Pharmacokinetics, Dosimetry and Toxicity of Rhenium-188-Labeled Anti-Carcinoembryonic Antigen Monoclonal Antibody, MN-14, in Gastrointestinal Cancer

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The biodistribution, pharmacokinetics and dosimetry of ^{188}Re-labeled MN-14, an IgG anti-carcinoembryonic antigen monoclonal antibody (MAb), were assessed in patients in advanced gastrointestinal cancer. In addition, the dose-limiting toxicity (DLT) and maximum tolerated dose of fractionated doses of this agent were determined. **Methods:** Eleven patients were administered radioactive doses of directly labeled ^{188}Re-MN-14 IgG, ranging from 20.5 mCi to 161.0 mCi (2.0 mg–4.9 mg). Ten of these patients received two or three MAb infusions, given 3–4 days apart, delivering total doses of 30 mCi/m^2–80 mCi/m^2. External scintigraphy was used to evaluate the MAb biodistribution, and quantitative external scintigraphic methods were used to determine the organ and tumor radiation doses. **Results:** The biodistribution studies showed enhanced ^{188}Re-MN-14 uptake in the liver, spleen and kidneys, compared to that of ^{131}I-MN-14. The biological $T^{1/2}$ values for ^{188}Re-MN-14 in the blood and whole body (in hours) were 8.2 ± 4.1 (n = 7) and 107.8 ± 104.2 (n = 9), respectively (mean ± s.d.). The radiation absorbed doses (cGy/mCi) delivered to the total body, red marrow, lungs, liver, spleen and kidneys were 0.5 ± 0.05, 3.6 ± 1.6, 2.0 ± 0.8, 5.9 ± 2.5, 7.1 ± 1.9 and 8.5 ± 2.8, respectively. Red marrow suppression was the only DLT observed. The maximum tolerated dose of fractionated doses of ^{188}Re-MN-14 was estimated to be 60 mCi/m^2. **Conclusion:** Despite its relatively increased renal and hepatic uptake, red marrow suppression is the only DLT of ^{188}Re-MN-14. The feasibility of administering relatively high doses of ^{188}Re on a completely outpatient basis may make this agent a preferred candidate for radioimmunotherapy.

Key Words: carcinoembryonic antigen; rhenium-188; monoclonal antibodies; radioimmunotherapy; gastrointestinal cancer

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Radioimmunotherapy (RAIT) with monoclonal antibodies (MAbs) has been proven to be successful in the treatment of chemotherapy-resistant Hodgkin's and non-Hodgkin's lymphomas (*1–6*), and is beginning to show encouraging results in other tumor types, such as ovarian (*7*), breast (*8*), medullary thyroid (*9*) and gastrointestinal (*10*) cancers. Several radioisotopes have been used for labeling the various MAbs that are used in therapy. However, ^{131}I and ^{90}Y remain the most widely used radionuclides for clinical RAIT. Both radioisotopes are beta emitters, thus providing a suitable therapeutic particle, but they also have certain limitations. The mean pathlength of ^{131}I in tissue is only about 0.4 mm and may, therefore, not be ideal for tumors with markedly heterogeneous antibody distribution. Moreover, radiation safety concerns and current regulations restrict the administration of therapeutic doses of ^{131}I in the inpatient setting. Yttrium-90 has a longer mean path length in tissue (about 2.5 mm) and results in a more homogeneous distribution of the radiation dose (*11*). Therapeutic doses of ^{90}Y can be given on an outpatient basis, but imaging with the commonly used doses of this radioisotope is impractical, requiring the use of ^{111}In as a surrogate, albeit imperfect, label for ^{90}Y biodistribution. There is, therefore, a need for alternative therapeutic radionuclides that may combine several advantageous features of the currently used isotopes.

Rhenium-188, an isotope with a 16.9-hr half-life, may be an attractive isotope for RAIT. It decays through beta emission, with a maximum energy compared to that of ^{90}Y, but it also emits a 155-KeV (15%) gamma photon that is suitable for imaging. Although this relatively low yield of gamma emission allows images of reasonable quality, it does not constitute any significant radiation hazard, making the treatment with this isotope possible on an outpatient basis. Most importantly is the availability of carrier-free ^{188}Re-perrhenate by saline elution of ^{188}W/^{188}Re alumina generators (*12*), providing ^{188}Re at any time in the clinical setting, at a reasonable cost.

Knapp et al. (*12–15*) have stimulated the clinical use of ^{188}Re for MAb labeling by optimizing the reactor production and processing of the ^{188}W parent and providing large (>1 Ci), clinical-scale, alumina, chromatographic-type generators (*12*). In this article, we describe our initial clinical experience in patients with advanced gastrointestinal cancer, using a ^{188}Re-labeled MAb, MN-14 IgG, directed against carcinoembryonic antigen (CEA). The principal objective of this article is to provide initial data on the pharmacokinetics, dosimetry, tumor targeting and the potential usefulness of this agent in cancer therapy.

MATERIALS AND METHODS

Patients

Patients with histologically proven, CEA-producing, gastrointestinal cancer were eligible for study. To enter the therapy studies, the patients had to be at least 4 wk beyond any major surgery, radiation or chemotherapy and must have recovered from any prior treatment-induced toxicity. The patients must have had a performance status of ≥70 on the Karnofsky scale (ECOG 0–2), a minimal life expectancy of 3 mo, no severe anorexia, no nausea or vomiting, normal hepatic and renal function, white blood cell count of ≥3000/mm^3 or a granulocyte count of ≥1500/mm^3, and a platelet count of ≥100,000. Subjects were excluded from treatment if they were pregnant or had extensive irradiation to more than 25% of their red marrow. All patients signed an informed consent form. All protocols were approved by the governing Institutional Review Board and Radiation Safety Committee.

A total of 11 patients (4 men, 7 women; age range 40–83 yr) were enrolled in the study. Ten patients had colon cancer, and one

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TABLE 1
Antibody Infusions and Sites of Disease

Patient no.	Sex	Age (yr)	Cancer type	No. of injections	Date*	Antibody infusion	Sites of disease†
1	F	74	Pancreas	1	0	20.5 mCi ^{188}Re-MN-14 (4.9 mg)	Lungs, pancrease, left adrenal gland
2	F	61	Colon	1	0	27.9 mCi ^{188}Re-MN-14 (1.0 mg)	Lungs
				2	3	19.9 mCi ^{188}Re-MN-14 (1.0 mg)	
3	M	73	Colon	1	0	25.0 mCi ^{188}Re-MN-14 (1.0 mg)	Lungs, liver
				2	3	28.0 mCi ^{188}Re-MN-14 (4.7 mg)	
				3	7	22.3 mCi ^{188}Re-MN-14 (4.5 mg)	
4	F	83	Colon	1	−60	26.0 ^{99m}Tc-NP-4 Fab′ (1.1 mg)	Lungs, adrenal glands
				2	0	24.4 mCi ^{188}Re-MN-14 (1.0 mg)	
				3	3	25.6 mCi ^{188}Re-MN-14 (4.7 mg)	
				4	7	20.0 mCi ^{188}Re-MN-14 (3.6 mg)	
5	F	48	Colon	1	−14	22.7 mCi ^{99m}Tc G-9 Fab′ (0.9 mg)	Liver, pelvic wall
				2	0	52.0 mCi ^{188}Re-MN-14 (1.7 mg)	
				3	3	28.0 mCi ^{188}Re-MN-14 (1.5 mg)	
6	F	41	Colon	1	−9	24.6 mCi ^{99m}Tc Mu-9 F(ab′)$_2$ (1.0 mg)	Lungs, liver
				2	0	52.0 mCi ^{188}Re-MN-14 (1.7 mg)	
				3	5	28.0 mCi ^{188}Re-MN-14 (0.8 mg)	
				4	7	28.1 mCi ^{188}Re-MN-14 (0.8 mg)	
7	M	71	Colon	1	−5	27.8 mCi ^{99m}Tc-Mu-9 Fab′ (1.1 mg)	Lungs, ribs, liver
				2	0	50.5 mCi ^{188}Re-MN-14 (0.9 mg)	
				3	3	30.0 mCi ^{188}Re-MN-14 (0.9 mg)	
				4	7	29.0 mCi ^{188}Re-MN-14 (1.6 mg)	
8	M	57	Colon	1	0	49.3 mCi ^{188}Re-MN-14 (4.2 mg)	Liver
				2	3	34.0 mCi ^{188}Re-MN-14 (4.2 mg)	
				3	6	34.1 mCi ^{188}Re-MN-14 (4.7 mg)	
9	M	40	Colon	1	−7	28.6 mCi ^{99m}Tc G-9 Fab′ (0.8 mg)	Lungs, liver
				2	0	78.0 mCi ^{188}Re-MN-14 (1.8 mg)	
				3	3	39.7 mCi ^{188}Re-MN-14 (1.6 mg)	
10	F	46	Colon	1	−7	24.2 mCi ^{99m}Tc G-9 Fab′ (0.8 mg)	Lungs, paraaortic nodes, liver
				2	0	48.2 mCi ^{188}Re-MN-14 (1.9 mg)	
				3	3	37.7 mCi ^{188}Re-MN-14 (1.8 mg)	
				4	7	29.0 mCi ^{188}Re-MN-14 (1.6 mg)	
11	M	51	Colon	1	0	78.0 mCi ^{188}Re-MN-14 (1.8 mg)	Lungs
				2	3	41.0 mCi ^{188}Re-MN-14 (1.4 mg)	
				3	8	42.5 mCi ^{188}Re-MN-14 (1.7 mg)	

*0 indicates the date of the first therapy infusion of ^{188}Re-MN-14, and the numbers indicate the days thereafter or before.
†Site of disease by CT, magnetic resonance imaging, bone scan, radiography, ultrasound or surgery at the time of admission.
M = male; F = female.

had pancreatic cancer. Table 1 lists the patients, their sex, ages and tumor types, the ^{188}Re-MN-14 infusions they received and their sites of disease. Three of the 11 patients (Patients 5, 9 and 10) given ^{188}Re-MN-14 had previously received a diagnostic infusion of ^{99m}Tc-anti-mucin G-9 Fab′ 1–2 wk prior to their therapy with ^{188}Re-MN-14. One patient (Patient 7) received ^{99m}Tc-anti-mucin Mu-9 Fab′ 1 wk before the therapy with ^{188}Re-MN-14, and another patient (Patient 6) received ^{99m}Tc-anti-mucin Mu-9 F(ab′)$_2$ 2 wk before the ^{188}Re-MN-14 therapy. Patient 4 received a diagnostic infusion of ^{99m}Tc-anti-CEA NP-4 Fab′ 8 wk before therapy with ^{188}Re-MN-14. All these studies were performed for diagnostic purposes only.

Radiolabeled Antibody Preparation

The murine IgG$_1$ MN-14 (Immu-14) MAb (Immunomedics, Inc., Morris Plains, NJ) is directed against the class-III, CEA-specific epitope according to the classification of Primus et al. (*16*). MN-14 is a second-generation anti-CEA MAb that was found to have a 10-fold higher affinity ($1 \times 10^9\ M^{-1}$) than does the first-generation NP-4 MAb, and it has demonstrated superior tumor targeting in a human colon carcinoma xenograft model (*17*). One or 5 mg of MN-14 IgG were formulated for direct labeling with ^{188}Re-perrhenate (lyophilized or liquid phase), as described previously (*18*). Tungsten-188/^{188}Re generators were supplied by Oak Ridge National Laboratory (Oak Ridge, TN). Each generator and each injectate were tested for tungsten breakthrough, alumina, pyrogen and general safety (*19*). The generators were eluted one to three times a week with saline for injection. Briefly, ^{188}Re, dissolved in saline, was added to the antibody, and the labeling yield was monitored over time by instant thin-layer chromatography (ITLC). The optimal labeling time was 1.5–2.0 hr, and the total time required to prepare the MAb so that it was ready for patient infusion was 3 hr. Because ^{188}Re incorporation was >95%, no purification of the final product was required. The final product had <3.0% unbound ^{188}Re with <1.8% colloid, as determined by ITLC. Two ITLC solvents were used. The first was 0.9% sodium chloride solution, in which sodium perrhenate migrates to the top of the strip, and ^{188}Re-labeled MAb remains at the origin. The second system used was 5:2:1 water:ethanol:ammonium hydroxide. For this system, strips were prespotted at the origin with 5% human serum albumin. This system distinguishes colloids, which remain at the origin from all other species that elute at the solvent front. The immunoreactive fraction determined by a CEA immunoadsorbent averaged 83% ± 8.4% (range 63%–91%).

Antibody Infusions

The patients entered were part of a Phase I dose-escalation trial to determine the dose-limiting toxicity (DLT) and the maximum

tolerated dose (MTD) of fractionated doses of ^{188}Re-MN-14 IgG. The DLT was defined as a reversible grade 3 or 4 thrombocytopenia or leukopenia, and the MTD was defined as the dose of ^{188}Re-Mn-14 IgG at which fewer than one-third of patients (i.e., zero of six or one of six) experience DLT, with the next higher dose having two of three or two of six encountering DLT. The trial was designed so as to administer three infusions of ^{188}Re-MN-14 IgG, 3–4 days apart, over a 1-wk period. The initial total dose was set at 40 mCi/m^2 and was escalated by 20-mCi/m^2 increments. One rationale behind the escalation of fractionated rather than single doses of ^{188}Re-MN-14 was to test the feasibility of administering multiple therapeutic injections within a relatively short period of time (3–4 days) rather than a more prolonged time interval ($\geq$1 wk), especially because an isotope with a short half-life of only ~17 hr was used. Moreover, this dose schedule allowed us to essentially use the first MAb infusion as an initial pharmacokinetic/dosimetry study for each specific patient, particularly because there was, at the time of initiation of the study, no previous experience with the administration of ^{188}Re-labeled MAbs in patients. The pharmacokinetic and dosimetry data obtained from the initial (first) infusion of each patient could then be used to modify the second or third MAb infusions in the same patient. Initially, the total dose was divided in three approximately equal MAb infusions. In subsequent studies, to improve the quality of the imaging scans, half of the total dose was given in the first infusion, with the other half being divided into the remaining two infusions. The maximum radioactive dose given in any single infusion was 78 mCi. However, the radiation exposure reading taken at 1 m immediately after the end of this infusion was ~2 mR/hr, suggesting that single doses of up to 195 mCi of ^{188}Re-MAb could be given on a completely outpatient basis.

Seven of the 11 patients studied completed three infusions of radiolabeled MAb given within the 1-wk period. Three patients received only two of the three MAb infusions, and one patient received only one MAb infusion. Patient 1 elected not to continue with treatment after the first MAb infusion. Patient 2 was found to have only one functioning kidney, and because she received a renal dose of 700 cGy in the first two infusions, it was decided that she would not receive her last infusion. Patient 5 had low hemoglobin values (<10 mg/dl) and required a red blood cell transfusion before entering into the study. Although the hemoglobin was >10 mg/dl at the start of the first infusion, her values fell below 10 mg/dl, suggesting continued (not treatment-related) bleeding abnormalities, and she was therefore not eligible for further treatment. Patient 9 was shown to have a high uptake in her bone marrow; hence, the last infusion was canceled.

Human Anti-Mouse Antibody Monitoring and Follow-Up Studies

A baseline plasma human anti-mouse antibody (HAMA) titer was determined in all patients, with follow-ups at days 3 and 7 and at 2, 4, 8 and 12 wk, using a HAMA titer assay (*17*) or, more recently, the ImmuSTRIP® HAMA IgG assay (Immunomedics, Inc., Morris Plains, NJ). Normal values for the ImmuSTRIP assay are <74 ng/ml. Correlative radiological studies, such as CT, were performed within 4 wk, usually within 1–2 wk, before antibody imaging or treatment, with follow-up CT studies performed at a minimum of 1 and 3 mo. Circulating CEA was measured on the day of treatment and at 1- to 3-mo intervals for 1 yr or more thereafter. CEA was determined in heat-extracted plasma samples to eliminate interference with HAMA (*20*). Other assays were performed by registered clinical laboratories.

Pharmacokinetic Analysis

Plasma samples taken at 1 hr after the antibody infusion were analyzed by size-exclusion high-performance liquid chromatography (HPLC) for radioantibody stability and potential complexation with circulating antigen. The conditions used for HPLC analysis were a Zorbax GF 250 size-exclusion column (250 mm × 9.4 mm) (Dupont, Wilmington, DE) run in 0.2 *M* sodium phosphate buffer (pH 6.5) at a flow rate of 1 ml/min. Recoveries ranged between 70% and 95% for all but one plasma sample (a total of 29 samples). However, the columns were run for 20 min once the samples were injected, and all possible species associated with ^{188}Re were shown to elute from the column. Rhenium-188-MAb eluted around 9 min, presumably low-molecular weight, reduced ^{188}Re eluted around 12–13 min and free ^{188}Re-perrhenate eluted around 15 min. HPLC analysis was also performed on two urine samples taken from one patient (recoveries were 75% and 76% for two samples).

Blood clearance rates were determined by counting samples of whole blood at various times after the end of the infusion. Three to five blood samples were taken over the first 24 hr, and an additional sample was taken at 48 hr. Curve-fitting programs were used to generate both monoexponential or biexponential clearance curves. The term blood $T^{1/2}$ (biological) used in this article refers to the time (in hours) taken to clear 50% of the initial radioactivity from the blood. The biological $T^{1/2}$ describes the clearance half-life of the overall radioactivity present in the blood, which includes all forms in which the MAb is present (i.e., the native MAb form and the high- and low-molecular weight fractions). This overall clearance half-life was used because the pharmacokinetics of the overall radioactivity is what ultimately determines the important parameters of the red marrow dose and hematological toxicity, not those of the native MAb alone. Total-body clearance rates were determined by urine collection and by whole-body external scintigraphy. The urine collection was taken at three separate times, and the whole-body scintigraphy was performed daily with a rate meter at 1 m from the patient. The term total-body $T^{1/2}$ used in this report refers to the time (in hours) taken to clear 50% of the initial radioactivity from the body.

Imaging and Dosimetry

Planar images (500 kcts per view) consisting of anterior and posterior scans of the head, chest, abdomen and pelvis were obtained using DS-X or DS-7 Sopha cameras (Sopha Medical Systems, Columbia, MD), equipped with a high-energy collimator. The high-energy rather than the low-energy collimator was used because we found substantial interference from the high-energy Bremsstrahlung associated with ^{188}Re, which penetrated the collimator's septa and resulted in image degradation when a low-energy collimator was used. The high-energy collimator clearly resulted in a dramatic improvement in the image quality. Images were taken at 1–2, 3–5, 24 and, in three patients, 48 hr after the MAb infusion using a 128 × 128 matrix. SPECT studies (64 × 64 matrix) of the chest, abdomen and pelvis were also obtained at 3–5 hr postinfusion in 8 of the 11 patients and at 24 hr in 5 patients. SPECT was used to better identify the site of tumor by improved contrast resolution. An activity quantification technique for the gamma camera was used for the dosimetric calculations, as previously described (*21*). Tumor volumes were measured by CT, and standard organ weights given by the Medical Internal Radiation Dose (MIRD) (*22*) were used. The organ and tumor time-activity data were then fit to an exponential function by either a nonlinear, least squares, curve-fitting routine or by a trapezoidal modeling method, and the data were then integrated to obtain the cumulated activity. The cumulated activity in the red marrow was calculated from the blood by multiplying this concentration by 1500, which is the weight (in grams) of the marrow in an average adult (*23*). The mean dose in cGy to the various target organs, with the exception of the tumors, was then obtained according to the MIRD schema with correction for the remainder of the body activity (*22,24*). The

TABLE 2
Pharmacokinetic Parameters of Rhenium-188-MN-14 Infusions

Patient no.	HAMA (ng/ml)	CEA (ng/ml)	MN-14/CEA*	1-hr HPLC			Biological $T^{1/2}$† (hr)	
				HMW (%)	LMW (%)			
					Free ^{188}Re	Reduced Re	Blood	Total body‡
1	<74	215	10.4	13.9	0.0	0.0	13.0	90.6
2	<74	15.7	35.4	13.2	2.6	0.0	12.6	75.1
2§	<74	19.6	28.4	15.0	2.1	3.4	7.8	139.3
3	<74	3368.1	0.1	87.5	1.5	0.6	11.9	90.5
3§	<74	3147.8	0.5	86.7	1.0	0.9	10.9	192.0
3¶	<74	4492.7	0.3	90.0	0.0	0.0	10.7	107.1
4	121	50.5	7.2	18.9	2.3	1.3	20.8	140.4
4§	129	27.0	63.3	10.4	2.3	1.3	24.6	93.0
4¶	158	21.2	61.7	10.3	3.6	0.0	23.9	168.3
5	<74	131.3	6.2	17.3	3.0	5.6	4.2	78.7
5§	<74	136.8	5.3	22.8	1.1	3.2	5.9	63.3
6	<74	1237.4	0.5	60.6	2.9	14.3	nd	79.1
6§	812	2764.6	0.1	60.7	4.1	10.9	nd	59.2
6¶	19864	2549.2	0.1	53.2	14.2	14.3	0.3	76.4
7	<74	138.7	2.6	41.0	4.3	10.1	4.3	43.3
7§	<74	131.0	2.9	34.0	3.2	15.6	3.8	39.1
7¶	<74	164.1	4.1	39.5	2.7	3.7	3.5	75.3
8	150	944.6	1.8	73.0	0.0	0.0	3.3	114.5
8§	<74	858.9	2.0	48.4	0.9	4.8	5.8	72.0
8¶	90	923.2	2.1	51.8	0.9	1.5	6.2	57.7
9	<74	11671.3	0.06	80.4	1.3	4.6	4.5	98.6
9§	<74	9664.8	0.06	84.9	1.3	0.0	9.3	57.9
10	<74	50.1	18.7	35.8	0.6	8.7	nd	34.6
10§	<74	37.2	24.8	30.8	2.3	8.4	19.6	48.5
10¶	<74	15.3	51.4	32.8	0.3	6.3	9.7	72.0
11	<74	33.5	19.3	21.1	0.9	6.3	6.7	379.8
11§	<74	41.7	11.8	18.9	2.1	9.5	6.0	108.4
11¶	133	52.7	11.6	nd	nd	nd	nd	nd

*The MN-14/CEA ratio in plasma was calculated assuming that the plasma volume is 4% of the body mass and using the molecular masses of 150,000 and 180,000 D for MN-14 and CEA, respectively.

†$T^{1/2}$ is the time (in hours) required for 50% of the injected activity to be cleared from the blood or body. In most cases, the blood clearance curves were described by a biexponential model, and the total body clearance curves were described by a single exponential model.

‡Clearance was based on whole-body scans.

§Second MAb infusion given in the same patient.

¶Third MAb infusion given in the same patient.

HMW = high molecular weight; LMW = low molecular weight; nd = not determined.

mean dose in cGy to the tumors was obtained by the method reported previously (*21*).

Toxicity and Tumor Response

Toxicity was graded according to the Radiation Therapy Oncology Group criteria. All patients given ^{188}Re-MN-14 were followed for toxicity by weekly monitoring of complete peripheral blood cell counts. Renal and hepatic functions were assayed 7 and 28 days post-therapy. Tumor responses were assessed at 1–3 mo after treatment and every 3 mo thereafter, for up to 1 yr. If disease progression occurred after 3 mo, no further follow-up was attempted. In addition to physical exams, chest x-rays, CT and magnetic resonance imaging were used to assess therapeutic response. Plasma CEA level was assessed at 1–3 mo, for up to 1 yr post-therapy. Reduction in CEA level that was >25% for at least 1 mo was considered to be an indication of an antitumor effect.

RESULTS

Pharmacokinetics

Table 2 lists the HAMA and CEA plasma levels, the results of the 1-hr HPLC profile, and the blood and total-body clearance data for all ^{188}Re-MAb infusions given to the 11 patients.

Nine patients, including five who had a diagnostic injection with ^{99m}Tc-MAb fragments 1–2 wk before the therapy study, had normal (<74 ng/ml) HAMA titers at the time of the first ^{188}Re-MN-14 infusion. One patient (Patient 6), who had her diagnostic study 8 wk before RAIT, had a relatively low HAMA titer of 121 ng/ml at the time of the first ^{188}Re-MAb infusion, and one patient (Patient 8), who never had a prior MAb infusion, also had a baseline HAMA titer of 150 ng/ml. Interestingly, the HAMA levels remained essentially unchanged during the 1-wk course of treatment in 9 of the 10 patients who received more than one infusion of ^{188}Re-MN-14. Only in Patient 6, who received a diagnostic injection of ^{99m}Tc-Mu-9 $F(ab')_2$ 2 wk before the ^{188}Re study, did HAMA increase from <74 ng/ml to 812 ng/ml after the first infusion and even to 19,864 ng/ml after the second infusion, resulting in a more rapid clearance of the radiolabeled MAb.

All patients had elevated plasma CEA levels ranging from 15.7 ng/ml to 11,671 ng/ml (median = 139 ng/ml), and the 1-hr plasma HPLC showed 10.3%–90.0% (median = 35.8%) of the activity associated with the high-molecular weight fraction. Moreover, there was generally a good correlation between complexation and the ratio of MN-14 IgG given to total plasma

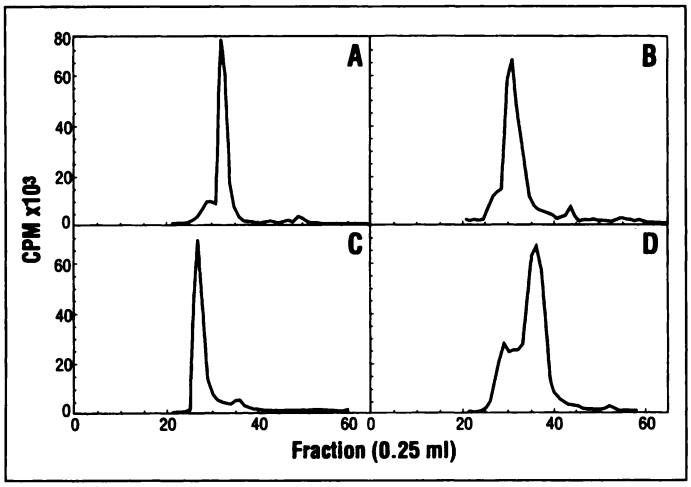

FIGURE 1. A set of radiochromatograms illustrating the results of HPLC performed using the 1-hr plasma of Patients 2, 9 and 11 (A, C and D, respectively) and the 24-hr plasma of Patient 2 (B). Beginning from the left of each profile, the first fraction represents high-molecular weight complexes, the second represents the native MAb and the third and fourth represent low-molecular weight reduced ^{188}Re and free ^{188}Re-perrhenate, respectively.

CEA content (MN-14-to-CEA ratio). MN-14-to-CEA ratios of <2.0 consistently resulted in >50% complexation, whereas values of >8.0 generally resulted in <20% complexation. The only exception was Patient 10, who had an MN-14-to-CEA ratio of ~18.7 and a CEA plasma level of only 50.1 ng/ml but had 35.8% complexation of the MAb in plasma. The reason for this relatively high level of complexation may have been due to a human anti-murine MAb directed against a structure in the variable rather than the constant region of the murine Mab (heterophile antibody).

The 1-hr plasma HPLC also showed 0%–15.6% (median = 4.6%) of the activity associated with the low-molecular weight, reduced rhenium and 0%–14.2% (median = 2.1%) of the activity associated with free perrhenate. In one patient (Patient 2, Fig. 1B), HPLC was also performed on the 24-hr plasma, and little difference was noted between the 1-hr and 24-hr HPLC profiles in this patient. The amount of reduced ^{188}Re increased from 0% at 1 hr to 2.1% at 24 hr, whereas that of free perrhenate decreased from 2.6% at 1 hr to 0% at 24 hr. The HPLC performed on two voided urine volumes collected within 24 hr in one patient (Patient 9) showed that 28%–39% of the activity excreted as reduced rhenium, whereas 39%–62% of activity was excreted as perrhenate and <3% was excreted as native MAb (Fig. 2). These metabolites are expected after antibody catabolism, similar to other low-molecular weight metabolites (iodinated tyrosine and free iodine) seen with radioiodinated MAbs.

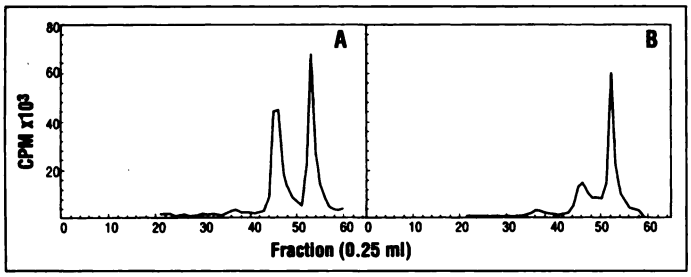

FIGURE 2. Two radiochromatograms representing the HPLC profiles of two samples of voided urine obtained over the first 4 hr (A) and the next 20 hr (B) in Patient 9. The largest two peaks in each profile represent low-molecular weight reduced ^{188}Re and free ^{188}Re-perrhenate.

The biological $T^{1/2}$ values of ^{188}Re-MN-14 in the blood for the various MAb infusions in patients with normal HAMA levels by our assay (i.e., < 74 ng/ml) ranged from 3.5 hr to 20.8 hr, and there was generally a relatively good agreement between the blood $T^{1/2}$ values for the various MAb infusions given in the same patient. This suggested a minimal alteration in the blood pharmacokinetics of the subsequent MAb infusions, compared with the first infusion, and negligible (if any) influence of residual protein from the preceding MAb infusions on the blood pharmacokinetics of subsequent infusions. However, to exclude any influence of previous ^{188}Re-MN-14 infusions on the measured pharmacokinetic parameters, the average $T^{1/2}$ in the blood was calculated for the first MAb infusions only (with HAMA being <74 ng/ml) and was found to be 8.2 ± 4.1 hr (n = 7). The blood $T^{1/2}$ values for the first MAb infusions could not be obtained in two patients due to noncompliance.

There was no statistically significant difference between the blood $T^{1/2}$ values of patients with high CEA and high amounts of complexation in the plasma and those with low CEA levels and relatively low complexation (i.e., ≤20%), even when the patients with abnormal HAMA levels (i.e., > 74 ng/ml) or heterophile MAb were excluded. High-molecular weight complexes, ranging from 41% to 87% were seen in three of the seven patients, and in those, the average blood $T^{1/2}$ was 6.9 ± 4.3 hr, compared to 9.1 ± 4.4 hr in the four patients with MAb complexation ranging from 13% to 21% (p, not significant). This suggested that factors other than the plasma CEA level and complexation, such as the in vivo stability of the radiolabeled MAb, may influence its clearance.

Figure 1 shows the 1-hr plasma HPLC profiles of Patients 2, 9 and 11. Patient 2 (Fig. 1A, B) had only ~13% high-molecular weight complexes (~16 ng/ml CEA) and low values of 2.6% free perrhenate in the 1-hr plasma. Yet, the blood $T^{1/2}$ in this patient was only 12.6 hr. Patient 9 (Fig. 1C) had almost 80% complexation of the radiolabeled MAb at 1 hr postinfusion, with relatively low values of reduced ^{188}Re and free perrhenate (4.6% and 1.3%, respectively). The blood $T^{1/2}$ in this patient was only 4.5 hr. However, Patient 11 (Fig. 1D), who had a moderate amount of complexation of 21% (34 ng/nl CEA) but a substantially reduced ^{188}Re level of 9.5% (free perrhenate was 2.1%), also had a short half-life of only 6.7 hr.

The biological $T^{1/2}$ values of ^{188}Re-MN-14 in the total body also showed considerable variability for the various MAb infusions (in patients with HAMA levels of <74 ng/ml), with biological $T^{1/2}$ values ranging from 34.6 hr–379.8 hr, based on the whole-body scan, and from 41.3–382.0 hr, based on the urine collection method. However, most striking was the large variation in the total-body $T^{1/2}$ values between the various infusions in the same patient, regardless of the method used for their calculation, probably due to variable amounts of urinary activity excreted and, hence, remaining total-body activity from infusion to infusion. The average $T^{1/2}$ in the total body in HAMA-negative patients calculated for the first MAb infusions only (to exclude any influence of previous ^{188}Re-MN-14 infusions on the measured pharmacokinetic parameters) was 107.8 ± 104.2 hr (n = 9), using the whole-body scan, and 98.0 ± 37.8 hr (n = 5), using the urine collection method. When Patient 11, who had an unusually long $T^{1/2}$ of 379.8 hr, was excluded, the average total-body $T^{1/2}$ determined by the scan was 73.8 ± 23.0 hr. Because the whole-body scintigraphy method was used in our prior studies with ^{131}I-MN-14 IgG, the whole-body clearance by this method was used for comparison.

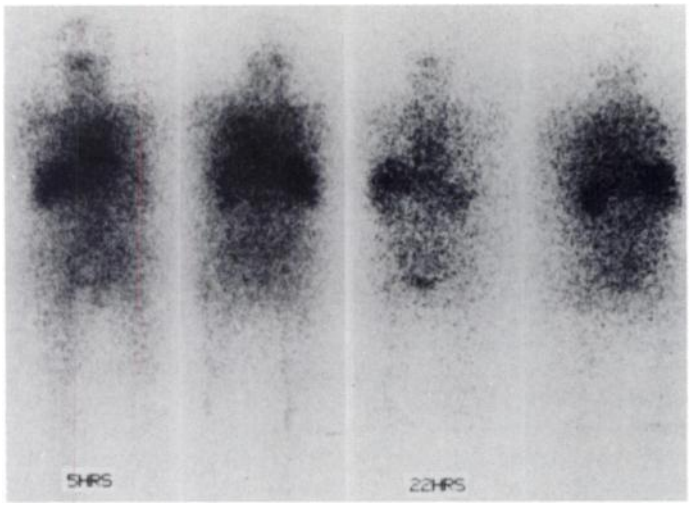

FIGURE 3. Anterior and posterior whole-body scans obtained 4.5 and 22 hr after the intravenous infusion of 19.9 mCi ^{188}Re-MN-14 IgG in Patient 2 with a plasma CEA level of 15.7 ng/ml. Note the relatively rapid blood pool clearance and high hepatic and renal uptake at 22 hr.

TABLE 3
Myelotoxicity in Patients Given Rhenium-188-MN-14 Anti-Carcinoembrybronic Antigen Monoclonal Antibody

Patient no.	No. of infusions	Cumulative radioactivity (mCi)*	Myelotoxicity grade	TTR
1	1	20.5 (12.0)	0 (WBC), 0 (PLT)	na
2	2	47.8 (30.0)	0 (WBC), 0 (PLT)	na
3	3	75.3 (40.0)	0 (WBC), 0 (PLT)	na
4	2	70.0 (40.0)	1 (WBC), 0 (PLT)	6 (WBC)
5	3	80.0 (46.0)	2 (WBC), 4 (PLT)	7 (WBC), 14 (PLT)
6	3	108.0 (60.0)	0 (WBC), 0 (PLT)	na
7	2	111.5 (60.0)	0 (WBC), 0 (PLT)	na
8	3	117.4 (60.0)	0 (WBC), 0 (PLT)	na
9	2	117.7 (67.0)	2 (WBC), 3 (PLT)	14 (WBC), 7 (PLT)
10	3	114.9 (70.0)	3 (WBC), 2 (PLT)	44 (WBC), 32 (PLT)
11	3	161.5 (80.0)	0 (WBC), 0 (PLT)	na

*Numbers in parentheses are values in terms of mCi/m^2.
WBC = white blood cells; PLT = platelets; TTR = time (days) to full recovery from the nadir of myelotoxicity; na = not applicable.

Biodistribution and Imaging Studies

Planar MAb scans were acquired at 1–2, 3–5, 24 and, in three patients, 48 hr postinfusion. SPECT scans of the chest, abdomen and pelvis were also performed in eight patients at 3–5 and, in five patients, 24 hr postinfusion. The MAb scans obtained at 1–2 or 3–5 hr after infusion showed a biodistribution pattern that was mainly characterized by increased uptake in the "fast compartment" organs, such as the liver, spleen and red marrow, usually seen after radiolabeled MAb infusions (Fig. 3). However, by 24 hr, a relatively rapid blood pool clearance was noted, with only little activity seen in the blood pools of the heart, lungs or major vessels. Moreover, high uptake was still seen in the liver and spleen, and an unusually increased uptake was noted in the kidneys. In few instances, a slightly increased uptake was observed in the bowel. When the 48-hr images were obtained, very little activity remained in the heart or lungs, with persistently high uptake in the liver, spleen and kidneys. The activity in the bowel also increased, compared to 24-hr images.

Because the patients entered in this study had large, bulky tumors with, as expected, slow MAb uptake kinetics, relative to the short physical half-life of ^{188}Re, and because most patients were imaged only up to 24 hr postinfusion, optimal tumor visualization was not expected in this trial. Tumor imaging was further complicated by the relatively high uptake and retention of activity in the normal liver, resulting in the hepatic metastases appearing "cold" or having only "rimmed" uptake. Because imaging was not performed beyond 24 hr, a potential "filling in" of initially cold tumor lesions could not be shown. However, approximately one-third (8 of 27) of tumor lesions that were >2 cm in diameter could be visualized on the MAb scan. Figure 4 shows an example of targeting of a large (6 × 2.5 cm) chest wall lesion in Patient 4 with metastatic colon carcinoma, 24 hr after the infusion of ^{188}Re-NN-14 IgG.

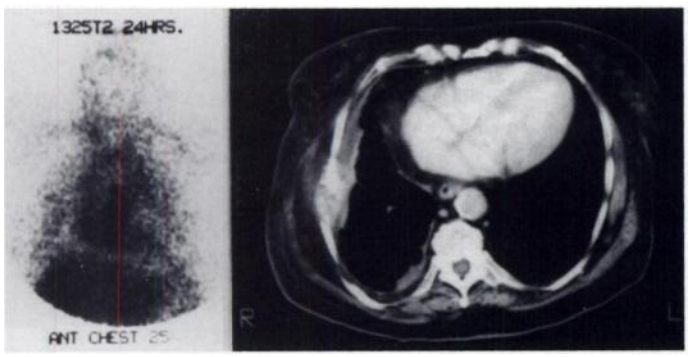

FIGURE 4. (Left) A planar scan of the anterior chest obtained 24 hr after the infusion of 25.6 mCi ^{188}Re-MN-14 IgG in Patient 4 with a plasma CEA level of 50.5 ng/ml, showing tumor targeting in an anterior chest wall tumor seen by CT (right).

Organ and Tumor Dosimetry

The mean total-body and organ radiation absorbed doses delivered with ^{188}Re-MN-14 IgG were calculated from data obtained after the first MAb infusion. The radiation absorbed doses (cGy/mCi; mean ± s.d.) to the total body, red marrow, lung, liver, spleen and kidneys were 0.5 ± 0.05, 3.6 ± 1.6, 2.0 ± 0.8, 5.9 ± 1.9, 7.1 ± 1.9 and 8.5 ± 2.8, respectively.

Due to the inability to visualize lesions adequately at the activity administered and at the imaging times performed, the absorbed tumor doses were estimated to only three known lesions (peritoneal carcinomatosis and periaortic lymph nodes in one patient and a bony lesion in another patient). Tumor weights were estimated to be 34, 119 and 14 g. The biological half-lives of ^{188}Re-MN-14 in the three lesions were 45, 38 and 58 hr, respectively (mean ± s.d. = 47.2 ± 8.3 hr). The calculated tumor doses were 31.2, 7.0 and 10.5 cGy/mCi (mean ± s.d. = 16.2 ± 10.7), and the tumor-to-red marrow ratios were 5.3, 1.2 and 4.5 (mean ± s.d. = 3.7 ± 1.8), respectively. The mean tumor-to-total body, tumor-to-red marrow, tumor-to-lung, tumor-to-liver and tumor-to-kidney dose ratios for the three lesions were 32.0 ± 20.2, 3.7 ± 1.8, 7.7 ± 4.4, 5.0 ± 4.3 and 1.3 ± 0.8, respectively.

Toxicity

No adverse experiences were observed with any of the MAb infusions, including the two patients with HAMA. Table 3 lists the myelotoxicity observed in the 11 patients who received the radiolabeled MAb. Two patients received 12 or 30 mCi/m^2 of ^{188}Re-MN-14, given in one or two MAb infusions, respectively. Neither patient experienced myelotoxicity (grade 0 leukopenia or thrombocytopenia). Of the three patients who received 40–46 mCi/m^2, given in two or three MAb infusions, one had a grade 0 leukopenia and thrombocytopenia, one had a grade 1 leukopenia and a grade 0 thrombocytopenia and one had a grade 2 leukopenia and a grade 4 thrombocytopenia. However, the latter patient had her last chemotherapy cycle, consisting of carboplatin, methotrexate, leucovorin and 5-fluorouracil, only 2

mo before RAIT, and although her blood values were in the normal range to be eligible for RAIT, she was still recovering from myelotoxicity. Hence, considering the relatively low level of toxicity seen in the other two patients, dose escalation resumed to 60 mCi/m^2. None of the three patients given 60 mCi/m^2 of ^{188}Re-MN-14 had DLT (all three had grade 0 leukopenia and thrombocytopenia). However, two of the three patients who received doses higher than 60 mCi/m^2 (range = 67–80 mCi/m^2) developed grade 3 thrombocytopenia (one patient) or leukopenia (one patient), and thus, no further escalation was pursued. Myelotoxicity, particularly of white blood cells or platelets, occurred from 3–4 wk after treatment. However, all patients recovered fully within approximately 6 wk from nadir. No other organ toxicity was observed in any of the patients. Also, no therapeutic effects were observed in any of the patients.

HAMA

As mentioned above, only 1 of the 10 patients who received more than one infusion of ^{188}Re-MN-14 developed HAMA during the 1-wk course of MAb infusions, thus allowing completion of all MAb infusions within this critical period. However, HAMA eventually developed in seven of these nine patients within 2–3 wk after the first MAb infusion.

DISCUSSION

The purpose of this investigation was to examine the biodistribution, pharmacokinetics and dosimetry of the anti-CEA MN-14 IgG labeled directly with ^{188}Re and to determine the DLT and the MTD of fractionated doses of this agent as a new potential candidate for the therapy of CEA-producing tumors.

The blood clearance data showed that the biological half-life of ^{188}Re-MN-14 was shorter than that previously reported for ^{131}I-MN-14 (8.2 compared to 27.3 hr, respectively) in a similar cohort of patients, predominantly with colorectal cancer (*25*). This was also apparent on the MAb scans, showing a relatively rapid blood pool clearance of ^{188}Re-MN-14 and unusually high renal uptake for the intact IgG. Although the blood clearance rates may have been influenced by the high amount of complexation of ^{188}Re-MAb with circulating CEA and the large bulky disease in some patients, with a trend toward shorter half-lives in patients with high rather than low complexation with CEA, the difference was not statistically significant. These data suggest that the shorter blood half-life of ^{188}Re-MN-14 may have been related, at least in part, to a relative in vivo instability of the used ^{188}Re-conjugate. Interestingly, the in vivo instability of the ^{188}Re-MN-14 preparations could not be predicted reliably by the 1-hr plasma HPLC results obtained in all patients or even by the 24-hr plasma HPLC performed in one patient. For example, Patients 1 and 2 had 0% reduced ^{188}Re and 0%–2.6% free perrhenate in their first infusions, yet the blood $T^{1/2}$ values in the two patients were only ~13 hr. Both patients also had only small amounts of high-molecular weight complexes of ~13.5% and a relatively low tumor burden, unlikely to result in the rapid clearance observed. This finding probably suggests that the ^{188}Re-MN-14 breakdown occurred gradually in the patients and that any released radioactive species were rapidly removed from the plasma, probably into the kidneys. Although the HPLC recoveries ranged from 70% to 95% for most plasma samples, the activity unaccounted for (5%–30%) could not have been reduced ^{188}Re or ^{188}Re-perrhenate because all radioactive species, including the latter species, were shown to elute from the column. The activity unaccounted for is, therefore, most likely due to the technologist's overestimation of the actually applied radioactivity to the column compared with the activity standard measured.

Other factors that, at least in part, influenced the clearance of ^{188}Re-MN-14 in this study were the very high CEA plasma levels and/or MAb complexation in 5 of the 11 patients, which was also associated with a large tumor burden in the liver and lungs. These patients generally had short blood $T^{1/2}$ values that were consistent with our and other investigators' findings of a rapid clearance of CEA–MAb complexes in colorectal cancer patients with large bulky tumors (*25–27*). However, in this study, this effect could not be reliably separated from that of the instability of the radiolabeled MAb.

Despite the much shorter blood clearance of ^{188}Re-MN-14 compared with ^{131}I-MN-14, the whole-body clearance of the former agent (based on the whole-body scan) was at least as long (considering the large s.d. observed) or even somewhat longer than that reported previously for ^{131}I-MN-14 (108 compared to 70 hr, respectively) (*25*). This finding is consistent with the chemistry of ^{188}Re as a residualizing radiometal; i.e., ^{188}Re, similar to ^{90}Y or ^{111}In, is retained after the intracellular degradation of the radiolabeled MAb, particularly in organs of known protein catabolism, such as liver and spleen, as was shown by the high uptake and long residence time (data not shown) of the MAb in these organs. In addition, the long whole-body half-life of ^{188}Re-MN-14, combined with the finding that (on average) only 16% of the activity was excreted at 24 hr, also suggest that most products of the MAb, which was degraded in the blood, were retained, probably in the kidneys, which also showed a long residence time of the radiolabel. The whole-body $T^{1/2}$ values in HAMA-negative patients with high CEA–MAb complexes were also relatively high (median = 84.8 hr; range = 43 hr–99 hr), suggesting that the complexes cleared into the liver were intracellularly retained, thereby resulting in long total-body $T^{1/2}$ values. Interestingly, the apparent increase in the total-body $T^{1/2}$ of the third infusion in Patient 6, who then had a HAMA of 19,864 ng/ml, may also be related to the long retention, this time, of the MAb–HAMA complexes in the liver, spleen and bone marrow.

The whole-body and normal organ dosimetry have indicated relatively high radiation doses in the liver, spleen and kidneys, compared to the red marrow or lungs. These findings are in agreement with the residualizing properties of ^{188}Re after the MAb's intracellular catabolism in the liver and spleen and are again consistent with the high uptake and long residence time of ^{188}Re seen in these organs. The relatively high renal doses seen in this study were probably related to the intracellular retention of the MAb's metabolic products. However, it is important to note that, despite the relatively high radiation doses in the liver and kidneys, no toxicity was seen in these organs. In fact, the current study demonstrates that red marrow suppression was the only observed DLT of ^{188}Re-MN-14.

The dosimetric estimates performed for three relatively well-vascularized tumors in two patients (peritoneal carcinomatosis and periaortic lymph nodes in one patient and a bony lesion in another) showed that the tumor-to-blood ratios or the tumor-to-red marrow dose ratios were in the same range as those previously obtained with ^{131}I-MN-14 IgG for tumors of comparable sizes (*25*).

In this study, the myelotoxicity data indicated a relatively poor correlation between the toxicity grade observed and the administered radioactive dose. For example, grade 3 or 4 thrombocytopenia or leukopenia was seen in Patients 9 and 10, who received 67 and 70 mCi/m^2, respectively, but grade 0 toxicity was seen in Patient 11, who received 80 mCi/m^2. All three patients had similar red marrow doses and blood clearance

parameters. This suggests that factors other than the administered activity or red marrow dose were important. Indeed, Patient 9 received her chemotherapy within 2 mo of RAIT and had, in addition, intense bone marrow uptake seen by antibody imaging, suggesting marrow metastases. Patient 10 also received her last chemotherapy regimen of mitomycin only 2 mo before the MAb infusions, had borderline normal white blood cell counts and was, therefore, probably still recovering from myelotoxicity caused by mitomycin, a severely myelotoxic agent. In contrast, Patient 11 had his last chemotherapy of streptpzotocin, mitomycin, 5-fluorouracil and leucovorin 3 mo before RAIT, and his baseline peripheral blood counts were high (platelets of 891,000 and white blood cell count of 10,600). These data, therefore, suggest that factors other than the delivered radioactive or red marrow dose, such as the timing of the most recent chemotherapy, bone marrow metastases and the baseline peripheral blood counts may be important. An analysis of the relative contribution of each of these factors has been reported in abstract form elsewhere (*28,29*).

The use of ^{188}Re-labeled MAbs for RAIT of cancer patients is intriguing. Unfortunately, our study showed that the stability of the ^{188}Re-MN-14 used was not ideal, as evidenced by the relatively short biological half-lives seen even in patients with low CEA and tumor burden. However, it is important to note that the effect of this short biological half-life on the effective half-life of ^{188}Re-MN-14 is expected to be less pronounced because the latter is mainly dictated by the relatively short physical half-life of ^{188}Re (16.9 hr). For example, the effective blood half-life of ^{188}Re-MN-14, with a biological half-life of 27.3 hr, would still be only 10.4 hr, compared to 5.9 hr using the biological half-life of 9.0 hr. Nevertheless, the development of more stable ^{188}Re-conjugates, including those using indirect labeling methods, will result in increasing the blood residence time of the MAb and potentially improved tumor targeting.

Several factors influencing the optimal utilization of ^{188}Re-labeled MAbs should be considered to define their potential role for RAIT. The use of ^{188}Re in patients with bulky, poorly vascularized solid tumors, with their expectedly slow MAb uptake kinetics relative to the short physical half-life of ^{188}Re, may not be ideal. The use of ^{188}Re-labeled MAbs may prove to be more favorable in patients with small-volume and/or well-vascularized tumors. The maximum uptake in such tumors could occur within less than 24 hr after the MAb infusion, and ^{188}Re-labeled MAbs could, therefore, have a more favorable dosimetry than that in large bulky tumors. Similarly favorable dosimetry may also be expected in malignancies with rapid accessibility for the radiolabeled MAb, such as leukemias and, possibly, lymphomas.

The antibody form (intact IgG or fragment) is another important issue with respect to the utilization of ^{188}Re for RAIT. Considering its relatively short physical half-life, its use in combination with bivalent or even monovalent fragments with faster accretion in tumor may be more advantageous. However, the use of the ^{188}Re radiometal in association with the fragments is also expected to result in high renal uptake and, hence, potentially excessive renal radiation doses (*30*). In this context, our experimental results of substantially reduced uptake of ^{188}Re-MN-14 Fab′ after cationic amino acid infusions are encouraging and may provide the basis for the future clinical use of this agent in combination with the appropriate amino acid administration (*28*). Finally, intralesional or regional (intraperitoneal or intrapleural) MAb delivery may also be more preferable for this isotope, again because of the relatively rapid and facilitated uptake of the MAb by these routes.

CONCLUSION

The data presented demonstrate that despite the relatively increased renal and hepatic uptake of ^{188}Re, red marrow suppression is the only DLT. The feasibility of administering relatively high doses of ^{188}Re on a completely outpatient basis may make this agent a potential candidate for RAIT.

ACKNOWLEDGMENTS

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EDITORIAL

All of the Above (With Caveats for Each)

The choice of radioimmunoconjugate in radioimmunotherapy (RIT) has been the subject of study and speculation for years. Two different and yet similar approaches to RIT are discussed in this issue of the *JNM* (*1,2*). Juweid et al. (*1*) describe their results with ^{188}Re-labeled anti-CEA antibody in patients with GI cancers and speculate on the utility of fractionated RIT (*3*) using short-lived radionuclides. Zhang et al. (*2*) used a two-step targeting technique to increase the therapeutic ratio of ^{90}Y and alleviate marrow toxicity.

Apart from the striking similarity in the beta-minus emissions of the two radionuclides (*4*), the studies underscore the need to improve the current dismal response rates seen with radioimmunotherapy in solid tumors. And they raise the issue of what radioimmunoconjugate would be ideal for successful RIT in solid tumors.

The sustained clinical responses seen in patients with B-cell lymphoma treated with radioimmunotherapy (*5,6*) have encouraged researchers to search for ways to obtain comparable successes in solid tumors. However, current trials have achieved modest results (*1,2,7–11*), despite dose-intensification schema that include bone marrow transplants (*12*). There is, thus, a need to define those characteristics that would make a radioimmunoconjugate likely to achieve major responses in solid tumors.

Initial RIT trials have been, and will be, carried out in patients with bulky disease who have failed conventional chemotherapy—a group least likely to respond to any therapy. Logically, bulkier disease would necessitate the use of long-lived nuclides with energetic beta-minus emissions capable of traversing the tumor. These nuclides would ideally be conjugated with intact immunoglobulins, to allow persistence of radioantibody in circulation with consequent accessibility to tumor.

Riethmuller et al. (*13*) found that patients with surgically treated Duke's C colon carcinoma who had received unlabeled MAb 17-1A, that reacts against an epithelial surface antigen (*14*), had longer disease-free and overall survivals than their randomized controls. Similar results, albeit in a nonrandomized trial, were reported by Epenetos' group using ^{90}Y-labeled anti-mucin MAb (*15*).

Yttrium-90, with its pure beta-minus emission, has the advantage that it can be administered in an outpatient setting, and its companion disadvantage that dosimetric measures cannot be used in treatment calculations. While its energetic beta-minus may make it useful for bulky disease, it may render it less effective for minimal disease, where ^{131}I may well prove more useful, as may less energetic nuclides such as ^{177}Lu. Moreover, current changes in NRC regulations in the U.S. may make it possible for larger amounts of ^{131}I-labeled MAbs to be administered to outpatients (*16*). Many other nuclides already may be administered to outpatients, including ^{186}Re (*17*), ^{177}Lu and the ^{188}Re used by Juweid et al. (*1*). Finally, the use of positron-emitting nuclides such as ^{86}Y (*18*) and ^{64}Cu (*19*) will permit understanding of the biokinetics of ^{90}Y, ^{67}Cu and other pure beta-emitters.

The increasing use of radioimmunoconjugates of all types in solid tumor therapy can only augur well for the future. Tailored therapy, stated so clearly by Humm and Cobb (*20*) and O'Donoghue et al. (*21*), entails the selection of a radionuclide with appropriate decay and emission characteristics, conjugated to a macromolecule of appropriate immunobiologic characteristics. It is possible to envisage the development of multi-step techniques using radionuclides of ever shorter path length attached to nonimmunogenic antigen-binding proteins of faster biologic clearance to treat ever smaller disease burdens.

Is differential tumor uptake of radioimmunoconjugate, however, sufficient for effective treatment, regardless of the nature of the radioimmunoconjugate? Another multi-step approach (*2*) therefore seeks to increase the differential uptake of radioactivity in tumor. Antibodies of dual specificities, with one arm reacting to a tumor associated antigen and the other recognizing a ligand, are first injected. When the antibody has cleared from the circulation, ^{90}Y-labeled ligand is injected, with the intention of increasing relative tumor uptake and thus minimizing toxicity. This promising approach is already in clinical trials. It is becoming apparent that many issues, including immunogenicity and nonspecific accumulation in organs such as the liver, will need to be addressed (*22–24*).

The development of targeted radiotherapy has been fraught with uncertainties, offset significantly by developments in protein chemistry, bioengineering and nuclear chemistry. With the development of nonimmunogenic molecules of varying size and biologic function (*25–32*), we are now on the threshold of becoming able to tailor targeted radiotherapy. Let us use all the weapons in our armamentarium, and use each wisely.

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