	0.1	0.23	0.74			—	0.2
3	0.1	0.68	2.48			—	0.6
4	0.5	0.39	0.59			—	1.7
5	0.5	0.26	1.09			—	0.2
6	0.5	0.47	1.22			1.3	0.9
7	1	0.36	1.38	7.9	22-fold	32.2§	11.9
8	1	0.45	1.18			0.3	0.2
9	1	3.24	1.93			—	0.2
10	5	0.31	0.74			1.2	0.2
11	5	0.41	0.79			11.4	1.6
12	5	0.43	1.95	3.0	7-fold	75.7	3.8‖
13	15	0.21	1.95			2.3	0.3
14	15	0.24	0.73			5.3	0.6
15	15	0.36	0.60			0.3	0.3
16	40	0.31	0.91			1.2	0.7
17	40	0.30	0.65			—	0.3
18	40	0.20	0.83			4.3	1.0

*Nonpenetrating serum doses.

†Data are not shown for tumors where uptake was not significant.

‡Not all patients had bone marrow core biopsies.

§Marrow was obtained several hours before biopsy so the ratio is a minimum value.

‖The biopsy was obtained several hours after the last blood sample, therefore serum radioactivity was calculated by extrapolation.

generally low in patients with B-cell neoplasms treated with mAbs.[2] This has been attributed either to the immunosuppression associated with B-cell lymphomas, especially CLL, or to the use of cytotoxic and immunosuppressive therapies in these patients, or to impure antibody preparations. However, pretreatment Ig levels, immunosuppressive therapy, and the dose of administered antibody did not correlate well with the development of HAMA in this trial. HAMA response persisted for up to 1 year. This persistence may be an impediment to re-treatment in this subset of patients.

Pharmacologic studies demonstrated two phases of serum clearance with median $T^{1/2}$s of 1.9 hours and 21.7 hours, and a total body clearance, with a median $T^{1/2}$ of 22 hours. This rapid clearance is similar to that seen in other studies,[8,9,13,38-40] and results in 0.2 to 0.5 rad/mCi to the whole body. Excretion of ^{131}I was largely via the kidneys, but also included gastrointestinal excretion following gastric secretion. Surprisingly, despite the large range of doses given in this trial, there did not appear to be a relationship between dose and pharmacokinetics, perhaps because even the largest dose used in this trial was too low to saturate either the available binding sites or the excretory mechanisms. Other studies with mAbs have observed either dose-related or -unrelated pharmacokinetics.[13,33,38-40] Prolonged total body and serum $T^{1/2}$s of ^{131}I were demonstrated in one patient each, resulting in significant increases in estimated whole body radiation doses. Therefore, pharmacokinetics should continue to be studied in individual patients in future trials using radiolabeled antibody at therapeutic levels to alert us to an unexpected risk of major hematologic toxicity. A more rapid clearance was seen in one patient, who had high levels of circulating antigen, a factor that needs to be assessed in order to more accurately estimate the radiation dose delivered by an mAb.

The availability of tumor biopsies in these patients allowed us to study the relationship between OKB7 target antigen expression and mAb uptake at the tumor site. Tumors with little or no antigen expression did not specifically take up ^{131}I-OKB7 as determined on scans or in biopsies. Similar results have been obtained in radiolocalization studies in patients with colon cancer.[40] This uptake (median, 0.0007%) might thus be considered nonspecific background. In contrast, several patients with antigen-positive tumors had significant specific uptake of OKB7. This uptake, expressed as percent of the injected dose per gram of tumor, did not depend on dose. Rather it appeared to vary inversely with the tumor burden (Fig 2). Patients with a large tumor burden, which included palpable splenomegaly, had the lowest uptake, even less than patients with no antigen expression. This reduction in tumor uptake (median, 0.00008%) is consistent with rapid absorption of antibody by the spleen. Studies in primates using T- and B-cell specific mAbs support this concept.[41] In patients with massive splenomegaly, the splenic lymphoma and B cells might be able to absorb much more than the 40 mg injected dose of OKB7, for example, as occurred in patient no. 17. In patients with large numbers of circulating OKB7-positive cells, for example, in patient no. 15, similar absorption would be expected to occur. Patients with multiple sites of disease and no palpable spleen had eight times more uptake (median, 0.0006%), but no more than antigen-negative tumors. Patients with minimal disease had a six times higher percentage uptake than those with multiple sites of disease (median, 0.0035%). Thus tumor burden changed median percentage uptake by more than 40-fold. At the levels used in this study, antibody dose did not appear to play a major role in determining percentage uptake (Table 4). It is of interest that the highest percentage uptakes, seen in patients given 1 and 5 mg doses, were as high or higher than the percentage uptakes seen in patients given 500-fold larger doses of antibody in another trial in patients with B-cell lymphoma, suggesting dose escalation alone does not always result in better mAb delivery to tumors.[13] This other trial also showed a clear relationship between dosimetry and tumor burden. We cannot predict how a similar dose escalation would affect OKB7 dosimetry.

In contrast, dose did influence in a direct manner the total OKB7 accumulation at a site. The total amount of antibody present (not the percentage of injected dose) at a tumor site increased proportionally with the dose over a 400-fold range (Table 4).

The biopsy dosimetry data were supported by whole body images, which clearly showed early and significant uptake in the spleen, especially, for example, in patient no. 17, and clear images of tumors in patients no. 7 and 12. Microdosimetry within target tissues using quantitative autoradiography[42] was not examined in this study. Pathologic examination of the nodular lymphomas clearly showed that only the lymphoma nodules, which represent 40% to 60% of the involved node, were OKB7 antigen-positive. Thus, it is possible that radioisotope doses to these lymphoma cells are twofold higher than can be predicted by weighing the entire node. Welt et al[39] were able to show considerable quantitative differences in the delivery of radioiodinated mAb to colon carcinoma metastases by examining different parts of large tumors.

With the exception of two patients with altered renal and vascular function, doses delivered to the whole body, marrow, blood, and organs other than the spleen and bladder were low. In patients no. 7 and 12 the cumulative rad per millicurie doses to the tumor as compared with the body were high enough that ^{131}I dose escalation to therapeutic levels should be feasible. At 200 rad to the whole body, 4,400 and 1,400 rad would be delivered to the lymphomas of patients no. 7 and 12, respectively.

The optimal delivery of mAbs specifically to tumors will require an understanding of an extraordinarily complicated pharmacologic system that involves not only serum antibody levels and clearance mechanisms, but also antibody affinity, antigen-antibody interactions, host and cellular responses to antibody, circulating and cell-surface antigen levels, and tumor burden. The difficult problems posed by antigen modulation, HAMA response, and lack of antibody cytotoxicity have been identified in prior trials.[1,2] The present trial underscores the additional obstacles posed by low antigen expression and large tumor burden. While the issue of antigen heterogeneity can be addressed by combined use of several antibodies, the problem of tumor burden is less easily solved. Therapy with mAb might be more usefully applied in an adjuvant setting, in splenectomized patients, or after cytoreduction. Alternatively, the tumor dose might be increased by increasing the dose of antibody as shown in a study of ^{131}I-MB1 in patients with NHL in which up to 10 mg/kg of antibody were infused.[13] However, even at these large doses, adequate tumor dosimetry was achieved only in one half of the patients, and grade 4 hematologic toxicity requiring marrow rescue was often seen. An alternative approach to increasing specific delivery of isotope to tumor sites might be to use repeated moderate doses of mAb to achieve a large cumulative dose at the tumor. This might reduce the total amount of antibody delivered to the tumor but might increase the specificity and consequently lower the toxicity.

ACKNOWLEDGMENT

We wish to thank Elizabeth Carswell, Mary John, Janet Lestella, Gerald Minniti, Linda Shapiro, Angeline Agregado, and Lucy Dantis and her staff without whom this trial would not have been possible. We thank Steven Larson for his advice and Linda Forte for preparation of the manuscript.

REFERENCES

1. Houghton AN, Scheinberg DA: Monoclonal antibodies: Potential applications to the treatment of cancer. Semin Oncol 13:165-179, 1986

2. Scheinberg DA, Houghton AN: Current status of antitumor therapy with monoclonal antibodies. Oncology 2:31-40, 1987

3. Miller RA, Levy R: Response of cutaneous T cell lymphoma to therapy with hybridoma monoclonal antibody. Lancet 2:226-230, 1981

4. Ritz J, Pesando JM, Sallan SE, et al: Serotherapy of acute lymphoblastic leukemia with monoclonal antibody. Blood 58:141-152, 1981

5. Foon KA, Schroff RW, Bunn PA, et al: Effects of monoclonal antibody therapy in patients with chronic lymphocytic leukemia. Blood 64:1085-1093, 1984

6. Waldmann TA, Goldman CK, Bongiovanni KF, et al: Therapy of patients with human T-cell lymphotrophic virus I-induced adult T-cell leukemia with anti-tac, a monoclonal antibody to the receptor for interleukin-2. Blood 72:1805-1816, 1988

7. Dillman RO, Shawler DL, Dillman DB, et al: Therapy of chronic lymphocytic leukemia and cutaneous T-cell lymphomas with T101 monoclonal antibody. J Clin Oncol 2:881-891, 1984

8. DeNardo SJ, DeNardo GL, O'Grady LF, et al: Pilot studies of radioimmunotherapy of B cell lymphoma and leukemia using I-131 lym-1 monoclonal antibody. Antibodies, Immunoconjugates Radiopharmaceut 1:17-27, 1988

9. Rosen ST, Zimmer AM, Goldman-Leikin R, et al: Radioimmunodetection and radioimmunotherapy of cutaneous T cell lymphomas using an ^{131}I-labeled monoclonal antibody: An Illinois Cancer Council study. J Clin Oncol 5:562-573, 1987

10. DeNardo SJ, O'Grady LF, DeNardo GC, et al: Radioimmunotherapy of lymphoproliferative disease. Blood 72:241a, 1988 (abstr)

11. Dyer MJS, Hale G, Hayhoe FGJ, et al: Effects of CAMPATH-1 antibodies in vivo in patients with lymphoid malignancies: Influence of antibody isotype. Blood 73:1431-1439, 1989

12. Hale G, Dyer MJS, Clark MR, et al: Remission induction in non-Hodgkin lymphoma with the reshaped human monoclonal antibody CAMPATH-1H. Lancet 2:1394-1399, 1988

13. Press OW, Eary JF, Badjer CC, et al: Treatment of refractory non-Hodgkin's lymphoma with radiolabeled MB-1 (Anti-CD37) antibody. J Clin Oncol, (in press, 1989)

14. Foon KA, Todd III RF: Immunologic classification of leukemia and lymphoma. Blood 68:1-31, 1986

15. Koziner B, Little C, Passe S, et al: Treatment of advanced diffuse histiocytic lymphoma: An analysis of prognostic variables. Cancer 49:1571-1586, 1982

16. Al Katib A, Koziner B, Kurland E, et al: Treatment of diffuse poorly differentiated lymphocytic lymphoma: An analysis of prognostic variables. Cancer 53:2404-2412, 1984

17. Portlock CS: "Good risk" non-Hodgkin's lymphomas: Approaches to management. Sem Hematol 20:25-34, 1983

18. Cabanillas F, Hagemeister FB, McLaughlin P, et al: Results of MIME salvage regimen for recurrent or refractory lymphoma. J Clin Oncol 5:407-412, 1987

19. Press OW, Appelbaum F, Ledbetter JA, et al: Monoclonal antibody 1F5 (Anti-CD20) serotherapy of human B cell lymphomas. Blood 69:584-591, 1987

20. Meeker TC, Lowder J, Maloney DV, et al: A clinical trial of anti-idiotype therapy for B-cell malignancy. Blood 65:1349-1363, 1985

21. Brown SL, Miller RA, Horning SJ, et al: Treatment of B-cell lymphomas with anti-idiotype antibodies alone and in combination with alpha interferon. Blood 73:651-661, 1989

22. Meeker T, Lowder J, Cleary ML, et al: Emergence of idiotype variants during treatment of B-cell lymphoma with anti-idiotype antibodies. N Engl J Med 312:1658-1665, 1985

23. Mittler RS, Talle MA, Carpender K, et al: Generation and characterization of monoclonal antibodies reactive with human B lymphocytes. J Immunol 131:1754-1761, 1983

24. Nemerow GR, Wolfert R, McNaughton ME, et al: Identification and characterization of the Epstein-Barr virus receptor on human B lymphocytes and its relationship to the C3d complement receptor (CR2). J Virol 55:347-351, 1985

25. Siaw MFE, Nemerow GR, Cooper NR: Biochemical and antigenic analysis of the Epstein-Barr virus/C3d receptor (CR2). J Immunol 136:4146-4151, 1986

26. Knowles II DM, Dodson LD, Raab R, et al: The application of monoclonal antibodies to the characterization and diagnosis of lymphoid neoplasms: A review of recent studies. Diag Immuno 1:142-149, 1983

27. Knowles II DM, Tolidijian B, Marboe CC, et al: Distribution of antigens defined by OKB monoclonal antibodies on benign and benign and malignant lymphoid cells and on non-lymphoid tissues. Blood 63:886-896, 1984

28. Nemerow GR, McNaughton ME, Cooper NR: Binding of monoclonal antibody to the EBV/CR2 receptor induces activation and differentiation of human B lymphocytes. J Immunol 135:3068-3073, 1985

29. Bohnsack JF, Cooper NR: CR2 ligands modulate human B cell activation. J Immunol 141:2569-2576, 1988

30. Snyder WS, Ford MR, Warner GG, et al: MIRD S Factors Pamphlet No. 11. Society of Nuclear Medicine Publishers, Oak Ridge, TN, 1975

31. Garin-Chesa P, Rettig WJ, Thomson PM, et al: Immunohistochemical analysis of nerve growth factor receptor expression in normal and malignant human tissues. J Histochem Cytochem 36:383-389, 1988

32. Tanimoto M, Scheinberg DA, Cordon-Cardo C, et al: Restricted expression of an early myeloid and monocytic cell surface antigen defined by monoclonal antibody M195. Leukemia 3:339-348, 1989

33. Scheinberg DA, Strand M: Kinetic and catabolic considerations of monoclonal antibody targeting in erythroleukemic mice. Cancer Res 43:265-272, 1983

34. Carrasquillo JA, Mulshine JL, Bunn PA Jr, et al: Indium-111 T101 monoclonal antibody is superior to iodine-131 T101 in imaging of cutaneous T-cell lymphoma. J Nucl Med 28:281-287, 1987

35. Carrasquillo JA, Bunn PA Jr, Keenan AM, et al: Radioimmunodetection of cutaneous T-cell lymphoma with ^{111}In-labeled T101 monoclonal antibody. N Engl J Med 315:673-680, 1986

36. Scheinberg DA, Strand M, Gansow OA: Tumor imaging with radioactive metal chelate conjugated monoclonal antibodies. Science 215:1511-1513, 1982

37. Benhua RS, Cicale NR, Sonenberg M, et al: The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid carcinoma. Am J Roentgen 87:171-178, 1962

38. Zalutsky MR, Moseley RP, Coakham HB, et al: Pharmacokinetics and tumor localization of ^{131}I-labeled anti-tenascin monoclonal antibody 81C6 in patients with gliomas and other intracranial malignancies. Cancer Res 49:2807-2813, 1989

39. Welt S, Divgi CR, Real FX, et al: Radiolocalization of ^{131}I-AS33 in colorectal cancer. Proc Am Soc Clin Oncol 8:106, 1989 (abstr)

40. Cohn KH, Welt S, Banner WP, et al: Localization of radioiodinated monoclonal antibody in colorectal cancer. Arch Surg 122:1425-1429, 1987

41. Letvin JL, Ritz J, Guida LJ, et al: In vivo administration of lymphocyte-specific monoclonal antibodies in nonhuman primates: I. Effects of anti-T11 antibodies on the circulating T cell pool. Blood 66:961-966, 1985

42. Del Vecchio S, Reynolds JC, Carrasquillo JA, et al: Local distribution and concentration of intravenously injected ^{131}I-9.2.27 monoclonal antibody in human malignant melanoma. Cancer Res 49:2783-2789, 1989