Pharmacokinetics, Immune Response, and Biodistribution of Iodine-131-Labeled Chimeric Mouse/Human IgG1,k 17-1A Monoclonal Antibody

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Pharmacokinetics, immunogenicity, and biodistribution of a ^{131}I-labeled mouse/human chimeric monoclonal antibody (C-17-1A) was studied in six metastatic colon cancer patients. Pharmacokinetics obtained from serum radioactivity or chimera concentration were identical after 5 mCi of ^{131}I-C-17-1A with mean alpha half-lives of 17.6 ± 2.3 and 19.7 ± 2.9 and mean beta half-lives of 100.9 ± 16.1 and 106.4 ± 14.1 hr, respectively. HPLC analysis documented the monomeric chimeric 17-1A without evidence of immune complexes or free ^{131}I. None of the patients developed antibody after ^{131}I-chimeric 17-1A exposure. Radiolocalization occurred in known areas of disease >4 cm in all patients. The half-life of total-body radioactivity was 58 ± 7 hr by whole-body counts and 64 ± 13 hr by urine measurements. Whole-body and bone marrow dose estimates ranged from 0.75–1.03 and 0.76–1.05 rad/mCi, respectively. These studies confirm the prolonged circulation and reduced immunogenicity of chimeric 17-1A versus murine 17-1A. Marrow radiation exposure using antibodies with prolonged circulation is a critical factor in planning for radioimmunotherapeutic applications.

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The clinical application of monoclonal antibodies and, in particular, radioimmunotherapy are currently the subject of intense investigation. One of the problems involved in early use of this modality or other types of immunotherapy using xenogeneic antibodies is that the antibody represents a source of foreign protein against which the host makes antibodies (*1–4*). An immune response against the therapeutically administered antibody can result in allergic reactions (sometimes severe) and can decrease effectiveness of therapeutic antibody administration by removing it from circulation before it reaches the target cells (*1,5*). One approach to this problem is the use of genetically engineered chimeric monoclonal antibodies (*6–9*). Using recombinant DNA techniques, a chimeric antibody was formed using the murine variable region of 17-1A (antibody against gastrointestinal cancer) with a human immunoglobulin G1,k constant region (*10,11*). By minimizing the amount of xenogeneic protein attached to a human constant region, there may be reduced immunogenicity. A previous phase I study with unlabeled chimeric 17-1A antibody (C17-1A) suggested that it was less immunogenic and also had a longer half-life in the circulation compared with its murine 17-1A counterpart (*12*).

The current study was undertaken to examine pharmacokinetics, stability, biodistribution, and immunogenicity of ^{131}I-labeled chimeric 17-1A in patients with metastatic colon cancer.

MATERIALS AND METHODS

Patient Selection

Six patients 18 yr of age or older with metastatic adenocarcinoma of the colon were selected. They had a Karnofsky performance score of 70 or greater, life expectancy of at least 6 wk, serum creatinine of <1.5 mg/dl, bilirubin of <2.0 mg/dl, and normal WBC and platelet counts. Patients were excluded from participation on the basis of previous monoclonal antibody therapy, mental deficiency, pregnancy, iodine sensitivity and chemotherapy, and/or radiation in the past 4 wk.

Study Design

Eligible, consenting patients underwent baseline evaluation prior to antibody infusion, including a history and physical examination, vital signs, body weight, performance status, ECG, chest x-ray, CT scan of areas of measurable disease, lesion measurements, urinalysis, thyroid function tests, blood chemistries, and hematologic studies. Following antibody infusion, vital signs

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were frequently monitored for the first 4 hr, and serial blood samples were drawn immediately postinfusion (0 time) and at 1, 2, 4, 24, 48, and 72 hr and on Days 8, 15, and 18 to monitor clearance of circulating antibody. Blood was drawn weekly for 12 wk to monitor human antibody response. Urine collection was carried out for five days to quantitate excretion of radioactive material. Gamma camera imaging and whole-body counting were also serially performed for 15 days following infusion. Subsequently, patients had follow-up examinations and blood studies at Days 29 and 43 after antibody administration. Toxicity grading utilized criteria standardly used by the Radiation Therapy Oncology Group (*13*).

Chimeric 17-1A and Radiolabeling Procedure

Chimeric G1,k 17-1A was produced as previously described (*11,14*) and provided through Centocor, Inc. as a solution of 2.24 mg/ml in 0.145 *M* NaCl. The purity and quality assurance requirements were in accordance with the approved IND application filed with the Food and Drug Administration. The radiolabeling procedure was the lodogen method (*15*) at a specific activity of 10 mCi/mg. The instant thin-layer chromatography (*16*) analysis indicated greater than 97% (range, 97.1–99.9) incorporation of iodine before purification. The free iodine was separated from ^{131}I-C17-1A by passage through a 1 × 22.5 cm Acrylamide desalting column (Clinitics, Inc, Tustin, CA). Quality control of the radiolabeled product included immunoreactivity by the method of Lindmo (*17*). An increasing number of colorectal carcinoma cells (SW1116) were added to 10 ng of ^{131}I-C17-1A. Following incubation at 37°C for 90 min and washing, the cell-associated radioactivity was determined. The percent maximum binding was extrapolated to infinite cell concentration. The average immunoreactivity of the radiolabeled preparations was 54% with a range of 40%–72%. HPLC analysis of the final products showed greater than 99% of radioactivity was eluted with C17-1A. Limulus amebocyte lysate assay was performed prior to infusion.

Antibody Administration

Patients received ten drops of a saturated potassium iodide solution before administration of the ^{131}I-labeled antibody and continued daily for 14 days. A test dose of unlabeled C-17-1A (2 mg) was infused intravenously over 30 min prior to injection of 2 mg C-17-1A labeled with approximately 5 mCi ^{131}I (actual dose 5.61–8.31 mCi).

Pharmacokinetics and HPLC Analysis

Sera were assayed for radioactivity using a LKB 1282 Compugamma CS counter. The counts per minute were converted to disintergrations per minute and backcorrected to 0 time for radioactive decay. The radioactive counts were then utilized to calculate the pharmacokinetic parameters as previously described (*12*). The sera were then stored for 10 wk to allow radioactive decay and then underwent immunoassay for chimeric 17-1A concentration (*12*). These concentrations were then used as an independent set of values to calculate the pharmacokinetic parameters in an identical fashion to the radioactive counts.

Selected postinfusion serum samples were analyzed (20-μl samples) for distribution of radioactivity using a Bio-Rad Quick Check Analyzer (Richmond, CA) system with a Bio-Sil TSK 250 column (600 × 7.5 mm). The elution buffer was 10 m*M* phosphate, pH 6.8, 0.3 *M* NaCl, 10% (v/v) dimethyl sulfoxide. The column was eluted at 1.0 ml/min and 1-ml fractions were collected. The fractions were counted in a Packard gamma counter (Gaithersburg, MD) and were corrected for decay.

Human Antibody to Chimeric 17-1A Assay

Serum was tested in triplicate for the presence of antibody to chimeric 17-1A utilizing a radiometric "double-antigen" assay system as previously described (*12*). Results were expressed as ng of ^{125}I-chimeric 17-1A bound/ml of plasma. A positive assay was defined as a statistically significant increase in ^{125}I-chimeric 17-1A bound which was at least twice the baseline pre-therapy value.

Dosimetry Data Collection

Whole-body counting at 13.5 feet from the patient's center was done with a NaI crystal interfaced with a multichannel analyzer (window 311- to 434 keV). Background counts were subtracted from the gross patients' counts. Urine collections for each 24-hr interval of the five days after infusion were brought to a volume of 3000 ml and counted under the same conditions as patient counts.

Multiple spot views of the trunk (and of other areas when indicated) were obtained using a wide field of view gamma camera with a high-energy parallel-hole collimator and a 30% window centered on 364 keV. Scans were scheduled at 4 hr after infusion of radiolabeled antibody and at multiple times up to 14 days. Organ and lesion doses were calculated from background-subtracted region of interest count rates with depth and dimensions estimated from contrast-enhanced CT images.

Cumulated activity for serum, whole-body, and regions of interest were the summation of segmental activities calculated from counts at each sample time. The adjusted total-body cumulated activity and the individual source organ (excess) cumulated activities were multiplied by the appropriate S values from MIRD Pamphlet No. 11 and summed to obtain radiation dose estimates for the organs of interest and for the total body (*18, 19*). Since the organ scan data were initially corrected for patient background, the cumulated activities obtained for the identified source organs were taken to represent excess above background rather than total cumulated activities for those organs. Consequently, the cumulated activity correction described by Cloutier et al. (*20*) was not applied. A simple subtraction of the sum of the source organ cumulated activities from that of the total body gave a value for the remainder of the body.

Data points for remaining total-body radioactivity determined from a gamma detection or urinary excretion for all six patients was analyzed using a non-linear regression computer program and a best fit logarithmic line was graphed. Data points for loss due to urinary excretion were taken as the measured value at the end of each collection interval.

RESULTS

The six patients (age range 30–73 yr) tolerated the antibody administration without any adverse reactions. Five of the six patients had liver metastases and three had other areas of spread as indicated in Table 1. Positive radioimmune imaging occurred in all patients in known lesions >4 cm in size, whereas smaller pulmonary, liver and lymph node metastases were not detected (Table 1). The earliest tumor imaging occurred at Day 4 in three patients and Day 7 in the remaining three patients. Four of the patients had successful imaging on one day (Day 4

or 7) while two had persistence of the positive uptake on a subsequent scan.

Metastatic lesions in the liver were the most frequently imaged tumor sites with positive uptake occurring at Day 4 or 7. Two patients had lesions in the pelvis or abdomen (Patients 4 and 5), which imaged successfully on Days 4 and/or 7. A moderate-sized lung metastasis (Patient 1) and porta hepatis lymph nodes (Patient 3) did not have a detectable antibody localization.

Pharmacokinetics and HPLC

Figure 1 illustrates the amount of radioactivity in the serum of Patient 1 over 14 days of postinfusion follow-up with radioactive counts backcorrected for decay to 0-time. The solid line represents a computer-generated curve for a two-compartment model with an alpha half-life of 17.9 hr and a beta half-life of 87.7 hr. The serum disappearance of radioactivity in all six patients best fit a two-compartment model with individual values listed in Table 2. The same serum samples subsequently underwent radioimmunoassay for chimeric 17-1A concentration with pharmacokinetic analysis of each patient's values (Table 3). The pharmacokinetic parameters based on these two independent measures of ^{131}I-labeled chimeric antibody are quite similar. As illustrated in Figure 2, plotting the mean values of all six patients expressed as percent of injected dose (radioactivity or protein concentration) results in two curves that do not significantly differ from each other indicating that the radiolabel remains bound to the chimeric antibody over 14 days in the circulation. HPLC analysis of serum samples drawn from 1 hr to 3 days postinfusion failed to show evidence of immune complexes or free ^{131}I.

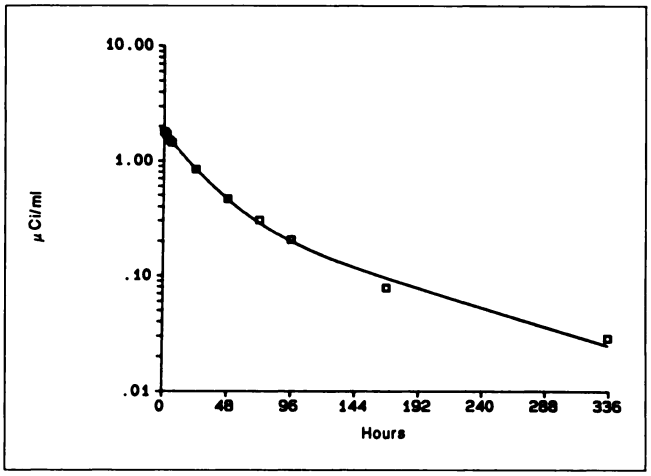

FIGURE 1. Pharmacokinetic curve of ^{131}I-labeled chimeric 17-1A monoclonal antibody in Patient 1. Patient received 6.72 mCi of ^{131}I-C17-1A (10 mCi/mg) on Day 0. □, measured radioactivity of ^{131}I in serum; solid line is a computer-generated curve for a two-compartment model for these values. Alpha $T_{½}$: 17.9 hr; beta $T_{½}$: 87.7 hr.

Dosimetry

The whole-body radioactivity derived from whole-body gamma counting or urinary excretion gave remarkably similar half-life kinetics with a mean of 58 versus 64 hr (Table 4). The six individual patients each had quite similar rates of disappearance of whole body radioactivity as measured by whole body counts (Fig. 3) or by urinary excretion (Fig. 4).

The radiation dose estimates for whole body and individual organs are shown in Table 5. The range of values for whole-body radiation (0.75–1.03 rad/mCi) and bone marrow radiation (0.76–1.05 rad/mCi) were quite narrow and had mean values of 0.83 and 0.86, respectively. The radiation exposure estimates for liver, spleen and thyroid were more variable among the six patients. The cumulated activ-

TABLE 1
Imaging of Metastatic Lesions in Colon Cancer Patients

Patient no.	Age/ Gender	Metastatic site	Days imaged*
1	56 M	Liver 5.0 × 5.0	4
		Liver 5.0 × 5.2	4
		Liver 4.0 × 5.0	4
		Lung 4.0 × 2.5	—
2	58 F	Liver 4.2 × 3.8	4
		Liver 5.0 × 5.0	4
3	42 F	Liver 9.5 × 8.0	7, 9
		Liver 4.5 × 4.0	7, 9
		Lymph nodes	—
		porta hepatis 2.0 × 3.0	—
		porta hepatis 2.0 × 3.0	
4	72 F	Liver 6.0 × 6.5	4, 7
		Liver 4.0 × 1.0	4, 7
		Abdomen 7.0 × 3.0	4, 7
5	73 M	Liver 5.0 × 4.0	7
		1.0 × 1.0	—
		1.0 × 1.0	—
6	30 F	Pelvis 3.5 × 4.5	7†

* Day 0 = day of infusion.

† Area of localization corresponding to known pelvic mass likely represents tumor and persists post-voiding but could not be separated from bladder on the anterior and posterior images obtained. Lateral images would likely have been helpful in distinguishing the tumor from normal structures but were not available.

TABLE 2
Pharmacokinetic Parameters of ^{131}I-C17-1A Based on Serum Radioactivity

Patient	α $T_{½}$ (hr)	β $T_{½}$ (hr)	AUC (mCi-hr/ml)	MRT (hr)	V_{dss} (ml/kg)
1 (GB)	17.9	87.7	82	81.2	75
2 (MB)	19.9	109.0	128	112.3	84
3 (JP)	12.4	76.3	65	85.9	70
4 (EL)	17.6	91.9	85	101.6	92
5 (BG)	10.9	65.3	99	71.8	110
6 (TH)	27.0	175.5	173	190.1	117
mean	17.6	100.9	105	107.1	91.3
s.e.m.	2.3	16.1	16	17.6	7.7

TABLE 3
Pharmacokinetic Parameters of ^{131}I-C17-1A Based on Serum Chimera Concentrations

Patient	α $T_{½}$ (hr)	β $T_{½}$ (hr)	AUC (μg-hr/ml)	MRT (hr)	Vd_{ss} (ml/kg)
1 (GB)	23.2	99.8	39	81.5	66.4
2 (MB)	25.7	106.7	66	116.1	80.5
3 (JP)	14.7	71.4	35	80.9	52.0
4 (EL)	8.0	94.7	47	112.9	74.2
5 (KBG)	21.5	93.5	68	80.9	68.2
6 (TH)	25.4	172.3	92	214.5	88.5
mean	19.7	106.4	58	114.5	71.7
s.e.m.	2.9	14.1	.9	21.1	5.1

ity from serum measurements of the six patients is not included as a component of the marrow dose and ranged from 194 to 318 mCi-hr ($\bar{x}$ = 232 ± 47).

Although tumor localization by imaging studies was noted for lesions >4 cm in all six patients, the increase in activity as compared to surrounding tissue was modest and transient. An estimate of dose to the most defined localization of and anterior abdominal wall mass was 2.05 rad/mCi, which represents a 2.33-fold increase over adjacent normal bowel.

Comparison of the peak organ uptake among the patients (Table 6) shows that the liver had the largest proportion of uptake and the least difference in uptake between patients. There was less than a two-fold difference in percent of activity found in the liver whereas the highest uptake values for spleen and thyroid were more than four-fold over those of the patients showing the least uptake.

Immune Response

Table 7 provides the data on antibody response to chimeric 17-1A over 12 wk postinfusion. There were no instances of significant increases in ^{125}I-chimeric 17-1A binding as compared to baseline values in each patient. A positive control rabbit anti-17-1A $F_{(ab)_2}'$ bound 198 ng at a 1:160 dilution and a serum sample from a patient treated with murine 17-1A from a prior study (*4*) bound 73.6 ng/ml of chimeric 17-1A.

TABLE 4
Comparison of Half-Lives of Radioactivity Measured by Whole-Body Gamma Counting Versus Urinary Excretion

Patient no.	$T_{½}$ (hr) Body counting	$T_{½}$ (hr) Urinary excretion
1	53	64
2	57	58
3	54	57
4	60	87*
5	71	69
6	54	49†
mean ± ISD	58 ± 7	64 ± 13

* Known to have lost part of urine collections.
† Only the first 48 hr of urine collection was available.

DISCUSSION

This study examines the pharmacokinetics and biodistribution of a genetically engineered ^{131}I-labeled chimeric mouse/human monoclonal antibody. There were no adverse side effects noted in patients receiving this reagent as was noted in our prior study using non-radioactive chimeric 17-1A (*12*).

The pharmacokinetics of this radiolabeled reagent were similar to that previously reported for non-radiolabeled chimeric 17-1A (*12*), indicating that the radiolabeling procedure has not induced alterations in the structure of

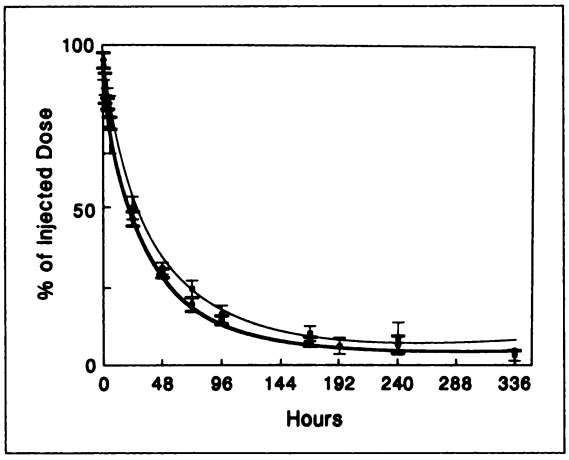

FIGURE 2. Pharmacokinetic curve of ^{131}I-labeled chimeric 17-1A monoclonal antibody in six patients receiving ^{131}I-C17-1A. Solid line indicates percent of injected dose measured by radioimmunoassay for C17-1A; the bold line indicates percent of injected dose measured by radioactivity in the serum of patients. Values are mean ± s.e.m. (n = 6).

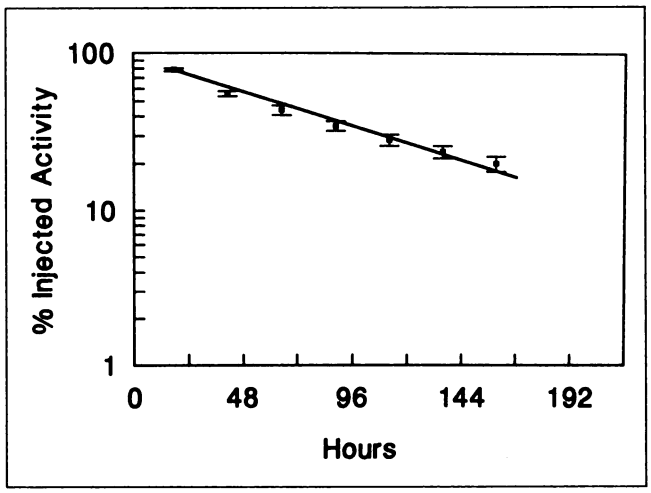

FIGURE 3. Remaining whole-body radioactivity determined by a gamma detector as a function of time after ^{131}I-C-17-1A infusion. Values are mean ± s.e.m. (n = 6).

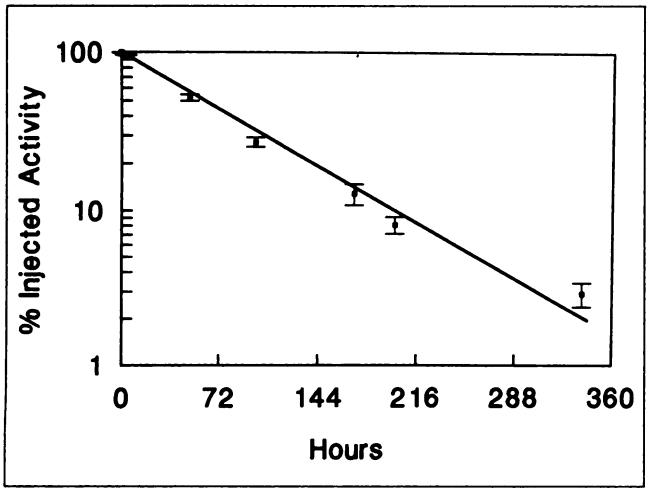

FIGURE 4. Remaining whole-body radioactivity determined by loss from urinary excretion. Radioactivity is expressed as a function of time after ^{131}I-C-17-1A infusion. Values are mean ± s.e.m. (n = 6).

this molecule that adversely affect its ability to circulate. Further, the beta half-life of the radiolabeled chimeric 17-1A is five to six times longer than that reported for murine 17-1A (*4*). These studies also demonstrate that the kinetics of the radiolabel and the chimeric protein are identical. Thus, the radioactive iodine binding to this chimeric antibody is highly stable and dehalogenation of the radiolabeled antibody in the plasma does not occur even over a 14-day period in the circulation (Fig. 2). In studies relevant to radioimmunotherapy, it is common to indicate that a shortcoming of ^{131}I radiolabeled antibodies is that dehalogenation occurs in vivo which accounts for short survival of radiolabel in the circulation (*21–24*) and as much as 50% of the radiolabel excreted in the urine in 24 hr (*25*). Few studies have attempted to differentiate between dehalogenation and antibody catabolism. We have recently participated in a trial of ^{131}I-LYM-1 (*26*), which demonstrated that a large percent of ^{131}I was excreted in the urine in 24–48 hr. Through radioimmunoassay, we found that only 24% ± 17% of the injected dose of antibody was circulating at 1 hr and <1% of the dose remained in circulation at 24 hr despite a range of doses from 25–448 mg (*27*). Thus, the ^{131}I excretion reflected catabolism. The findings in this trial of ^{131}I-chimera 17-1A demonstrate clearly that colon cancer patients do not carry out dehalogenation of circulating radiolabeled antibody in over 2 wk of circulation. We would suggest that prior reports of short circulating half-lives of ^{131}I-labeled antibodies more likely reflect plasma clearance of the antibody rather than dehalogenation. Dehalogenation is more likely to be a result of reticuloendothelial and other tissue breakdown of antibody rather than intra or extravascular dehalogenases.

TABLE 6
Peak Organ Uptake of Radioactivity

Patient no.	Injected activity (mCi)	Organ uptake liver	(% Injected activity) Spleen	Thyroid
1	6.7	11.9	3.1	0.3
2	5.6	8.4	1.5	0.5
3	6.2	10.5	2.6	0.2
4	7.7	6.2	0.9	0.2
5	8.3	7.9	1.4	0.4
6	7.5	11.7	3.9	0.9

The fact that this chimeric molecule had a plasma half-life which was five times as long as murine 17-1A suggested that imaging of tumor sites with a radiolabeled chimeric molecule might be difficult due to persistence of background radioactivity. All patients had successful imaging of tumor sites but the time of imaging was delayed to 4–7 days postinfusion as compared to earlier imaging days for murine studies (*28,29*). As previously reported with murine reagents, larger metastatic lesions were more readily imaged than smaller lesions (*29,30*).

As expected, the whole-body half-life of radioactivity for chimeric 17-1A was prolonged over that reported for murine monoclonal antibodies (*29,31*), where whole body half-life varied from 30 to 40 hr. The mean chimeric 17-1A whole-body half-life varied from 53 to 71 hr, quite similar to the whole-body half-lives of about 3 days reported by Leichner (*32*) for polyclonal xenogeneic radiolabeled antibody.

TABLE 5
Organ Dose Estimates (rad/mCi) for ^{131}I-C-17-1A

Patient no.	Whole-Body	Marrow	Liver	Spleen	Thyroid
1	0.77	0.81	2	3	22
2	0.79	0.82	2	4	29
3	0.78	0.76	4	4	12
4	0.88	0.94	2	4	42
5	1.03	1.05	2	*	43
6	0.75	0.79	2	2	66
mean ± ISD	0.83 ± 0.11	0.86 ± 0.11	2.1 ± 0.8	3.4 ± 0.6	36 ± 19

* Due to limited spleen localization, an accurate determination cannot be obtained.

TABLE 7
Chimeric 17-1A Antibody Response*

	#1	#2	#3	#4	#5	#6
Pre Rx	3.8	5.0	4.2	5.2	4.7	5.4
Wk 1	4.4	6.6	5.3	7.5	5.1	5.5
Wk 2	4.3	4.7	4.9	6.6	5.2	5.1
Wk 3	—	—	3.7	7.5	—	—
Wk 4	4.0	5.3	4.4	5.5	5.3	6.4
Wk 6	4.6	4.4	5.1	5.7	5.1	6.6
Wk 8	4.8	4.5	5.4	5.5	5.1	—
Wk 10	4.4	5.4	5.0	6.4	5.0	—
Wk 12	4.2	4.7	4.1	6.5	5.2	7.8

* Results are expressed as ng/ml bound to bead.

The estimate of radiation dose to the whole body (0.83 ± 0.11 rad/mCi) was similar to Siegel's estimates with ^{131}I-labeled anticacinoembryonic antigen antibody (*33*) and about twice that predicted for murine monoclonals (*2*).

No localization was detected in bone and marrow samples. These samples were not available for direct radioactivity measurements to determine marrow/blood ratios. Thus, our marrow dose estimates are generally lower than those reported for instances in which bone imaging allows calculation of a marrow-to-marrow dose contribution (*34, 35*) and those in which sampling determines a blood contribution to marrow dose which has been reported as 0.2–0.4 of the cumulated blood activity (*36*). The estimates of liver radiation in our study (2.1 ± 0.8 rad/mCi) were similar to that reported for polyclonal antiferritin (*32*) and anti-CEA (*33*). Although there was a higher peak uptake of radioactivity in the liver than other organs, the dose to the thyroid was much higher due to the prolongation of activity in this region. The wider variation of thyroid compared to liver uptake may reflect differences in patient compliance with the prescribed saturated potassium iodide solution. We were unable to estimate radiation doses to tumor sites since we successfully imaged generally at only one or two time points post infusion. Future studies will need to scan more frequently in the 4–9-day period post-infusion and possibly utilize SPECT techniques.

The radiometric double antigen assay system has previously been shown to readily detect 17-1A V region antibody binding ability in patients receiving murine 17-1A (*4,12*). None of the six patients in this study developed antibody response to chimeric 17-1A. Including four patients from our prior study (*12*), a total of 10 patients receiving a single infusion of chimeric 17-1A had no evidence of antibody response. In addition, six patients received three infusions of chimeric 17-1A at 2-wk intervals and only one of them had a weak antibody response to the V region of chimeric 17-1A (*12*). Thus, chimeric 17-1A seems to have a low immunogenic potential in patients with colon cancer (1/16 antibody responders). This may not be true of all chimeric mouse/human antibodies, since we have seen antibody responses to a second chimeric molecule [IgG-4K-B72.3 (*37*)] has produced frequent antibody responses in ongoing trials at our institution (*38*).

These studies suggest that ^{131}I-labeled chimeric 17-1A therapy would be associated with marrow suppression approaching that reported for polyclonal anti-ferritin (*39*) and substantially greater than that seen in several murine monoclonal trials. However, the lack of immunogenicity should allow more flexibility in regard to multiple dose fractions and the persistent blood levels of antibody may provide greater penetration and/or concentration of isotope into solid tumor nodules. These studies suggest that chimeric 17-1A would be a reasonable reagent to examine in phase I radioimmunotherapy trials, including ^{125}I isotope labeled antibody since preliminary studies indicate that the iodinated antibody internalizes (*40*).

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