Initial Clinical Evaluation of Iodine-125-Labeled Chimeric 17-1A for Metastatic Colon Cancer

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The internalizing properties of murine antibody 17-1A in human colon cancer cells make it attractive as a carrier for radionuclides with short range emissions such as ^{125}I. Murine 17-1A IgG2a antibody, which reacts against human gastrointestinal cancers, has been chimerized by joining its variable region with human IgG1 k constant region. A pilot clinical trial of increasing doses of ^{125}I-chimeric 17-1A in patients with metastatic colorectal cancer has been conducted. **Methods:** Patients were treated in groups of 2–4; 2 patients at Hahnemann University and 26 at the University of Alabama at Birmingham. Groups 1–5 received single administrations with ^{125}I doses of 20, 40, 60, 80 or 100 mCi. Subsequent groups received therapeutic doses of 150, 200 or 250 mCi, with the dose subdivided into infusing of 50 or 100 mCi at 4-day intervals. All treatments were delivered in an outpatient setting using radiation precautions. Labeling at 10 mCi/mg antibody was performed on the day of treatment. **Results:** Pharmacokinetics of circulating antibody was studied for initial patients, showing $\alpha T_{1/2}$ of 17–27 hr and $\beta T_{1/2}$ of 100–190 hr. Whole-body $T_{1/2}$ of radioactivity was determined by measuring urinary excretion or gamma emissions. Treatment was well tolerated without significant acute or late side effects. No significant bone marrow suppression or other dose-limiting toxicities were noted over this dose range. No objective responses were noted. **Conclusion:** These results show that high-dose outpatient radioimmunotherapy with an ^{125}I-labeled internalizing antibody can be achieved without significant patient toxicity or radiation hazard.

Key Words: colon cancer; iodine-125-chimeric 17-1A

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A variety of radionuclides have been used for radioimmunotherapy. The dose-limiting toxicity for most radionuclides, used with antibody conjugates, is bone marrow suppression. Hematopoietic toxicity results from a substantial radiation exposure due to the medium-long range beta and gamma emissions characteristic of most radionuclides currently used. An alternate approach to killing individual tumor cells while sparing the bone marrow is the use of low energy Auger electron emitters such as ^{125}I conjugated to antibodies that internalize into the target cells. Early approaches to this radionuclide therapy have included ^{125}I bound to DNA precursors, intercalating compounds, as well as translocated agents such as hormones and antibodies (*1–9*). Our study utilizes an antibody, 17-1A (*10–12*), which has characteristics of internalization, translocation to the nucleus (Rakowicz-Szulcynska EM, *personal communication*, 1994) and selective chromosomal toxicity when labeled with ^{125}I (*13*).

Efficient cell killing has been noted with ^{125}I nucleotide incorporation into DNA as well as with intranuclear localization of other ^{125}I-labeled compounds. Less toxicity has been noted with cytoplasmic localization and negligible toxicity with ^{125}I at the cell membrane as would be the case with nontarget cells such as the bone marrow (*4,6,8,14*). These results derive from the small gamma component of ^{125}I emissions (7%, 35 keV) and from the range of the Auger and internal conversion electrons (0.06–17 μm) being too small to effectively reach the chromatin without intranuclear translocation (*4,15,16*).

With ^{125}I internal conversion for 93% of decays, a shower of as many as 21 electrons with low energies and short ranges results in a high density of ionizations near the site of decay (*17*). This brings about 3–4 DNA strand breaks per decay (*3*). Although the ^{125}I must be near the DNA helix, its range is sufficient to result in both ipsilateral and contralateral DNA strand breaks, thus resulting in fragmentation of the DNA structure. The relative biologic effectiveness of ^{125}I is 7–8 compared to x-rays (*17*) due to irreversible DNA damage and the typical initial shoulder following x-irradiation of mammalian cells in the low dose range is eliminated (*18*). The highly efficient killing with intranuclear localization but sparing of nontarget cells makes ^{125}I-conjugates very attractive for cancer therapy.

Although previous clinical experience using ^{125}I-labeled antibodies in cancer patients has been reported (*19,20*), this study represents the first systematically dose escalating study.

In our current clinical trial, the chimeric version of 17-1A antibody was used. The chimeric antibody, designated as c-17-1A, contains the variable region of the murine 17-1A

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joined to constant regions comprised of human IgG1 heavy-chain and kappa light-chain sequences (*21*). Previous studies had confirmed that ^{125}I-c-17-1A behaved in a manner identical to that of ^{125}I-murine 17-1A in its extent of internalization, cytotoxicity and growth inhibition of human colon cancer xenografts in nude mice and the two antibody forms were equally effective in producing antibody dependent cell-mediated cytotoxicity (*22*). It was anticipated that the longer half-life and decreased immunogenicity of the chimeric antibody (*23*) would enhance the therapeutic potential of ^{125}I-c-17-1A radioimmunotherapy.

MATERIALS AND METHODS

Patient Selection and Trial Design

Study patients had pathologically proven colorectal cancer that was metastatic but not to the central nervous system. The patients were not judged to be curable with surgical resection. Patients had a performance status of ≥80 on the Karnofsky scale and had no history of other prior or concurrent malignancy. At the time of therapy, all patients had a WBC ≥2500/mm^3, platelet count ≥100,000/mm^3, BUN <30 mg%, creatinine <2 mg%, bilirubin <4.5 mg% and normal calcium, glucose and electrolytes. No known prior exposure to murine immunoglobulin was permitted and no patient received concurrent medications known to affect immune function. No patients were pregnant and none had received chemotherapy within 6 wk of treatment or radiation in 4 wk preceding treatment. Pretherapy, all patients had a physical examination, EKG, urinalysis, chest x-ray, laboratory studies, including a thyroid profile and radiographic studies of disease sites. All patients gave informed consent. Patients received Lugol's solution 1 day prior, on the day of treatment and 1 day post-therapy. The study was designed as a dose-escalating trial with at least 2 wk of observation for adverse experience before treatment of patients at the next dose level. Patients were treated in groups of 2–4 with single-dose levels of 20, 40, 60, 80 and 100 mCi. Subsequent groups received split-dose therapy of 150 mCi (100 mCi, Day 1; 50 mCi, Day 4), 200 mCi (100 mCi, Day 1; 100 mCi, Day 4) and 250 mCi (100 mCi, Day 1; 100 mCi, Day 4; 50 mCi, Day 8).

Permission was obtained through the Division of Radiation Safety and the State of Alabama Radiation Regulatory officials to administer as much as 100 mCi on an outpatient basis using radiation precautions and with exposure of <5 mR/hr at 1 meter from the patient. Patients and their families were counseled and given written guidelines for home radiation precautions.

The antibody preparation was aseptically injected as an intravenous bolus over 3 min by a freely running intravenous set-up. After infusion, vital signs were monitored immediately, at 30 min, 60 min and 24 hr.

Group 1 patients had blood samples obtained 1, 2, 4, 7, 10, 14 and 30 days postinjection, which were assayed for ^{125}I activity and antigen binding capability using a whole cell assay. Group 1 patients also had their total urine output collected daily for 72 hr postinjection. The urine volumes were measured and aliquots were counted in a scintillation counter. The counts obtained were converted to percent injected dose to determine the whole-body clearance of radioactivity. Determination of whole-body clearance of radioactivity from patients receiving ≥80 mCi doses was accomplished by serial whole-body gamma counting with a NaI detector probe at a distance of 13.5 feet. Blood samples were obtained weekly following therapy for CBC determination and evidence of human-anti-chimeric antibody (HACA) response. HACA assays were performed as previously described (*23*).

Patients were monitored at 6-wk intervals for evidence of response to therapy. Tumor measurements were recorded in centimeters as the longest perpendicular diameters. Complete remission was defined as disappearance of all clinical evidence and symptoms of active tumor for a minimum of 4 wk. Partial remission was defined as 50% decrease in the sum of the products of perpendicular diameters of all objectively measurable lesions and significant improvement in all evaluable (nonmeasurable) tumor sites. No simultaneous increase in the size of any lesion or the appearance of new lesions could occur and the remission had to be maintained for ≥4 wk. Stable disease was considered a response less than partial remission and not having evidence of progression for a minimum of 6 wk. There could be no appearance of new lesions and no worsening of symptoms. Progression was defined as an increase of ≥50% in the size of any measured lesions or the appearance of new lesion(s).

Antibody Preparation

G1K c-17-1A was supplied by Centocor, Inc., as a sterile, nonpyrogenic solution containing 2 mg of monoclonal IgG1 per ml in a solution which contains 0.03 *M* sodium phosphate, 0.15 *M* sodium chloride, pH 7.0. Each vial contained 2 mg of antibody. The product had been screened for the presence of murine viruses and had passed release tests including the general animal safety test, rabbit pyrogen test and final product sterility tests, all of which conform to 21 CFR requirements.

Radiolabeling was carried out aseptically using the Iodogen technique, Iodogen ~(1,3,4,6-tetrachloro-3α, 6α-di-phenylglycoluril) from Pierce (Rockford, IL). Specific activity was 10 mCi/mg, as previously described (*24*). Iodine-125I, NaI solution was obtained from Dupont NEN (Billerica, MA) (100 mCi/ml). The radiolabeled antibody was separated from the unbound iodine by gel filtration chromatography. The radiolabeled product passed quality control tests, including specific activity and Limulus amebocyte assay before patient administration.

RESULTS

All treatments were carried out without need for hospitalization. Patients and their social contacts were agreeable to home radiation precautions. Twenty patients received a single infusion and eight patients were treated with a split-dose schedule as shown in Table 1.

No severe hematologic or other toxicity was recorded during the 6-wk evaluation period after therapy. Only three patients had platelet counts that nadired <100,000/mm^3. Two patients who received 60 mCi ^{125}I-c-17-1A had platelet count nadirs of 94,000 and 66,000/mm^3 while one patient who received 150 mCi ^{125}I-c-17-1A had a platelet nadir of 97,000/mm^3 during the 6-wk follow-up. Baseline pretreatment platelet counts for the patients were 153,000, 174,000 and 121,000/mm^3, respectively, although it is notable that the first of these patients had a platelet count of 97,000 2 wk before treatment. Two patients at the 200 mCi ^{125}I level had a white blood cell count below the normal range (3800/mm^3) during the 6-wk follow-up.

No objective tumor responses were observed at the dose schedules used in this group of patients with advanced, metastatic disease that was generally refractory to systemic

TABLE 1
Dose Schedule of Iodine-125-c-17-1A

Group no.	No. of patients	^{125}I-c-17-1A (mCi) Total			
		Day 1	Day 4	Day 8	Dose (mCi)
1	4	20			20
2	4	40			40
3	4	60			60
4	4	80			80
5	4	100			100
6	3	100	50		150
7	3	100	100		200
8	2	100	100	50	250

chemotherapy. As shown in Table 2, 10 patients were stable at the 6-wk evaluation, 3 patients were considered to have disease progression on the basis of increased size of index lesions, 9 patients developed new areas of disease and 6 patients had general disease progression and decreased performance status.

Pharmacokinetics was undertaken using serial serum samples of patients in the lowest dose group (20 mCi ^{125}I-c-17-1A). The data best fit a two-compartment model with individual patient values shown in Table 3.

The whole body half-life of radioactivity in Group 1 patients receiving 20 mCi ^{125}I-c-17-1A was 82–112 hr based on determinations from urinary loss of radioactivity during the first 3 days after treatment. For patients receiving ≥80 mCi ^{125}I-c-17-1A whole-body half-life for loss of radioactivity ranged from 32 to 177 hr based on serial gamma probe counts.

As shown in Table 4, Patient 11 demonstrated an anti-c-17-1A assay value ≥2.5 times the pretreatment level during the initial 6-wk evaluation period. In this patient, an elevation to 29 ng/ml was observed 7 days post-therapy and had dropped to 9 ng/ml by 14 days. No other samples up to Day 94 exceeded the pretreatment level of 3 ng/ml. One other patient (Patient 18) had 10 ng/ml anti-c-17-1A antibody detected 47 days after therapy whereas the 6 weekly samples preceding this elevation were ≤3 ng/ml. Although study design excluded patients who had previously been exposed to murine antibodies, Patient 16 may have previously received a small amount of c-17-1A. This patient remained negative for an anti-c-17-1A antibody response.

DISCUSSION

The potential therapeutic advantages of ^{125}I bound to agents that allow close approximation to the DNA has been studied in several preclinical settings, including ^{125}I-17-1A treatment of human colon cancer cells in culture or as xenografts in nude mice (*2–9,13,25*). With the exception of one report (*26*), these studies showed tumor inhibition and the results prompted the initiation of the clinical trial reported here. The maximum tolerated dose was not reached with escalation to our highest dose of 250 mCi ^{125}I total dose, given in three portions over 8 days.

Since no significant hematologic toxicity was noted at the highest dose level, the infrequent Grade 1 toxicity level blood counts for three patients at lower dose levels are suspected of being coincidental rather than a true reflection of ^{125}I-related toxicity. Bone marrow cells do not react with c-17-1A and internalize it, thus the radiation exposure to the marrow should only be from the low level gamma emissions and not the more abundant Auger electrons. Although the dose to bone from the 7% 35 keV gamma emissions will be greater than to nontarget soft tissues due to the dominance of the photoelectric effect (*27*), this only affects a 10-micron transition zone at the bone-soft tissue interface and would still relatively spare most of the marrow cavity. Other ^{125}I-labeled antibody trials have not reported significant toxicities (*19,20*) after administrations of ≤50 mCi at intervals of ≥1 wk.

In this study of patients with bulky advanced metastatic colon cancer, no objective tumor regressions were observed while 10 patients were stable and 18 progressed. Without measurable tumor regressions, it is difficult to determine if some patients may have had therapeutic benefit from the ^{125}I-c-17-1A treatment. Four patients whose disease was stable 6 wk after a single treatment and who did not immediately receive other forms of therapy remained stable at last follow-up of 9, 12, 12 and 16 wk. Long-term tumor stability has been reported for three patients with advanced neuroblastoma who were treated with a single administration of ^{125}I-metaiodobenzylguanidine (MIBG) (*28,29*). One of these neuroblastoma patients who survived >1 yr had stable measurable tumor mass during that follow-up interval, whereas the tumor was rapidly growing before therapy. Subsequently, at >1 yr after treatment, tumor growth was again detected (*29*).

TABLE 2
Comparison of Disease Status after Therapy with Dose Administered

Disease response	Number of patients with response at each dose level of ^{125}I-c-17-1A							
	20 mCi	40 mCi	60 mCi	80 mCi	100 mCi	150 mCi	200 mCi	250 mCi
Stable		2		2	2	2	2	
Progression of known lesions				1		1		1
New sites of disease noted	3	2	2	1	1			
Clinical progression without measured lesions	1		2	1			1	1

TABLE 3
Plasma Pharmacokinetics Following a Single Infusion of Iodine-125-c-17-1A

Patient no.	$\alpha T_{1/2}$ (hr)	$\beta T_{1/2}$ (hr)	Area under the curve (hr μg/ml)	Mean residence time in plasma (hr)	VDss (ml/kg)	Clearance rate (ml/hr kg)
1	27	190	265	126	130	1.03
2	25	150	444	128	112	0.88
3	17	100	212	94	97	1.04
Mean ±1 s.e.	23 ± 3	147 ± 26	307 ± 70	116 ± 11	113 ± 10	0.98 ± 0.05

The lack of objective responses may be due to poor penetration of antibody through large human tumor masses and/or inadequate nuclear translocation. The fact that adjuvant use of multiple administrations of large doses (100–500 mg) of unlabeled 17-1A has shown a significant improvement in survival and freedom from distant metastasis as adjuvant for patients with risk of microscopic disease suggests that therapeutic benefit is greater with small disease deposits (*30*). One would expect greater efficacy with radiolabeled 17-1A, taking advantage of both early cell toxicity from the internalized rabiolabeled antibody and immunologic mechanisms that might be effective long after radioactivity decay. A low objective response rate (2/53) for measurable metastatic disease has been reported with multiple infusions of ^{125}I-labeled 17-1A (*20*). In that study, however, it is difficult to determine the effects of the ^{125}I-17-1A alone since patients also received external beam radiation in addition to the radioimmunotherapy.

The human immune response studies are consistent with our previous experience showing c-17-1A to be of low immunogenicity in humans (*23,37*). Chimeric 17-1A appears to have little immunogenic potential compared to its murine 17-1A counterpart (*32–34*) and other chimeric antibodies (e.g., ch-B72.3) (*35–37*).

TABLE 4
Anti-c-17-1A Antibody Levels before and after Treatment*

Patient no.	Pretreatment	Post-treatment	Day of abnormal value
6	3	2-3	
7	2	2-3	
8	2	2-3	
9	2	2	
10	2	2	
11	3	2-29	7
12	2	2	
13	1	4	
14	2	2-3	
15	3	6-8	
16	3	3-7	
17	2	2-3	
18	2	2-10	
19	2	3-8	
20	2	2-3	

*Values are expressed as ng/ml sera. A positive assay was defined as a post-therapy value which was at least twice the pretherapy value and exceeded 12 ng/ml, which is 2 s.d. above the mean (5.4 ± 3.3) of 44 colon cancer patients prior to exposure to murine antibody (*24*).

The pharmacokinetic parameters measured in Group 1 patients of this study (20 mCi ^{125}I-c-17-1A) were similar to pharmacokinetics studies of ^{131}I-c-17-1A in similar patients. The whole body half-life of radioactivity measurements among patients of the current study was more variable than that of patients receiving a tracer dose of ^{131}I-c-17-1A (*32*). This difference likely represents the limitations of measuring the low energy gamma component where scatter and attenuation, perhaps even from clothing, varies despite reproducible patient positioning.

CONCLUSION

This dose escalating trial shows that high-dose outpatient radioimmunotherapy with a ^{125}I-labeled internalizing antibody can be achieved without significant patient toxicity or radiation hazard to health care personnel.

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