

# Phase I Trial of Iodine-131-Chimeric B72.3 (Human IgG4) in Metastatic Colorectal Cancer

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Twelve patients with metastatic colorectal cancer participated in a Phase I trial of  $^{131}\text{I}$ -labeled chimeric B72.3 (human IgG4). Consecutive groups of patients received 18 mCi/m<sup>2</sup>, 27 mCi/m<sup>2</sup> and 36 mCi/m<sup>2</sup>. No acute side effects related to antibody administration were noted. Bone marrow suppression was the only side effect; it was dose-dependent and correlated with whole-body radiation dose estimates. The lowest dose level produced no marrow suppression, whereas 27 mCi/m<sup>2</sup> resulted in Grade 1 and 2 marrow suppression in two of three patients. The maximum tolerated dose was 36 mCi/m<sup>2</sup> with all six patients at this dose level having at least Grade 1 and two patients with Grade 3 and 4 marrow suppression. Eight of 12 patients had radioimmune imaging of tumor sites at 5–22 days. Seven patients had an antibody response to initial infusion. On retreatment, whole-body kinetics and imaging were altered for patients with a high anti-ch-B72.3 response. Thus, chimeric B72.3 (IgG4) has limited utility as a means of delivering multiple therapeutic doses of  $^{131}\text{I}$  in the majority of patients; alternative strategies including second generation anti-TAG-72 monoclonal antibodies, other radioisotopes and other chimeric human isotypes will need to be pursued.

**J Nucl Med 1992; 33:23–29**

One of the limitations of immunotherapy using xenogeneic antibodies is the tendency to develop an immune response against therapeutically administered antibodies. In an effort to overcome this, chimeric mouse/human antibodies have been constructed to decrease the amount of foreign protein while maintaining anti-tumor specificity. The IgG4 chimeric of murine B72.3 (ch-B72.3) was accomplished by recombinant DNA technology joining genes of the murine B72.3 (m-B72.3) variable region to human IgG4 and K constant regions (1). Murine B72.3 antibody is reactive with a tumor-associated glycoprotein

(TAG-72) having mucin features (2). Expression of TAG-72 antigen has been reported for several epithelial-derived cancers, including adenocarcinomas of the colon, breast, lung, ovary, pancreas and stomach (3–9). Radiolocalization of  $^{125}\text{I}$ - or  $^{131}\text{I}$ -labeled m-B72.3 to human tumor xenografts in athymic mice and in patients with colorectal carcinomas has been demonstrated (10–19). Characterization and biodistribution studies in mice predict distribution of ch-B72.3 similar to that of the native m-B72.3 (1, 20). This has been confirmed by localization of radiolabeled murine and mouse/human chimeric B72.3 to known sites of colon carcinoma lesions by direct analysis of biopsies and using gamma camera imaging (12,13,14,21). In this Phase I study,  $^{131}\text{I}$ -labeled mouse/human ch-B72.3 was administered to patients with metastatic colon cancer in an effort to study toxicity, tumor localization and to establish the maximum tolerated dose (MTD) of this radiolabeled chimeric antibody.

## MATERIALS AND METHODS

### Clinical Protocol

Patients with metastatic colorectal cancer with measurable disease, Karnofsky performance status  $\geq 60$  and original tumor documented to be TAG-72 positive by immunoperoxidase technique (22), were candidates for the protocol. They could not have had pelvic, chest or abdominal irradiation and had to be off all chemotherapy for at least 4 wk. Laboratory criteria for accrual included WBC  $> 3500$ , platelet count  $> 100,000$ , bilirubin  $< 2.0$ , estimated creatinine clearance  $\geq 50$  cc/min. This study was reviewed and approved by the Institutional Review Board of the University of Alabama at Birmingham. Signed informed consent was obtained from all patients.

The trial design involved sequential groups of three patients treated at 18 mCi/m<sup>2</sup>, 27 mCi/m<sup>2</sup> and 36 mCi/m<sup>2</sup> with expansion of the group to six at the MTD dose (36 mCi/m<sup>2</sup>) with labeling at 10 mCi/mg and 3.4–6.7 mg antibody were used in therapeutic infusions. The first four patients received a second administration 7–8 wk after the initial infusion. Doses were not increased for individual patients given a repeat infusion. Ten drops of saturated potassium iodide solution was prescribed beginning two days prior to administration of radioactive iodine and continuing daily for 14 days. Prior to each administration of radiolabeled antibody, a 100- $\mu\text{g}$  test dose of unlabeled antibody was infused and the

Received Apr. 24, 1991; revision accepted Aug. 9, 1991.  
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patient was carefully monitored for 30 min for evidence of an adverse reaction. If the test dose was well tolerated, <sup>131</sup>I-ch-B72.3 was infused over 1 hr. Vital signs were monitored every 15 min for 1 hr and every 30 min six times. Subsequent to therapy patients had serial gamma camera imaging, whole-body gamma counts and blood sampling for determination of an immune response against the administered antibody. Follow-up evaluation included history and physical exam, blood counts, liver, renal and thyroid function studies. Radiographic assessment of tumor response was done at six weeks. Toxicity grading utilized RTOG grading system (23) and a total bone marrow suppression score (grades of thrombocytopenia and leucopenia added together) was used for correlation analysis (4). Patients who responded or had stable disease were eligible for a second treatment  $\geq 6$  wk after initial therapy if they had recovered from hematologic toxicity and maintained their performance status.

### Dosimetry and Imaging Techniques

Dosimetry data collection by gamma camera imaging and whole-body gamma counts was as previously described (25). Radiation doses to tumors and organs were estimated using the MIRD formalism with data obtained from planar scintigrams of known tumor sites. The delayed and transient nature of the tumor imaging in this group of patients made it necessary to incorporate some assumptions in these calculations. The activity in each tumor at each time that tumor imaged was obtained from counts in a manually drawn region of interest with corrections for background and tissue attenuation. Tumor depth on which the attenuation correction was based was estimated from CT scans. Activity was assumed to have increased linearly from zero at the time of infusion to the level measured from the earliest positive scan. The resulting activity versus time curve was integrated in a piecewise fashion by fitting simple exponential functions to adjacent data points. Tumors were assumed to be spherical with dimensions estimated from gamma camera images. S-values for dose to each tumor from activity in that tumor were calculated from data in MIRD Pamphlet No. 8 (26). Doses to tumors from the remaining activity, assumed to be uniformly distributed in the total body, were estimated by means of S-values

from MIRD Pamphlet No. 11 (27) for abdominal organs with masses comparable to the tumor masses. Gamma camera images of localization sites were reported as positive for a score of 2-4 according to the following grading scale: 0 = within normal limits; 1 = probably negative; 2 = suspicious; 3 = positive; 4 = strongly positive.

### Chimeric B72.3 Antibody

The ch-B72.3 antibody was produced by Celltech, Ltd. (1) and supplied in vials containing 7.69 mg (1.01 mg/ml) in 50 mM phosphate buffer by the National Cancer Institute, Division of Cancer Treatment under IND #3082. Radiolabeling at 10 mCi/mg antibody utilized standard Iodogen methodology (28). After determination of the percentage of iodine incorporation by instant thin layer chromatography (29), free iodine was separated from <sup>131</sup>I-ch-B72.3 by passage through a 1 × 22.5 cm acrylamide desalting column (Clinitics, Inc.). Quality control of radiolabeled product included immunoreactivity by the method of Lindmo (30), HPLC analysis and Limulus ameocyte lysate assay.

### Human Anti-ch-B72.3 Assay

Assays for immune response against ch-B72.3 were done using a double antigen radiometric assay as previously described (31). A positive assay was defined as a post-therapy binding value at least twice the pre-therapy value and greater than 12 ng/ml. The upper limit of normal was established as 2 s.d. above the mean for 44 colon cancer patients binding ( $5.4 \pm 3.3$ ).

## RESULTS

Twelve patients (age 42-73 yr) with metastatic adenocarcinoma of the colon were selected. All had undergone resection of the primary tumor. Ten of the 12 patients previously received chemotherapy and had recovered from its toxicities. None had received intraperitoneal, abdominal or pelvic radiation. All 12 patients had liver metastases and eight had other sites of involvement, including lung, lymph nodes, abdominal wall and pelvis.

Table 1 provides the dose levels, doses administered,

TABLE 1  
Iodine-131-ch-B72.3 Dosimetry and Marrow Toxicity\*

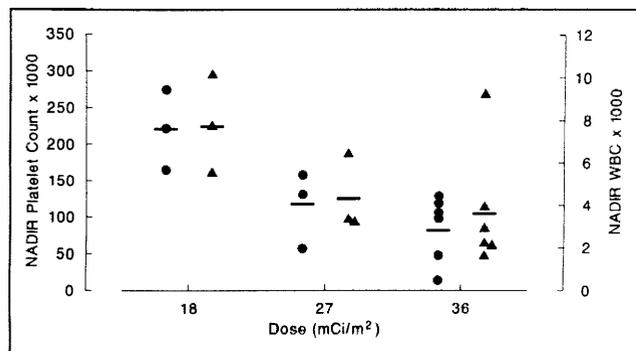
Patient no.	Dose Level (mCi/m <sup>2</sup> )	Dose (mCi)	Whole-Body T <sub>1/2</sub> (hr)	Whole-Body dose (cGy)	Nadir platelet count ( $\times 10^9$ )	Toxicity (grade)	Nadir WBC ( $\times 10^9$ )	Toxicity (grade)	Response
1	18	40	93	48	165	0	7.7	0	Stable
2	18	41	94	59	222	0	5.5	0	Stable
3	18	34	106	54	275	0	10.1	0	Stable
4	27	43	117	68	158	0	3.3	1	Stable
5	27	54	112	86	57	2	3.2	1	Progressed
6	27	55	117	91	131	1	6.4	0	Progressed
7	36	63	125	122	14	4	1.6	3	Progressed
8	36	59	109	86	98	1	3.9	1	Progressed
9	36	65	86	74	129	1	9.2	0	Progressed
10	36	61	100	88	48	3	2.1	2	Progressed
11	36	66	99	91	106	1	2.9	2	Progressed
12	36	67	113	106	119	1	2.2	2	Progressed

\* Toxicity Grading: Platelets  $\times 1000$  = Grade 0 (normal); Grade 1 (75.0-Normal); Grade 2 (50.0-74.9); Grade 3 (25.0-49.9); Grade 4 (<25.0). WBC  $\times 1000$  = Grade 0 ( $\geq 4.0$ ); Grade 1 (3.0-3.9); Grade 2 (2.0-2.9); Grade 3 (1.0-1.9); Grade 4 (<1.0).

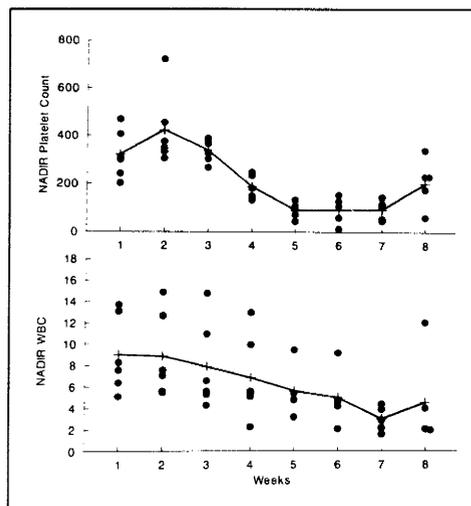
dosimetry estimates and effects of therapy. None of the patients experienced any clinical side effects from the initial infusion of  $^{131}\text{I}$ -ch-B72.3. Patient 2 experienced a transient increase in pain from a liver metastatic lesion and subsequently had less symptoms than prior to antibody administration. No tumor reduction was noted on radiographic studies however. Patients 1–4 had stable disease at the 6-wk evaluation, while Patients 5–12 had objective progression of disease.

The only toxicity noted in this trial was bone marrow suppression. The three patients receiving the first dose level ( $18\text{ mCi/m}^2$ ) had no significant leukopenia or thrombocytopenia. The three patients receiving the second dose level ( $27\text{ mCi/m}^2$ ) all had nadir platelet counts lower than pre-therapy levels with one patient reaching Grade 1 and one patient reaching Grade 2 thrombocytopenia. Two of these patients also reached Grade 1 leukopenia levels. The six patients treated at  $36\text{ mCi/m}^2$  all had significant thrombocytopenia with four Grade 1, one Grade 3 and one Grade 4. Five of six patients had significant leukopenia with one Grade 1, three Grade 2 and one Grade 3. As illustrated in Figure 1, the use of dosage levels based on patient size ( $\text{m}^2$ ) provided a consistent graduated decrement in marrow function. The timing and duration of thrombocytopenia and leukopenia can be seen in Figure 2 for the six patients receiving  $36\text{ mCi/m}^2$ . Table 1 and Figure 3 provide the data on estimated whole-body radiation dose (cGy) and degree of marrow suppression. All patients receiving a whole-body dose  $>60\text{ cGy}$  had some degree of marrow suppression. The correlation of whole body radiation dose and marrow suppression (Fig. 3) was  $r = 0.85$  ( $p = 0.0004$ ). Estimates of bone marrow dose by the method of Snyder (27,32) were quite similar to whole-body values (data not presented) and correlated similarly with marrow suppression ( $r = 0.85$ ;  $p = 0.005$ ). We also analyzed the effects of whole-body radioactivity half-life (catabolism, decay and excretion) and AUC on suppression of WBC and platelet count in the six patients who all received  $36\text{ mCi/m}^2$ . The correlation coefficients were 0.71 and 0.78 ( $p = 0.12$  and 0.07).

Positive tumor localization (imaging) tended to occur

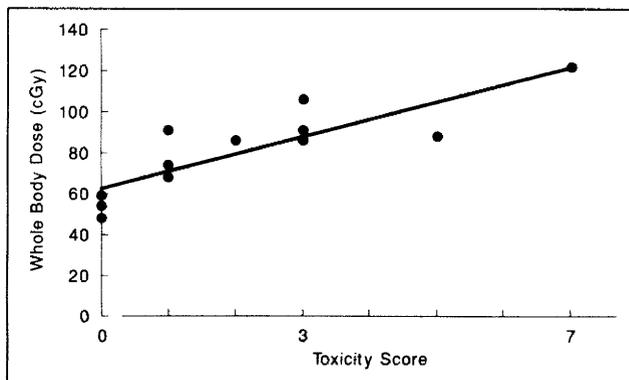


**FIGURE 1.** The nadir of WBC (▲) and platelet counts (●) is compared for the dose levels of  $18\text{ mCi/m}^2$ ,  $27\text{ mCi/m}^2$  and  $36\text{ mCi/m}^2$ . Each symbol represents counts for a single patient.



**FIGURE 2.** The time course for suppression and recovery of platelet counts (A) and WBC (B) after  $36\text{ mCi/m}^2$ . Data points represent values for individual patients. The solid line represents the mean for all patients. Time course is in weeks postinfusion.

late after infusion of antibody (Table 2). The earliest positive tumor localization was noted five days after treatment even though five patients had scans prior to that point. In Patient 8, the first localization was delayed until Day 16 with negative scans at Days 8 and 12. Localization of radioactivity in known areas of disease involvement was prolonged in most patients through the last time of scanning which ranged from Day 8 to Day 23 after administration. The liver was the most common site with positive localization occurring in 7 of 12 patients. Localization to known sites of disease was also noted in a pelvic mass (Patient 7) and an abdominal wall mass (Patient 3). Additionally, an occult bone lesion at the left sacroiliac joint was detected and later confirmed by radiographic studies. The overall rate of imaging was approximately 50% of lesions  $>2\text{ cm}$  in diameter. With the exception of localization of a small occult metastasis in Patient #1, most lesions imaged were  $\geq 4\text{ cm}$ , whereas adjacent smaller lesions were often not clearly defined.



**FIGURE 3.** Correlation of whole-body radiation dose estimates with marrow toxicity score ( $r = 0.85$ ;  $p = 0.0004$ ).

**TABLE 2**  
Imaging Localization following Infusion of <sup>131</sup>I-ch-B72.3

Patient no.	Days of scans	Days of localization	Number of lesions imaged	Number of known lesions $\geq 2$ cm	Size of smallest lesion that imaged*	Sites of known lesions	Sites imaged
1	5, 7, 10, 23	5-23	3	4	<1	Liver (3), lung	Occult pelvic lesion, liver (1), lung
2	3, 5, 8	8	1	2	10 × 8	Liver (2), lymph node (3)	Liver (2)
3	3, 5, 8	8	1	3	7 × 3	Liver (2), abdominal wall	Abdominal wall
4	3, 5, 13, 15	13	3	3	4 × 4	Liver (3)	Liver (1)
5	7, 9, 13, 15	none	0	1	—	Liver (3)	None
6	4, 6, 10, 12, 17	none	0	2	—	Liver (1), lymph node	None
7	10, 15, 17, 22	15-22	2	4	5 × 3	Liver (2), lymph node (2), pelvic mass	Liver (1), pelvic mass
8	8, 12, 16, 19	16, 19	3	3	7 × 9	Liver (3)	Liver (3)
9	9, 22	22	1	3	9 × 5	Liver (2), lymph node	Liver (1)
10	8, 15	none	0	3	—	Liver (2), lymph node (1)	None
11	5, 12, 15	none	0	1	—	Liver (1), lymph node (2)	None
12	8, 15, 22	8, 15, 22	1	1	5 × 3	Liver (1)	Liver (1)

\* Lesion sizes (in cm) have been rounded off to nearest whole number.

It is difficult to calculate tumor doses given the transient and delayed tumor imaging data. However, making the assumption of a linear increase in activity to areas of positive imaging, the dose estimates to tumor ranged from 2.3 to 5.9 cGy/mCi. It is notable that three distinct areas of localization in the liver of Patient 4 varied in dose from 4.0 to 5.9 cGy/mCi. Most of the total radiation dose to the whole body was typically delivered before the first positive radioimmune visualization of any tumor. Figure 4 shows both the daily contributions and cumulative exposure as percentage of the total dose for Patient 1. For this patient, more than 50% of the total radiation exposure occurred within the first four days.

The immune response to infusion of <sup>131</sup>I-ch-B72.3 is characterized in Table 3. Seven of 12 patients had evidence

**TABLE 3**  
Human Antibody Response to ch-B72.3

Patient no.	Time after Administration			
	Pre-Rx	Week 2	Weeks 3-4	Weeks 6-8
1	7*	23	68	142
2	5	70	127	133
3	10	9	9	5
4	5	5	17	8
5	9	24	18	16
6	10	12	12	18
7	15	39	55	74
8	12	245	371	231
9	10	88	393	426
10	6	6	6	7
11	7	7	12	9
12	7	8	9	7

\* Values expressed as ng of ch-B72.3 bound/ml sera.

of antibody response with two patients having modest levels (Patients 4 and 5) while five patients had moderate-high levels (Patients 1, 2, 7, 8 and 9). All elevated levels were competitively inhibited by an excess of competing ch-B72.3 (data not shown).

Patients 1-4 received a second infusion of <sup>131</sup>I-ch-B72.3 approximately 8 wk after the first infusion without dose alteration. Table 4 provides the whole-body kinetics, dosimetry and marrow suppression data. None of the patients had any acute adverse clinical effects from the second infusion. Patients 1 and 2 had a high level of antibody to ch-B72.3 (142 and 133 ng/ml) at the time of second infusion. They were noted to have a dramatic shortening of whole-body radioactive half-life and reduction in the estimates of whole-body radiation dose. They had no bone marrow suppression after this second infusion similar to the absence of suppression with the first dose. Patient 3 had no evidence of antibody to ch-B72.3 after initial infusion and the whole-body half-life and radiation dose of this second infusion were similar to first infusion. Grade

**TABLE 4**  
Whole-Body Half-life of Radioactivity, Dose and Toxicity Following Initial and Repeat Administration of <sup>131</sup>I-ch-B72.3

Patient no.	Whole-Body $T_{1/2}$ (hr)		Whole-Body radiation dose (cGy)		Marrow toxicity grade	
	1st	2nd	1st	2nd	1st	2nd
	Dose	Dose	Dose	Dose	Dose	Dose
1	93	24	48	12	0	0
2	94	18	59	11	0	0
3	106	105	54	60	0	1
4	117	84	68	54	1	2

1 thrombocytopenia was noted eight weeks after the second dose. No toxicity was observed after the first treatment cycle. Patient 4 had a modest antibody response (17 ng/ml at Week 3) which returned to the normal range by the time of second infusion (8 ng/ml). This patient had a modest shortening of whole-body radioactive half-life (117 hr versus 84 hr) and a modest reduction in whole body radiation dose. Suppression of platelet production after the second dose was greater with Grade 1 thrombocytopenia (platelet nadir of 77,000) compared to a platelet nadir of 158,000 after first infusion (Table 1). This patient experienced transient Grade 1 leukopenia after each course of therapy. Table 5 provides the radioimmune imaging results from first and second infusions of  $^{131}\text{I}$ -ch-B72.3. Patients 1 and 2 had no antibody localization with the second infusion secondary to the rapid clearance of antibody. Patients 3 and 4 had improved imaging both in terms of number of sites imaged, number of positive imaging days, and intensity of radioactive uptake compared to the first cycle.

## DISCUSSION

A major objective of this study was to examine the toxicity of a radiolabeled long-lived chimeric monoclonal antibody of the human IgG4 isotype and establish a maximum tolerated dose. We chose to utilize dosage increments of radioactivity which were based on patient size. This seemed reasonable in that for any fixed dose, patient size would affect serum concentration of isotope and radioactivity/gm of normal tissues (whole-body dose, etc.). This represented a departure from prior studies which utilized fixed dose increments (33,34). As seen in Figure 1, this approach gave a gradual increment in marrow toxicity ranging from no significant marrow suppression (18 mCi/m<sup>2</sup>) to mild marrow suppression at 27 mCi/m<sup>2</sup> (2/3 Grade 1 or 2) and maximal tolerated dose at 36 mCi/m<sup>2</sup> (6/6 marrow suppression with two instances of Grade 3 or 4) over a two-fold dose range. Marrow toxicity was the only side effect noted in this group of 12 patients. Additional trials will be required to confirm that dosage levels utilizing patient size will provide more predictable radiobiologic effects as suggested by this study.

A dose level of 36 mCi/m<sup>2</sup> (dose administration of 60–70 mCi) for MTD is considerably lower than prior trials of  $^{131}\text{I}$  conjugated murine monoclonal antibodies or poly-

clonal antisera. This was not unexpected given the much longer plasma half-life (242 hr) of this IgG4 chimeric molecule (35) as compared to the 24–60 hr reported in those prior studies utilizing murine monoclonal antibodies including B72.3 (36,37). The longer antibody plasma half-life results in longer whole-body radioactivity half-lives and larger whole-body radiation doses than has generally been reported for  $^{131}\text{I}$ -murine antibodies. For example, estimates of  $0.7 \pm 0.5$  cGy/mCi were reported for murine  $^{131}\text{I}$ -anti-CEA whole-body radiation dose (38) while a murine anti-lymphoma antibody (MB-1) resulted in an average exposure of  $0.6 \pm 0.3$  cGy/mCi (39). A recent study of  $^{131}\text{I}$ -chimeric 17-1A had a plasma half-life of  $101 \pm 16$  hr and whole-body dose estimates of  $0.83 \pm 0.11$  cGy/mCi (25). Thus, as expected, radioimmunotherapy with  $^{131}\text{I}$ -ch-B72.3 was associated with rather high whole-body radiation doses, which correlated quite well with the degree of marrow suppression (Fig. 3). This would presumably be true of other molecules with similarly long plasma half-lives.

A second objective of this study was to examine the ability of a chimeric monoclonal antibody to localize to tumor sites. In general, successful radioimmune imaging is best seen at approximately 1–2 plasma half-lives after infusion. This equates with 48–72 hr postinfusion for intact murine antibodies and 4–24 hr for antibody fragments. This same observation was noted with this long-lived antibody with successful imaging noted at 8–23 days postinfusion (Table 2). The long delay reflected the time required to lower background radioactivity and makes such a reagent impractical as a useful tumor imaging agent.

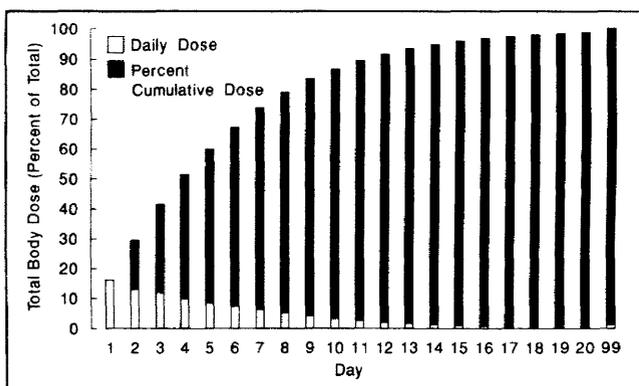
A third objective of this trial was to examine the feasibility of repeat infusions of this radiolabeled reagent. A prior trial with chimeric 17-1A (human IgG1) documented the ability to administer two repeated infusions in each of six patients without alteration of kinetics or interfering human immune response (31). The experience with chimeric B72.3 was quite different. Overall, 58% of the patients had an immune response to chimeric B72.3. A second infusion in two of these patients (nos. 1 and 2) at a time when they had a high antibody response to chimeric B72.3 resulted in a dramatic shortening of whole-body radioactive half-life (Table 4) and prevention of radioimmunolocalization at sites previously positive for radioimmune imaging (Table 5). No adverse effects occurred in the two patients and the dramatic reduction in whole-body radiation doses (Table 4) prevented any cumulative radiation effects on the bone marrow. Patient 3 had no immune response detected to first infusion of chimeric B72.3 and had similar whole-body radiation half-lives and radiation dose estimates. Patient 4 had a modest, transient antibody response after the initial infusion, which had returned to the normal range by the time of second infusion. The second infusion had a modest (20%–30%) decrease in whole-body half-life and radiation dose (Table 4). Both patients (nos. 3 and 4) had more marrow suppression

**TABLE 5**  
Radio-localization with Repeat Infusion of  $^{131}\text{I}$ -ch-B72.3

Patient no.	Days of imaging localization		Number of lesions imaged	
	1st Dose	2nd Dose	1st Dose	2nd Dose
1	5, 7, 10, 23	none	2	0
2	8	none	2	0
3	8	3, 5, 8, 11, 16	1	3
4	13	8, 12, 15, 19	1	3

following the second infusion probably reflecting the cumulative effects of radiation. Radioimmune localization was similar or superior on second infusion emphasizing the feasibility of repeated delivery of radioisotopes in the absence of patient immune response. Accelerated decline of whole-body radioactivity following repeat infusion in the face of elevated anti-ch-B72.3 titers is presumed to be the result of more rapid catabolism of the iodinated antibody and excretion in the urine as has been described for murine B72.3 (19). In addition, we have recently examined the human antibody response to murine B72.3 after a single imaging dose of 1 mg (40). Seventy-one percent of 52 patients had a positive antibody response with antigen binding values approximately twice those measured in this study. This increased response may reflect the antibody specificity to both murine constant and variable regions as compared to murine variable region only in this trial.

Finally, this study suggests that the delivery of radiation to tumor sites with  $^{131}\text{I}$  by conjugation to an intact chimeric antibody of the IgG4 isotype represents an inefficient strategy with excessive whole-body radiation due to the long plasma half-life of the antibody. As seen in Figure 4, the whole body received a large proportion of radioactivity prior to the first detectable radiolocalization to tumor sites. Iodine-131 was chosen for beta emissions of sufficient range to reach surrounding cells since radiolocalization studies have demonstrated heterogeneity of antibody distribution in tumor. However, due to its relatively short effective half-life compared to the time required for tumor localization, therapeutic gain is less than might be achieved with an isotope having a longer half-life. The use of other chimeric isotypes, chimeric antibody fragments or novel genetically engineered molecules (41) may provide better vehicles for delivery of gamma and beta emitting isotopes (42). Finally, the use of a higher affinity anti-TAG-72 monoclonal antibody (i.e., CC49) with a human IgG1



**FIGURE 4.** Daily cumulative whole-body radiation exposure for Patient 1. Each bar represents the percentage of total body radiation accrued which has occurred on each day following therapy. The increment in percentage is the daily increment in radiation exposure.

chimeric construct may provide better tumor localization and improved biodistribution (43,44).

## ACKNOWLEDGMENTS

The authors wish to express appreciation to Sharon Garrison for preparation of the manuscript and to Mimi Markiewicz for pharmaceutical services. This study was carried out on the General Clinical Research Center NIH grant #M01-RR-00032 and was supported by NCI contract #CM87215, NCI grant #CA45232, Celltech, Inc., and the Veterans Administration Medical Center.

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## EDITORIAL

# Radiolabeled Monoclonal Antibodies for Cancer Therapy and Diagnosis: Is It Really a Chimera?

*chi-mer-ra or chi-mae-ra n (L chimeara, fr. Gk chimaira she-goat, chimera; akin to Gk cheimon winter) 1. cap: a fire breathing she-monster in Greek mythology having a lion's head, a goat's body, and a serpent's tail, 2. an illusion or fabrication of the mind, especially an unrealizable dream (1).*

Considerable research over the past few years has attempted to use the high specificity and affinity of monoclonal antibodies as the basis of radiolabeled in vivo diagnosis and therapy of cancer. Results of preclinical and clinical evaluations demon-

strated that these antibodies are subjected to the same physiological and metabolic processes as drugs and hormones. As a result, the tumor accretion of these agents has been less than originally hoped (2,3). In general, uptake of the radionuclides into tumors of patients was in the range of 0.001%-0.01% of the injected dose per gram of tumor, and approximately 80% of known lesions were detected (4-6). With rare exception

the limit of detection appears to be 1.0-1.5 cm (7). This limited success leads one to ask whether our hope is really a *chimera*, as found in definition 2 above.

One approach to increase the tumor uptake of radiolabeled antibodies, as described in the previous article by Meredith et al. (8), is the use of chimeric immunoglobulins. (see definition 1 above): most of the antibody is human with binding sites derived

Received Oct. 10, 1991; accepted Oct. 10, 1991.  
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