A Phase I Study of a Combination of Yttrium-90–Labeled Anti–Carcinoembryonic Antigen (CEA) Antibody and Gemcitabine in Patients with CEA-Producing Advanced Malignancies

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Abstract

Purpose: To determine the maximum tolerated dose of combined therapy using an yttrium-90–labeled anti–carcinoembryonic antigen (CEA) antibody with gemcitabine in patients with advanced CEA-producing solid tumors.

Experimental Design: The chimeric human/murine cT84.66 is an anti-CEA intact IgG1, with high affinity and specificity to CEA. This was given at a fixed yttrium-90–labeled dose of 16.6 mCi/m^2 to subjects who had and an elevated CEA in serum or in tumor by immunohistochemistry. Also required was a tumor that imaged with an ^{111}In-labeled cT84.66 antibody. Patients were treated with escalating doses of gemcitabine given i.v. over 30 minutes on day 1 and 3 after the infusion of the yttrium-90–labeled antibody. Patients were treated in cohorts of 3. The maximum tolerated dose was determined as the highest level at which no >1 of 6 patients experienced a dose limiting toxicity.

Results: A total of 36 patients were enrolled, and all but one had prior systemic therapy. The maximum tolerated dose of gemcitabine in this combination was 150 mg/m^2. Dose limiting toxicities at a gemcitabine dose of 165 mg/m^2 included a grade 3 rash and grade 4 neutropenia. One partial response was seen in a patient with colorectal cancer, and 4 patients had a >50% decrease in baseline CEA levels associated with stable disease. Human antichimeric antibody responses were the primary reason for stopping treatment in 12 patients.

Conclusions: Feasibility of combining gemcitabine with an yttrium-90–labeled anti-CEA antibody is shown with preliminary evidence of clinical response.

Radiolabeled monoclonal antibodies have been studied as a possible treatment for human malignancies. Monoclonal antibodies have shown potential to act as therapeutic agents and have shown efficacy especially with hematologic malignancies as evidenced by the approval of rituximab and more recently of yttrium-90–labeled ibritumomab tiuxetan for low-grade non–Hodgkin's lymphoma (1–3). Solid tumors have been treated with immune-guided radiotherapy, albeit with lower response rates due to complex factors related to tumor targeting, tumor vasculature, vascular permeability, and therapeutic index (4, 5).

Radiosensitization has been a strategy to increase the efficacy of immune-guided radiotherapy. A recent study has shown the feasibility of combining a 120-hour infusion of 5-fluorouracil with the anti-CEA yttrium-labeled IgG1 murine monoclonal antibody designated T84.66 (6). Stable disease and two mixed responses were seen. Other studies have also shown the feasibility of this approach (7).

Gemcitabine is currently Food and Drug Administration approved for a variety of tumors including pancreas, breast, ovarian, and lung cancer. Laboratory studies have shown strong radiosensitization properties possibly due to inhibition of ribonucleotide reductase, effects on deoxyribonucleotide pool composition, and to incorporation into DNA with subsequent early chain termination. Preclinically radiosensitization was greatest when cells were exposed to gemcitabine between 2 and 24 to 48 hours before radiation. Radiosensitization was observed for ~2 days after exposure (8, 9). The maximum radiosensitization correlated with a drop in adenosine diphospate and occurred at relatively low gemcitabine doses (10). Gemcitabine has also shown significant radioenhancing properities with immune-guided radiotherapy *in vivo* (11–13).

Clinical studies combining gemcitabine with radiation have confirmed potent radiosensitizing properties. In head and neck patients, doses of gemcitabine needed de-escalation from a starting weekly dose of 300 mg/m^2 (10). At doses of 30 mg/m^2, gemcitabine triphosphate levels were in the same range as with

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Translational Relevance

This article describes the feasibility of immune-guided radiotherapy using a monoclonal anti – carcinoembryonic antigen antibody combined with gemcitabine at radiosensitizing doses. Importantly, evidence of clinical activity was seen in this cohort of heavily pretreated patients. This combination could be applied to less heavily pretreated patients in future trials, which could lead to higher response rates with better demonstration of clinical benefits. This regimen might have even greater utility in low-volume tumor states, including in the adjuvant setting in carcinoembryonic antigen (CEA)-positive gastrointestinal cancer or other sites penetration of bulky tumors would not be an issue. In these settings, immune guided-radiotherapy would represent a systemic agent with a unique mechanism of action that could potentially be integrated into multimodality treatment.

the 150 mg/m^2 dose. The levels of dFdCTP in biopsy specimens were similar to those seen in *in vitro* radiosensitizing experiments, suggesting that significant interactions were occurring at these dose levels. Other studies report tolerance of radiation and gemcitabine in upper gastrointestinal tumors, also with less than full systemic doses (14, 15). Studies with lung cancer have also be reported, albeit with increased esophagitis (16).

Based on this information, we designed this study to determine the tolerance of a combination of gemcitabine and ^{90}Y-T84.66 anti-CEA antibody. Gemcitabine was given in 2 equal doses 48 hours apart to maximize radiation sensitization with starting doses based on previous phase I data on twice weekly dosing schedules (15, 17).

Materials and Methods

Antibody production and conjugation. Human/murine cT84.66 is an anti-CEA intact IgG1, with high affinity ($K_A = 1.16 \times 10^{11}$ M^{-1}) and specificity to CEA. Details of its production, characterization, purification, conjugation, and radiolabeling have been reported previously (18). Briefly, for this study, cT84.66 was conjugated to isothiocyanatobenzyl diethylenetriaminepentaacetic acid (DTPA). Preparation of the radiolabeled dose involved incubation of ^{111}In at a ratio of 1 mCi to 1 mg and yttrium (^{90}Y) at a ratio of 10 mCi to 1 mg followed by size exclusion high performance liquid chromatography purification. All administered doses showed radiolabeling of >90%, endotoxin levels of <1 unit/mL, and immunoreactivity of >95%. The final vialed lot of purified conjugated antibody met standards set by the Food and Drug Administration. Investigational New Drug applications for ^{111}In-DTPA-cT84.66 and ^{90}Y-DTPA-cT84.66 are currently on file with the Food and Drug Administration.

Clinical trial design. The primary objective of this trial was to determine the maximum tolerated dose (MTD) and associated toxicities of gemcitabine in combination with ^{90}Y-DTPA-cT84.66. Patients were enrolled in cohorts of 3 with escalating doses of gemcitabine (Table 1). Gemcitabine was administered i.v. over 30 min beginning on day 1 and on day 3 after infusion of the therapeutic dose of ^{90}Y-DTPA-cT84.66 (16.6 mCi/m^2). This therapeutic dose was determined in a previous phase I study of ^{90}Y-DTPA-cT84.66 as single agent (19). Gemcitabine dose escalation continued until a dose-limiting toxicity (DLT) was noted defined as any treatment-related grade III nonhematologic toxicity not reversible to grade II or less within 24 h, or any grade IV toxicity. Up to three cycles of therapy were allowed with DLTs determined based on first cycle tolerance. Toxicity was graded using the National Cancer Institute common toxicity criteria version 2.0. Further patients were entered and further dose escalation was continued if no further DLTs were noted in a completed cohort of six patients. The MTD was defined as the highest level at which ≤1 of 6 patients experienced a DLT. Biodistribution, tumor targeting, absorbed radiation dose estimates, and clearance of the antibody were also evaluated through serial blood samples, 24-h urine collection, and nuclear scans done at time points out to 7 d after antibody infusion.

The following studies were done before antibody administration: complete blood count and platelet count, complete metabolic panel, creatinine clearance, electrocardiogram, pulmonary function tests, urinalysis, serum HIV testing, serum pregnancy testing if indicated, plasma CEA levels, and serum human antichimeric antibody (HACA) response. Additionally, chest X-ray, and computed tomography scans of relevant anatomic locations corresponding to areas of metastatic or suspected metastatic disease were obtained. If clinically indicated, bone scan, magnetic resonance imaging, or positron emission tomography images were also done to assess disease location and extend. All blood studies were done within 2 wk and all radiological studies within 6 wk of antibody infusion.

For the initial cycle of therapy, each patient first received an imaging dose of 5 mCi/5 mg ^{111}In-DTPA-cT84.66, which was used to track antibody activity and evaluate tumor targeting. The therapeutic dose of ^{90}Y-DTPA-cT84.66 was subsequently given within 2 wk and included 5 mCi of indium-111 – labeled ^{90}Y-DTPA-cT84.66. Initially, a test does of 100 μg of radiolabeled antibody was administered i.v. over 5 min. After 15 min., if there were no side effects, the remainder of the antibody was administered over 30 min. Subsequent cycles of therapy were not preceded by a separate imaging infusion. Serial blood samples were taken for pharmacokinetics at 30 min, 1, 4 h, and at each scan time after antibody infusion. Urine collections (24 h) were done daily for 5 consecutive d after antibody administration for pharmacokinetic analysis. Blood and urine samples were counted for ^{111}In activity on a Packard γ counter (Model 5530; Packard, Inc.) with a window setting of 150 to 500 keV and were processed on a size exclusion high performance liquid chromatography Superose 6 column. Planar and whole body imaging studies were done at 6, 24, 48 h, and 4 to 7 d after antibody administration using a Toshiba dual head 7200 camera with single-photon emission computed tomography capability. In all cases, 20% energy windows were set over each of the two γ-ray energies of ^{111}In. A medium energy high-resolution collimator was used throughout. Scan speed of 20 cm/min over a distance of 200 cm was used for the whole body imaging. Single-photon emission computed tomography scans were done of relevant areas of 48 h and 4 to 7 d after antibody administration.

Gemcitabine in escalating doses was given i.v. on day 1 over 30 min, followed within 5 h by the therapeutic dose of ^{90}Y-DTPA-cT84.66, which was 16.6 mCi/m^2 in all patients. A second dose of gemcitabine was given on day 3.

Table 1. Gemcitabine dose escalation schema

Level	Dose (mg/m^2)
1	30
2	45
3	60
4	75
5	90
6	105
7	120
8	135
9	150
10	165

DTPA as a calcium salt was given at a dose of 250 mg/m^2/24 h in divided doses every 12 h for 3 d after the dose of ^{90}Y-DTPA-cT84.66 in an effort to reduce hematologic toxicity. This approach has been used in previous trials including the trial that established the MTD of ^{90}Y-DTPA-cT84.66 as monotherapy (19). A previous trial using ^{90}Y-1,4,7,10-tetra-azacylododecane N,N[primeJ,N[dprimeJ,NftprimeJ-tetraacetic-c84.66 documented an increase in hematologic toxicity with the omission of the Ca-DTPA infusion (20).

Radiological studies, including computed tomography scans, were repeated at 5 to 6 wk posttherapy to assess tumor response. Response criteria were defined as follows: complete response, disappearance of all measurable and evaluable disease, and no new lesions; partial response, $\geq$ 50% decrease from baseline in the sum of the products of perpendicular diameters of all measurable lesions, with no progression of evaluable disease or development of new lesions; stable disease, does not qualify for complete response, partial response, or progression; progressive disease, 25% increase in the sum of products of measurable lesions over the smallest sum observed, or reappearance of any lesion that had disappeared, or appearance of any new lesion/site.

HACA response. Serum HACA responses to cT84.66 and cT84.66-DTPA were assayed before infusion and at 2 wk, 1, 3, and 6 mo postinfusion using a double capture solid-phase quantitative, RIA as described previously (18). Serum samples incubated with ^{111}In-DTPA-cT84.66 were also examined by size exclusion high performance liquid chromatography using two tandem Superose 6 columns to detect possible immune responses not found by RIA. Patients were felt to have anti-idiotype response if serum samples were positive by high performance liquid chromatography assay but were negative by RIA.

Pharmacokinetic analysis and absorbed dose estimates. Blood and urine samples were counted for ^{111}In activity on a γ counter and were processed on a high performance liquid chromatography size-exclusion Superose 6 column. Samples containing both ^{111}In and ^{90}Y were counted sequentially in γ and β well counters. In the latter case, Cerenkov radiation was used with quench correction to determine the amount of ^{90}Y present. Samples were homogenized in aqueous media and bleached before counting. Standards were used to calibrate the absolute accuracy of the counting systems.

For those organs seen in both projections, ^{111}In activity in normal organs was estimated using parallel-opposed nuclear images to construct the geometric mean uptake as a function of time. Otherwise, single view images were acquired. All resultant curves demonstrating ^{111}In activity versus time were corrected for background and patient attenuation. Attenuation was estimated using each patient's computed tomography scans and attenuation coefficients obtained from a separate series of experiments involving γ camera efficiency in counting a planar ^{111}In phantom source as a function of tissue-equivalent absorber thickness. Given the geometric mean or single view uptake values and measured blood and urine activity, a five-compartment modeling analysis was done to estimate residence times for ^{111}In and ^{90}Y activity in blood, urine, liver, and whole body. Details of this compartmental model have been published previously (21). ^{90}Y radiation doses to normal organs based on biodistribution of ^{111}In-cT84.66 were estimated with the medical internal radiation dose method (22) using S values obtained from the MIRDDOSE3 program (23). Doses were calculated using male and female phantom organ sizes in these estimates. As previously reported, ^{90}Y-DTPA-cT84.66 and ^{111}In-DTPA-cT84.66 biodistributions were comparable in the mouse model (24). Red marrow radiation dose estimates were done using the American Association of Physicists in Medicine algorithm (25) based on blood residence times determined from the five compartmental model.

Tumor-absorbed radiation doses were estimated using ^{111}In uptake versus time curves determined from serial nuclear imaging data. Regions of interest were drawn around each tumor lesion, and the conjugate view method (26) was used to estimate activity. Trapezoidal interpolation was used to integrate the time activity curve and estimate residence time. Computed tomography scans were used to define tumor volume as well as the effective attenuation factor for the conjugate view method. For lesions not clearly defined by computed tomography scans, nuclear medicine region of interest (length and width) was used to estimate the tumor volume, assuming an ellipse with the third dimension defined by the geometric mean of the length and width. Absorbed fraction was a function of tumor size and determined via separate Monte Carlo simulation. Edge effects were thus taken into account (27). Uniform uptake was assumed within the tumor. This methodology still uses the medical internal radiation dose strategy but requires that we compute the effective β loss caused by the finite range of ^{90}Y β radiation (28) using the formula:

$$\beta \text{ dose} = 2.12\ \text{E}\beta\text{AUC(tumor)} * \text{absorbed fraction}/(\text{tumor mass}),$$

where $E\beta$ is the mean β energy of ^{90}Y or 0.93 MeV, area under the curve (residence time) is in hours and tumor mass is in grams.

Results

A total of 36 patients were enrolled. The majority of patients were diagnosed with colorectal cancer and other gastrointestinal malignancies and all but one had previous systemic treatment (Table 2). Four patients did not image with ^{111}In-DTPA-cT84.66 and no further treatment was given except in one case. This one patient was initially felt to image at the right adrenal gland, a site of known disease. However, it was subsequently determined that imaging represented a dilated gallbladder and a false positive on target and the patient received no further therapy beyond the first course.

The MTD level was established at a gemcitabine dose of 150 mg/m^2. Toxicities at 1 dose level above this (165 mg/m^2) included grade 3 rash and grade 4 hematologic. Grade 3 rash was noted in a 53-year-old female with metastatic pancreatic cancer who had had prior treatment with ifosfamide and etoposide was well as gemcitabine and capecitabine. The patient developed a pruritic erythematous rash over the chest, back, abdomen, and extremities beginning on day 3 after administration of the ^{90}Y-DTPA-cT84.66 and resolved over the next 2 weeks. The patient had stable disease after the first course, but developed a HACA reaction and no further protocol therapy was given. The second patient developed grade 4 neutropenia but recovered uneventfully. This patient was a 76-year-old female with stage IV non–small cell lung cancer with no previous radiation but with previous systemic therapy including carboplatin/paclitaxel, carboplatin/docetaxel, pemetrexed, and gemcitabine.

Three of 36 patients completed the protocol maximum of 3 treatment cycles with four further patients completing 2 cycles. Twelve patients developed a HACA response precluding further therapy, all after the first treatment. Reasons for stopping therapy in 33 treated patients are listed in Table 3A with progressive disease or HACA being the most common.

The most frequent first cycle toxicities were hematologic. There was a trend for more leucopenia with increasing dose of gemcitabine with scattered instances of thrombocytopenia. Rash was also seen at various levels but reached a grade 3 DLT level with a gemcitabine dose of 150 mg/m^2. Rash occurred between day 1 and 5 and, in all cases, resolved when treatment was stopped. Other toxicities, including nausea, fluid retention, fever, or pulmonary toxicity were not seen. See Table 3B for further details.

Table 2. Patient characteristics

Characteristic	No. patients
Gender	
Male	20
Female	16
Median Age	62.7
Race/Ethnicity	
Caucasian	32
Asian	3
African American	1
Diagnoses	
Colorectal	18
Appendix	1
Gastric/esophagus	3
Pancreas	2
Lung	7
Breast	2
Medullary thyroid	2
Testicular	1
Prior Treatment	
Chemotherapy	35
Radiation	10
Surgery	35

A 59-year-old female patient with colon cancer with pelvic and peripancreatic disease had a partial response after the first cycle of treatment and received 2 treatment cycles with a gemcitabine dose level of 45 mg/m^2. Her CEA level was stable during treatment staying within 15% of baseline. She had been diagnosed with T3N2 colon cancer 4 years earlier and had received 1 year of adjuvant 5-fluorouracil. Subsequent treatment for recurrent disease included capecitabine, irinotecan, 5-fluorouracil and leucovorin, capecitabine/gemcitabine, as well as postsurgical radiation to a mass causing left hydronephrosis.

CEA levels were tabulated and correlated with clinical outcome. Progressive disease was noted in 6 of 7 patients with a 50% or greater increase in CEA, and stable disease was seen in all 4 cases with a CEA decrease of >50%.

Individual tumor radiation doses were estimated in cases where a clear delineation of a target lesion was possible, and responses for each of these lesions were recorded (Table 4A and B). Lesions where a partial response was noted had a higher average dose (8,702 $\pm$ 1,411 rad), but a reverse trend was seen in comparing stable (2,834 $\pm$ 5,763) and progressive lesions (5,872 $\pm$ 4,216), with large SDs in each case. Estimated organ and total body doses are similar to previous reports (Table 5; ref. 19). Tumor size with estimated Y-90 dose is presented in Table 4A. When doses are tabulated by tumor volumes, the tumors with the highest dose included those below 10 cc with all tumors receiving a dose of >100 rad/mCi in this size range (Fig. 1).

Discussion

This study shows the feasibility of combining gemcitabine with the ^{90}Y-DTPA-cT84.66 anti-CEA antibody. The MTD was defined at a gemcitabine dose of 150 mg/m^2 given on day 1 and 3 of radioimmunotherapy. Overall, the primary toxicity was hematologic, which was well tolerated with resolution before 6 weeks and with no instances of neutropenic fever.

Rash was noted in several patients at several dose levels. This rash occurred between 1 and 5 days after initiation of treatment and resolved within 1 to 2 weeks. Rash has been noted with single agent gemcitabine in the past and it is possible that its occurrence could be related to gemcitabine alone (29). However, interaction with radiation and skin toxicity has been noted with gemcitabine in the context of radiation recall (30) and with increased skin toxicity during radiation (10). It is difficult to determine if the skin toxicity is clearly greater than what might be caused by gemcitabine alone due to the small number of cases but an interaction is possible. Rash has also been reported with immune-guided radiotherapy alone, possibly due to an immune mediated process (31, 32). This remains a possibility in this study as instances of rash appeared sporadic and not clearly associated with higher doses of gemcitabine. A HACA response was associated with the rash in two of three cases but not seen in the DLT defining case.

The gemcitabine dose escalation scheme was conservative due to evidence for a strong interaction with radiation, and one of the concerns was that of increased hematologic effects. Results, including the lack of neutropenic fever, do not suggest a prohibitive interaction between radioimmunotherapy and gemcitabine. In addition, there were no clinically significant instances of thrombocytopenia and no patient required a platelet transfusion. This is despite the use of doses that have been documented to be radiosensitizing in other studies (10).

It is of interest that the patient with a partial response was treated at a relatively low dose of gemcitabine (45 mg/m^2) and had received and progressed through previous gemcitabine. As noted, in head and neck cancer patients treated with weekly gemcitabine and radiation, dFdCTP levels in tumor biopsies obtained during treatment were similar in patients receiving gemcitabine doses of 50 to 300 mg/m^2. The fact that more objective responses were not seen at higher levels is likely due to the heavily pretreated nature of the study population. However, 4 patients did have at least a 50% decrease in CEA level that was associated with stable disease in all cases. These cases were spread through out various gemcitabine dose levels and are a further indication of possible clinical benefit.

Table 3. Tolerance of treatment

A. Reason for treatment cessation

HACA	12
Protocol completion*	4 (1 with 2 cycles)
Disease progression	13
Toxicity	3

B. Cycle 1 toxicities (grade 3/4)

Treatment Level	1	2	3	4	5	6	7	8	9	10
Leukopenia			1		2		2	1	2	2
Lymphopenia	2	3		1			2		2	1
Platelet		1			1				1	
Rash						1†			1†	1
Anemia									2	

*The protocol had included two cycles of treatment but was amended to allow up to three cycles.
† Grade 2.

Table 4. Summary of Y-90 dose to tumors

A.

Patient (dose)*	Diagnosis	Location	Volume (cc) †	Y-90 AUC (mCi*hr/mCi)	Y-90 Dose (rad/mCi)	Delivered Dose (rad)	Response
1 (45)	Colorectal	Perihilar	10.3	0.162	31.2	989.7	Stable
		Pancreas	203.7	0.648	6.3	200.1	Stable
		Periclavicular	9.1 ‡	0.029	6.4	202.0	—
2 (60)	Colorectal	Left lingular	0.4	0.076	392.9	11079.1	Progression
		Perihilar	0.3	0.054	403.1	11368.7	Progression
		Right hepatic	149.2	whole liver dose	37.7	1064.1	Stable
3 (90)	NSCLC	Mediastinum	14.1	0.873	122.5	3392.2	Progression
4 (120)	Colorectal	Subcarinal	36.1	0.649	35.7	3502.4	Progression
		Right lung	17.2	0.152	17.6	1728.1	Stable
		Left lung	3.6	0.179	98.9	9700.3	Partial response
5 (120)	NSCLC	Right lower lobe	179.6	2.121	23.4	552.9	Stable
6 (135)	Colorectal	Mesenteric node	4.0	0.517	253.4	7704.2	Partial response
		Subcarinal	3.4	0.079	46.5	1414.8	Stable
7 (135)	Teratoma	Left lung	688.3	3.729	10.8	433.2	Stable
8 (150)	Colorectal	Perihilar	12.7	0.321	50.0	1795.7	Progression
9 (150)	Colorectal	Right hepatic	470.5	whole liver dose	40.4	1005.1	Stable
		Paratracheal	3.5	0.293	164.4	4093.9	Progression
10 (150)	Colorectal	Lung nodule	0.5	0.192	740.0	191667.0	Stable
		Right liver	89.5	3.115	69.0	1788.5	Stable

B.

	Volume (cc)	Y-90 dose (rad/mCi)	Delivered dose (rad)
Average	99.8	134.2	4272.8
SD	184.4	190.6	5172.5
Maximum	688.3	740.0	19167.0
Median	12.7	46.5	1788.5

Abbreviations: NSCLC, non–small cell carcinoma.
*Gemcitabine dose level, g/m^2.
† By computed tomography scan as noted.
‡ By nuclear medicine scan.

Although CEA levels are not measurable in terms of response, levels, especially if changed by >50%, have been associated with clinical response (33, 34). Of note, two of four patients with an initial increase in CEA maintained stable disease during further treatment. This may indicate that in some cases an increased CEA early in treatment may have been due to tumor necrosis and may predict response rather than progression (35, 36).

There was a lack of clear correlation with radiation dose and response when individual tumors were evaluated. This may again be because to the heavily pretreated and heterogeneous nature of the patients enrolled on this study. It is of interest that the two tumors showing a partial response did receive relatively high radiation doses, and also higher levels of gemcitabine. However, tumors with stable disease when compared progressive lesions, received a lower dose on average across a broad range of gemcitabine doses. There was a tendency for smaller tumors to have a higher Y-90 dose suggesting better antibody penetration possibly based on better perfusion and lower interstitial pressure. However, among the 6 lesions with a dose of >100 rad/mCi, there were 1 partial response, 1 stable disease, and 4 instances of progressive disease, again suggesting a lack of correlation between dose and response. Tumor doses ranged between 6.3 to 740.0 rad/mCi, indicating an overall good therapeutic ratio when compared with red marrow and total body estimates.

In several cases, grade 3 lymphopenia was noted, scattered across treatment levels (Table 3A). Radiation therapy has been associated with lymphocyte depletion in the past with differing effects on various lymphocyte subsets (37). There is also evidence that chemotherapy in combination with external beam radiation may increase lymphocytopenia (38). No specific clinical consequence related to increased rates of infection were noted during the course of this study. Among patients with grade 3 lymphopenia, 8 of 11 developed a HACA response.

HACA responses continue to be a problem, and were the primary reason for stopping treatment in 12 patients. It is possible that a number of these cases could have had a more prolonged period of stable disease or experienced a response with continued treatment. The primary strategies to overcome

Table 5. Organ Y-90 dose estimates

Organ (n = 23)	Average (rad/mCi)	SD
Marrow	3.00	1.28
Liver	21.78	8.86
Kidney	11.15	3.55
Total body	2.09	0.45

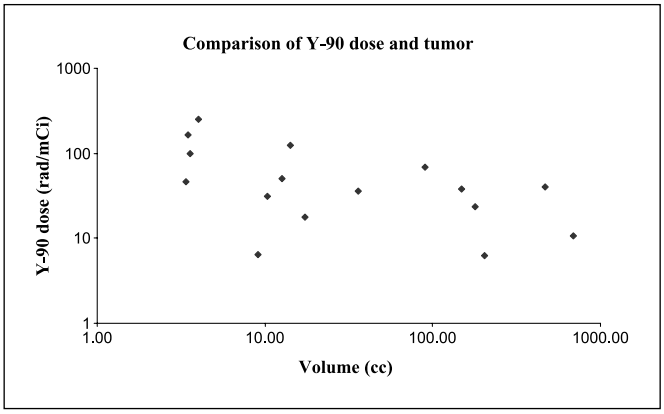

Fig. 1. Y-90 dose (rad/mCi) to individual tumors compared with the volume of the individual tumors.

this would include using more humanized antibodies, use of antibody fragments, and potentially use of immunosuppressive agents such as cyclosporine (5). These strategies would potentially allow the repetitive dosing that would allow for more effective treatment.

Although the formal definition of DLT was met, further dose escalation might have been possible given the nature of toxicities seen. However, several factors contributed to our decision to forgo further dose escalation. First, as noted, the dose of gemcitabine was in the range noted to be radiosensitizing in other studies, and there was evidence for clinical activity, including a partial response, at levels below the ultimate MTD. Second, HACA responses, as noted, were limiting, and we were transitioning to a humanized version of the ^{90}Y-DTPA-*c*T84.66 antibody. A clinical trial has since been initiated evaluating the ^{90}Y-labeled humanized- T84.66.

Responses consisted mainly of stable disease, with one patient showing an objective response. Although this combination seems feasible, activity as a primary therapy in patients with bulky disease seems limited. This may be related to tumor factors including heterogeneity of vasculature and interstitial pressure that impede macromolecule penetration, although the degree of IgG penetration into solid tumors in not yet completely defined. Strategies for the future include studying combination therapy in minimal disease, use of antibody fragments with potentially improved therapeutic ratios, and using radioimmunotherapy in combination with full-dose chemotherapy as a chemosensitizer (5, 39, 40).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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