*Featured Article*

# A Phase I Trial of $^{90}$Y-Anti-Carcinoembryonic Antigen Chimeric T84.66 Radioimmunotherapy with 5-Fluorouracil in Patients with Metastatic Colorectal Cancer

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## Abstract

***Purpose:*** **Targeted systemic radiation therapy using radiolabeled antibodies results in tumor doses sufficient to produce significant objective responses in the radiosensitive hematological malignancies. Although comparable doses to tumor are achieved with radioimmunotherapy (RIT) in solid tumors, results have been modest primarily because of their relative lack of radiosensitivity. For solid tumors, as with external beam radiotherapy, RIT should have a more important clinical role if combined with other systemic, potentially radiation-enhancing chemotherapy agents and if used as consolidative therapy in the minimal tumor burden setting. The primary objective of this trial was to evaluate the feasibility and toxicities of systemic $^{90}$Y-chimeric T84.66 (cT84.66) anti-carcinoembryonic antigen RIT in combination with continuous infusion 5-fluorouracil (5-FU).**

***Experimental Design:*** **Patients with chemotherapy-refractory metastatic colorectal cancer were entered. The study was designed for each patient to receive $^{90}$Y-cT84.66 anti-carcinoembryonic antigen at 16.6 mCi/m$^2$ as an i.v. bolus infusion combined with 5-FU delivered as a 5-day continuous infusion initiated 4 h before antibody infusion. Cohorts of patients were entered at 5-FU dose levels of 700, 800, 900, and 1000 mg/m$^2$/day. Upon reaching the highest planned dose level of 5-FU, a final cohort received $^{90}$Y-cT84.66 at 20.6 mCi/m$^2$ and 5-FU at 1000 mg/m$^2$/day. For all patients, Ca-diethylenetriaminepentaacetic acid at 125 mg/m$^2$ every 12 h was administered for the first 72 h after $^{90}$Y-cT84.66. Patients were eligible to receive up to three cycles of $^{90}$Y-cT84.66/5-FU every 6 weeks.**

***Results:*** **Twenty-one patients were treated on this study. All had been heavily pretreated with 19 having previously received 5-FU and 16 having failed two to four chemotherapy regimens. A maximum-tolerated dose of 16.6 mCi/m$^2$ $^{90}$Y-cT84.66 combined with 1000 mg/m$^2$/day 5-FU was reached. These dose levels are comparable with maximum-tolerated dose levels of each agent alone. Thirteen patients received one cycle and 8 patients two cycles of therapy. Hematopoietic toxicity was dose-limiting and reversible. RIT did not appear to increase nonhematopoietic toxicities associated with 5-FU. Two of 19 patients assayed developed a human anti-chimeric antibody immune response after the first cycle of therapy, which is significantly less than that observed in a previous trial evaluating $^{90}$Y-cT84.66 alone. No objective responses were observed. However, 11 patients with progressive disease entering the study demonstrated radiological stable disease of 3–8 months duration and 1 patient demonstrated a mixed response.**

***Conclusions:*** **Results from this trial are encouraging and demonstrate the feasibility and possible advantages of combining continuous infusion 5-FU with $^{90}$Y-cT84.66 RIT. The addition of 5-FU does not appear to significantly enhance hematological toxicities of the radiolabeled antibody. In addition, 5-FU reduces the development of human anti-chimeric antibody response, permitting multicycle therapy in a larger number of patients. Future efforts should continue to focus on integrating radiation therapy delivered by radiolabeled antibodies into established 5-FU regimens.**

## Introduction

Ionizing radiation has proven to be an effective form of cancer therapy for over a century. Methods of delivering radiation have ranged from directed teletherapy, using devices to generate highly collimated, energetic photon or particle beam radiation to brachytherapy strategies to deposit sealed radionuclide sources directly into the tumor. Dramatic responses and cures with radiation therapy alone have been reported for a wide variety of tumor types, with therapeutic successes seen particularly with small volume, early-stage disease and as adjuvant therapy to control microscopic disease. Regardless of the mode of delivery, the fundamental goal of any radiation therapy delivery system has been to maximize absorbed dose to the tumor target while minimizing absorbed dose to normal organs.

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RIT[9], or the use of radiolabeled antibodies to specifically target therapeutic doses of radiation to tumor, offers a theoretically attractive delivery system for systemic-guided radiation therapy. Objective responses have been observed primarily in radiosensitive hematological malignancies (1–9). These efforts have recently lead to the first FDA-approved radioimmunotherapeutic directed against CD20-positive hematological malignancies (10).

Although radiolabeled antibodies against solid tumors have been just as successful in targeting radiation dose to tumor, antitumor effects have been less dramatic primarily because of decreased radiosensitivity of solid tumors relative to lymphomas and leukemias. Objective responses have been less frequent, with most studies instead reporting stable disease, occasional mixed responses, and serological responses (11–26).

To further increase therapeutic efficacy of RIT, a number of investigators have explored combining RIT with other systemic therapies, particularly chemotherapy agents that are potentially radiation-enhancing (6, 27–32). 5-FU, a pyrimidine analogue, is an active agent in gastrointestinal malignancies with demonstrated radiation-enhancing effects when combined with external beam radiation *in vitro*, *in vivo*, and in the clinic (33–36). Other investigators have also shown a potential role for combining 5-FU with RIT in experimental systems (37–42). The purpose of this Phase I trial was to evaluate the feasibility of combining RIT, delivered by $^{90}$Y-radiolabled anti-CEA monoclonal antibody, with systemic continuous infusion 5-FU to evaluate the toxicities and antitumor effects of this combined modality therapy in patients with colorectal cancer.

## 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 (43–47). Briefly, for this study, cT84.66 was conjugated to isothiocyanatobenzyl DTPA. Preparation of the radiolabeled dose involved incubation of $^{111}$In at a ratio of 1 mCi to 1 mg and $^{90}$Y at a ratio of 10 mCi to 1 mg followed by size exclusion HPLC purification. All administered doses demonstrated radiolabeling $>$ 90%, endotoxin levels $<$ 1 unit/ml, and immunoreactivity $>$ 95%. The final vialed lot of purified conjugated antibody met standards set by the FDA. Investigational New Drug applications for $^{111}$In-DTPA-cT84.66 and $^{90}$Y-DTPA-cT84.66 are currently on file with the FDA.

**Clinical Trial Design.** The primary objective of this trial was to determine the MTD and associated toxicities of continuous infusion 5-FU in combination with $^{90}$Y-cT84.66 RIT. Biodistribution, tumor targeting, absorbed radiation dose estimates, and clearance of the antibody were also evaluated through serial blood samples, 24-h urine collections, and nuclear scans performed at time points out to 7 days after antibody infusion.

Patients were eligible if they were 18 years of age or older and had evidence of advanced or metastatic colorectal cancer and had either failed or refused conventional therapies. Tumor CEA production was documented by either elevated serum CEA levels or immunohistochemistry staining of tumors. All patients had to demonstrate a Karnofsky performance status of $>$60% and completion of any previous therapy at least 4 weeks before protocol therapy. The following laboratory values were required: hemoglobin $\geq$ 10 g%; WBC $\geq$ 4000/$\mu$l; platelet count $\geq$ 140,000/$\mu$l; serum creatinine $\leq$ 1.5 mg/dl; creatinine clearance $\geq$ 60 ml/min; total bilirubin $\leq$ 1.5 mg/dl; liver transaminases $\leq$ 2 times upper limits of normal; and lung diffusion capacity and forced expiratory volume in one second $\geq$ 50% of predicted. Patients with a history of previous antibody exposure and a positive HACA response to cT84.66 were excluded from the study. In addition, patients with active brain or leptomeningeal metastatic disease or previous radiotherapy to $>$50% of the bone marrow were excluded. Finally, patients with over one-third of the liver involved with metastatic disease were excluded based on previously published observations of rapid clearance of the antibody in patients with extensive liver metastases (46).

The following studies were performed 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 HACA response. Additionally, chest X-ray, and CT scans of relevant anatomical 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 performed to assess disease location and extent. All blood studies were done within 2 weeks and all radiological studies within 6 weeks of antibody infusion.

Each patient first received an imaging dose of 5 mCi/5 mg $^{111}$In-DTPA-cT84.66. Initially, a test dose of 100 $\mu$g 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. Serial blood samples were taken for pharmacokinetics at 30 min, 1 h, 4 h, and at each scan time after antibody infusion. Urine collections (24 h) were done daily for 5 consecutive days after antibody administration for pharmacokinetic analysis. Blood and urine samples were counted for $^{111}$In activity on a Packard gamma counter (Model 5530; Packard, Inc., Downers Grove, IL) with a window setting of 150–500 keV and were processed on a size exclusion HPLC Superose 6 column. Planar and whole body imaging studies were performed at 6 h, 24 h, 48 h, and 4–7 days after antibody administration using a Toshiba dual head 7200 camera with SPECT capability. In all cases, 20% energy windows were set over each of the two $\gamma$-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. SPECT scans

[9] The abbreviations used are: RIT, radioimmunotherapy; 5-FU, 5-fluorouracil; HPLC, high-performance liquid chromatography; CEA, carcinoembryonic antigen; cT84.66, chimeric T84.66; CT, computed tomography; HACA, human anti-chimeric antibody; DTPA, diethylenetriaminepentaacetic acid; MTD, maximum-tolerated dose; DLT, dose-limiting toxicity; FDA, Food and Drug Administration.

were performed of relevant areas at 48 h and 4–7 days after antibody administration.

If at least one known tumor site was imaged with $^{111}$In-labeled antibody, patients would then receive therapy. Because of known background uptake of $^{111}$In-labeled antibody to normal liver, an exception was made for patients with disease confined to the liver, who received the therapy dose even if activity in hepatic metastases did not exceed that of surrounding normal liver. Therapy was initiated ~7–8 days after the infusion of the imaging dose of $^{111}$In-cT84.66. Patients were entered on this dose escalation Phase I trial at 5-FU dose levels of 700, 800, 900, or 1000 mg/m$^2$/day × 5 days. At the initiation of this trial, the administered activity of $^{90}$Y-cT84.66 was 16.6 mCi/m$^2$, which was one dose level below the MTD for this agent as defined in a previous Phase I trial (18). When DLTs were not reached at the highest 5-FU dose level, the administered activity of $^{90}$Y-cT84.66 was increased to 20.6 mCi/m$^2$ and an additional cohort of patients entered.

On the first day of therapy, continuous infusion 5-FU was initiated through a central venous catheter. Approximately 4 h later, the radiolabeled antibody therapy dose was administered i.v. over 25 min, consisting of 5 mg of cT84.66 labeled with the therapeutic amount of $^{90}$Y and 5 mCi of $^{111}$In. Immediately after the therapy infusion, $Ca^{2+}$-DTPA (Heyl, Iserlohn, Germany) was administered i.v. at 125 mg/m$^2$ every 12 h for 3 days (6 doses), which are comparable with doses and schedules reported previously (48). Continuous infusion 5-FU was administered for a total of 5 days. As with the pretherapy imaging dose, blood samples, 24-h urine collections, and nuclear scans were performed at serial time points posttherapy infusion. Patients were followed weekly with differential blood counts, serum electrolytes, liver function studies, serum calcium, blood urea nitrogen, and serum creatinine.

Radiological studies, including CT scans, were repeated at 5–6 weeks 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, ≥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.

Toxicity was scored using Southwest Oncology Group Toxicity Criteria, which is comparable with National Cancer Institute Common Toxicity Criteria, version 2.0. DLT was defined as grade 3 nonhematological or grade 4 hematological toxicity after the first cycle of therapy. A maximum of three therapy cycles at 6-week intervals was planned for each patient. Patients were eligible to receive second and third cycles if they demonstrated at least radiological stable disease, toxicities reversible to baseline, and absence of a HACA response to cT84.66. Dose reduction was allowed for second and third cycles of therapy depending on toxicities observed with the previous cycle. As with the first therapy cycle, 5 mCi of $^{111}$In-cT84.66 was coadministered with each subsequent $^{90}$Y-cT84.66 therapy infusion.

Informed written consent was obtained for each patient before protocol entry. This protocol had full review and approval from the City of Hope Institutional Review Board.

**HACA Response.** Serum HACA responses to cT84.66 and cT84.66-DTPA were assayed before infusion and at 2 weeks, 1, 3, and 6 months postinfusion using a double capture solid-phase quantitative radioimmunoassay as described previously (47). Serum samples incubated with $^{111}$In-DTPA-cT84.66 were also examined by size exclusion HPLC using two tandem Superose 6 columns to detect possible immune responses not found by radioimmunoassay. Patients were felt to have an anti-idiotype response if serum samples were positive by HPLC assay but were negative by radioimmunoassay.

**Pharmacokinetic Analysis and Absorbed Dose Estimates.** Blood and urine samples were counted for $^{111}$In activity on a gamma counter and were processed on a HPLC 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 CT scans and attenuation coefficients obtained from a separate series of experiments involving gamma 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 performed 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 (49). $^{90}$Y radiation doses to normal organs based on biodistribution of $^{111}$In-cT84.66 were estimated with the medical internal radiation dose method (50) using S values obtained from the MIRDOSE3 program (51). 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 (52). Red marrow radiation dose estimates were performed using the American Association of Physicists in Medicine algorithm (53) 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 (54) was used to estimate activity. Trapezoidal interpolation was used to integrate the time activity curve and estimate residence time. CT 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 CT 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 (55). 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 (56) using the formula:

$$\beta \text{ dose} = 2.13\, E_\beta\, \text{AUC(tumor)} \times \text{absorbed fraction}/(\text{tumor mass}),$$

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.

**Statistical Analysis.** For this Phase I dose escalating study, data were summarized using tabulations of individual data and simple descriptive statistics. Tests of hypotheses were made using *t* tests or Wilcoxon rank-sum tests to compare levels of continuous measures between groups or Fisher's exact test to compare proportions between groups. All tests were two-tailed using an α level of 0.05.

## Results

The primary objective of this Phase I dose escalation trial was to define the DLTs and MTD of $^{90}$Y-DTPA-cT84.66 combined with 5-FU delivered as a 5-day continuous infusion. The 5-day infusion schedule was selected to deliver 5-FU over a period of time comparable with the time course of radiation delivery at the tumor site. Twenty-seven patients with advanced or metastatic colorectal cancer were entered on to this study and were administered cT84.66. Four patients (patient nos. 7, 12, 14, and 24) failed to demonstrate antibody targeting to tumor. One patient (no. 19) developed a small bowel obstruction after study entry and did not receive therapy. An additional patient (no. 13) demonstrated unusually rapid clearance of activity and therefore also did not receive therapy. The remaining 21 patients went on to receive therapy with $^{90}$Y-DTPA-cT84.66 and 5-FU and form the basis for this analysis (Table 1). Fourteen were male and 7 female, ranging in age from 36 to 85 years old. Eighteen patients presented with metastatic disease and three with disease confined to the pelvis. Optimum tumor imaging was observed ~48–72 h after antibody infusion (Fig. 1). All patients were heavily pretreated, with 20 patients having received prior chemotherapy (one to four regimens). Nineteen had previously received 5-FU with 16 receiving two or more prior 5-FU chemotherapy regimens. Ten patients previously received radiation therapy with 8 receiving radiation to the pelvis. Seventeen presented with elevated serum CEA levels ranging from 12.7 to 1305 ng/ml.

Total administered activity ranged from 25.5 to 47.2 mCi. Thirteen patients received one cycle and 8 patients two cycles of therapy. The highest dose reached was 1000 mg/m$^2$/day 5-FU and 20.6 mCi/m$^2$ $^{90}$Y-cT84.66, with DLTs being grade 4 thrombocytopenia and grade 4 mucositis. The MTD was therefore defined at 1000 mg/m$^2$/day 5-FU and 16.6 mCi/m$^2$ $^{90}$Y-cT84.66. For most patients, toxicities were primarily reversible leukopenia and/or thrombocytopenia (Table 2) with 19 of 21 patients experiencing hematological toxicity and count nadirs at ~4–6 weeks after RIT infusion. Eighteen patients experienced nonhematological toxicities characteristic of 5-FU, most grade 1–2 and occurring 1–2 weeks after RIT infusion. This group included 13 patients with fatigue, 11 with mucositis, 8 with nausea, 9 with diarrhea, 6 with erythema or rash, 6 with anemia, and 1 with transient rise of liver function tests. One patient developed grade 4 mucositis after receiving 20.6 mCi/m$^2$ $^{90}$Y-cT84.66 and 1000 mg/m$^2$/day 5-FU. This patient had previously tolerated systemic 5-FU/leucovorin but had significant mucositis with previous intrahepatic 5-fluoro-2′-deoxyuridine.

HACA response was assayed in 19 patients out to 1 month and in 7 patients out to 6 months. Five patients developed a HACA response, 2 after the first cycle and 3 after the second cycle. Two of these 5 patients demonstrated an anti-idiotype response. Of the 10 patients eligible for multiple cycles of therapy, HACA response prevented additional therapy in 2 patients. The observed HACA incidence (5 of 19) was significantly less when compared with the incidence after $^{90}$Y-cT84.66 alone observed in a previous Phase I trial, which resulted in a HACA response in 10 of 22 after a single cycle of therapy and prevented additional cycles in 8 of 12 patients (18). This difference was statistically significant ($P = 0.019$).

Thirteen patients received one cycle and 8 received two cycles of therapy, with most requiring 7–10 weeks between cycles to allow for recovery of counts (Table 2). With the second cycle of therapy, 5 experienced comparable hematological toxicity, whereas 3 (patients 8, 20, and 27) experienced greater hematological toxicity. No objective responses were observed. However, 11 patients with progressive disease entering the study demonstrated radiologically stable disease of 3–8 months duration, and 1 patient demonstrated a mixed response. In addition, three lesions demonstrated shrinkage by 53–100%. No decreases in serum CEA levels were observed.

A summary of estimated $^{90}$Y radiation doses to kidney, liver, lungs, marrow, spleen, and whole body is presented in Table 3. Normal organ doses and dose/administered mCi are comparable with those previously reported with $^{90}$Y-cT84.66 alone (18). $^{111}$In and $^{90}$Y organ residence times for radiolabeled cT84.66 were comparable for the imaging infusion *versus* the therapy infusion (given with 5-FU; data not shown), suggesting that the addition of continuous infusion 5-FU had no demonstrable effects on antibody biodistribution and pharmacokinetics. Radiation dose estimates were compared between cycle 1 and cycle 2 for the 8 patients receiving more than one cycle of therapy, using paired *t* tests for each organ and for total body. The only significant difference ($P = 0.029$) was found for total body estimated dose, where the mean dose was 1.796 cGy/mCi $^{90}$Y for cycle 1 compared with 1.724 cGy/mCi $^{90}$Y for cycle 2. There was no obvious correlation between antibody pharmacokinetics and initial serum CEA levels as was observed in previous clinical trials with the $^{90}$Y-cT84.66 (3945, 3448, 3773).

Absorbed radiation dose estimates were possible for 31 tumor and lymph node sites. As shown in Table 4, total doses ranged from 46 to 6400 cGy, with a mean dose of 1320 cGy for each cycle of therapy. Tumor doses/unit administered $^{90}$Y activity ranged from 1.0 to 212 cGy/mCi $^{90}$Y for each cycle. No correlation was observed between lesion volume and antibody

*Table 1* Patient summary

| Patient no. | Disease sites | Pretherapy CEA (ng/ml) | Prior chemotherapy | Prior radiotherapy |
|---|---|---|---|---|
| 1 | Lung, liver, lymph nodes | 7.8 | Adjuvant 5-FU/Levamisole<br>5-FU/leucovorin | None |
| 2 | Liver | 23.4 | Mitomycin-C/5-FU/leucovorin<br>CPT-11 | Pelvis |
| 3 | Pelvic/presacral | 37.2 | Adjuvant 5-FU/levamisole<br>5-FU/leucovorin<br>Continuous infusion 5-FU<br>5-FU/CPT-11/leucovorin<br>CPT-11 | Pelvis<br>Abdominal wall |
| 4 | Liver | 4.7 | 5-FU/leucovorin | Pelvis |
| 5 | Pelvis/presacral | 475.5 | Adjuvant 5-FU/levamisole | Pelvis |
| 6 | Lung | <2.5 | Adjuvant 5-FU/leucovorin<br>5-FU/leucovorin | Pelvis |
| 8 | Abdomen | <2.5 | Adjuvant 5-FU/levamisole | |
| 9 | Pelvis | 49.4 | None | Pelvis |
| 10 | Lung, liver | 1020 | 5-FU/leucovorin<br>CPT-11 | |
| 11 | Liver, lymph nodes | 303.8 | 5-FU/leucovorin<br>CPT-11 | |
| 15 | Liver, lung | 220.7 | Adjuvant 5-FU//leucovorin<br>CPT-11 | |
| 16 | Lung, bone | 91.3 | Adjuvant<br>5-FU/leucovorin/levamisole<br>CPT-11 | Left hip, lung, chest |
| 17 | Liver, lung, abdomen | 36 | 5-FU/leucovorin<br>CPT-11 | |
| 18 | Lung | 12.7 | Adjuvant 5-FU/leucovorin<br>5-FU<br>Xeloda<br>5-FU/CPT-11 | Pelvis |
| 20 | Liver | 17.6 | 5-FU<br>FUdR (intra-arterial)<br>CPT-11 | |
| 21 | Liver, pelvis, lung, clavicle | 69.5 | 5-FU/LV<br>CPT-11<br>Xeloda | Clavicle left |
| 22 | Liver | 14.3 | 5-FU/LV<br>portal vein FUdR<br>CPT-11 | |
| 23 | Liver, lung, lymph nodes | 999 | 5-FU/LV<br>CPT-11<br>5-FU | Pelvis |
| 25 | Liver, lymph nodes | 15.7 | Mitomycin-C/FUdR (hepatic artery)<br>CPT-11<br>Xeloda | |
| 26 | Liver, lung | 1305 | 5-FU/LV<br>5-FU/LV/CPT-11 | |
| 27 | Liver, lung, lymph nodes | 67.9 | 5-FU/levamisole | |

uptake as measured by dose/unit administered activity (data not shown), although uptake values $\geq$ 50 cGy/mCi were only observed in lesions $\leq$ 20.1 ml.

## Discussion

Through molecular engineering, agents can now be custom designed against specific tumor targets with properties optimized for therapy. Monoclonal antibodies against tumor antigens were one of the first of these agents to be evaluated. Conjugated to radionuclides, monoclonal antibodies-guided radiation therapy or RIT, demonstrated significant promise in laboratory models. This promise has been realized in the clinic for the radiosensitive hematological malignancies, with overall response rates ranging from 30 to 85% (1–9) and complete responses rates as high as 80% with myeloablative, bone marrow transplant supported doses (1). Recently, the FDA approved a $^{90}$Y labeled anti-CD20 monoclonal antibody for clinical use in patients with low-grade non-Hodgkin's lymphoma (10).

For solid tumors, results have been less impressive but remain encouraging. At nonmyeloablative doses in patients with chemotherapy refractory, often bulky, metastatic disease current RIT regimens have reported primarily stable disease, mixed responses, serological responses, and minor responses in patients with colorectal, breast, medullary thyroid, and ovarian cancer (19–26). Table 5 compares objective response rates and absorbed radiation doses to tumors for each cycle of therapy from a number of clinical trials. Also shown are tumor dose estimates from the current study and from two earlier biodistri-

*Table 2* Administered doses and toxicities for each patient

| Patient no. | Cycle no. | $^{90}$Y-cT84.66 mCi/m$^2$ | Total administered activity (mCi) | 5-FU mg/m$^2$/day | Marrow dose (cGy) | Platelet toxicity | WBC toxicity | Other toxicities |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 16.6 | 31.4 | 700 | 47 | Grade 1 | Grade 1 | Grade 1 nausea/vomiting/erythema |
| 2 | 1 | 16.6 | 35.7 | 700 | 32 | Grade 1 | | Grade 1 facial erythema/diarrhea |
| | 2 | 16.6 | 35.7 | 700 | 29 | Grade 1 | Grade 1 | Grade 1 fatigue/erythema |
| 3 | 1 | 16.6 | 30.9 | 700 | 39 | Grade 1 | | |
| | 2 | 16.6 | 30.9 | 700 | 33 | Grade 1 | | |
| 4 | 1 | 16.6 | 33.9 | 800 | 50 | Grade 3 | Grade 3 | |
| | 2 | 16.6 | 33.9 | 800 | 33 | Grade 3 | Grade 3 | |
| 5 | 1 | 16.6 | 27.6 | 800 | 67 | Grade 2 | Grade 2 | Grade 1 fatigue<br>Grade 2 mucositis |
| 6 | 1 | 16.6 | 30.2 | 800 | 127 | Grade 1 | Grade 3 | Grade 1 nausea/fatigue |
| 8 | 1 | 16.6 | 27.2 | 800 | 87 | Grade 2 | Grade 1 | Grade 1 diarrhea/fatigue |
| | 2 | 12 | 19.7 | 700 | 50 | Grade 3 | Grade 1 | |
| 9 | 1 | 16.6 | 28.9 | 800 | 49 | Grade 1 | | Grade 1 nausea/fatigue/mucositis/diarrhea |
| 10 | 1 | 16.6 | 33.8 | 800 | 198 | Grade 2 | Grade 2 | Grade 1 rash/mucositis |
| 11 | 1 | 16.6 | 35.7 | 900 | 54 | Grade 3 | | Grade 1 fatigue/mucositis/diarrhea |
| | 2 | 12 | 26.0 | 800 | 55 | Grade 4 | | Grade 1 fatigue/nausea |
| 15 | 1 | 16.6 | 28.4 | 900 | 24 | Grade 1 | | |
| 16 | 1 | 16.6 | 25.5 | 900 | 30 | Grade 1 | Grade 1 | Grade 1 fatigue/nausea |
| 17 | 1 | 16.6 | 26.2 | 1000 | 19 | Grade 1 | | Grade 2 mucositis<br>Grade 1 diarrhea |
| 18 | 1 | 16.6 | 33.2 | 1000 | 119 | Grade 3 | Grade 3 | Grade 1 nausea |
| | 2 | 12 | 24.0 | 900 | 79 | Grade 3 | Grade 1 | |
| 20 | 1 | 16.6 | 34.0 | 1000 | 81 | Grade 1 | Grade 1 | Grade 1 mucositis, diarrhea, fatigue |
| | 2 | 16.6 | 34.0 | 1000 | 97 | Grade 4 | Grade 3 | Grade 1 fatigue, diarrhea |
| 21 | 1 | 20.6 | 46.0 | 1000 | 53 | | | Grade 1 nausea, fatigue, mucositis, diarrhea, anemia |
| 22 | 1 | 20.6 | 47.2 | 1000 | 49 | | | Grade 4 mucositis;<br>Grade 1–2 nausea, diarrhea, fatigue, rash; anemia |
| 23 | 1 | 20.6 | 40.2 | 1000 | 167 | Grade 4 | Grade 3 | Grade 2 anemia, mucositis; grade 1 fatigue |
| 25 | 1 | 16.6 | 30.2 | 1000 | NA[a] | Grade 1 | Grade 2 | Grade 1 fatigue, anemia and mucositis |
| 26 | 1 | 16.6 | 29.5 | 1000 | NA | Grade 3 | Grade 2 | Grade 1 diarrhea, mucositis, increase liver function tests, and Grade 2 rash |
| 27 | 1 | 16.6 | 34.4 | 1000 | 27 | Grade 1 | Grade 1 | Grade 1 anemia and fatigue |
| | 2 | 16.6 | 34.4 | 1000 | 22 | Grade 3 | Grade 2 | Grade 2 anemia<br>Grade 3 fatigue |

[a] NA, not available.

bution (nontherapy) trials with $^{90}$Y-cT84.66, where tumor dose estimates were derived directly from biopsies. The range and reported median and mean tumor doses are comparable for solid tumor antibody delivery systems *versus* anti-lymphoma antibody delivery systems, yet response rates are greater for lymphomas. The differences in observed response rates between hematological and solid tumors are in large part attributable to differences in radiosensitivity because comparable radiation doses to tumor are achievable. This is even after accounting for effects of the unlabeled anti-lymphoma antibodies because clinical trials have demonstrated no significant response rates with unlabeled antibodies such as Lym-1 (57, 58), or as in the case of Y2B8, a 26% increase in response rate was observed with the addition of radiolabeled antibody compared with unlabeled antibody alone in a recent randomized trial (59).

Through antibodies directed against tumor antigens, many

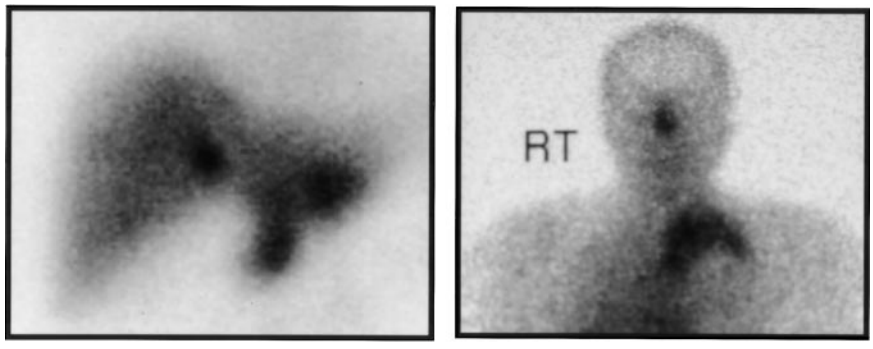


*Fig. 1* Figure on the *left* is a 48-h anterior spot view of liver, demonstrating antibody targeting to right and left lobe liver metastases in a patient with metastatic colorectal cancer. Figure on the *right* is an anterior view at 120 h, demonstrating antibody localization to a left supraclavicular mass in a patient with metastatic mucoepidermoid cancer.

*Table 3* Normal organ $^{90}$Y dose estimates

| Organ ($n$ = 27) | Estimated dose cGy/mCi (mean, range) | Total dose cGy (mean, range) |
|---|---|---|
| Kidneys | 4.6 (0.6–12.2) | 154 (21–514) |
| Liver | 29 (13.3–50.0) | 912 (534–1719) |
| Lungs | 1.0 (0.6–1.6) | 30 (17–48) |
| Red Marrow | 2.0 (0.6–5.9) | 64 (19–198) |
| Spleen | 12.0 (4.0–27.9) | 379 (111–759) |
| Total Body | 1.8 (1.4–2.5) | 57 (39–75) |

had hoped that RIT would offer another means of delivering radiation doses comparable with traditional teletherapy or brachytherapy systems. However, because of hematopoietic toxicity, tumor doses achievable by RIT are a fraction of what can be delivered by conventional delivery systems. Regardless of the antibody, antigen target, or tumor type studied, the radiation doses achievable at the tumor site have been comparable for most antibodies, with median or mean doses in the range of 1000–2000 cGy and with subsets of tumors achieving values in the range of 2000–7000 cGy (Table 5). Doses in the range of 2000 cGy result in partial and complete responses in many lymphomas, whether delivered by conventionally fractionated external beam radiation or by RIT. However, identical doses result in ~3 log kill in solid tumors and therefore explain the lack of objective responses in bulky disease.

Although less than initially anticipated, tumor doses currently achievable with RIT are at levels that can potentially result in clinically important antitumor effects in solid tumors, particularly in subclinical or microscopic disease and when combined with radiation-enhancing chemotherapeutic agents. Withers *et al.* (60) reviewed the clinical literature evaluating adjuvant radiation for solid tumors. Radiation doses ranged from 2000 to 5000 cGy conventionally fractionated on the various studies. An inverse linear relationship between radiation dose and tumor recurrence was observed. More importantly, there was no threshold effect, and lower doses still resulted in measurable decreases in tumor recurrence. This can be explained by the fact that there is a broad range of tumor burden in patients with subclinical disease, ranging from $10^0$ to $10^8$ cells. As a result, doses in the range of 2000 cGy can have clinically measurable effects, particularly in those patients with lower tumor burdens. This is in contradistinction to macroscopic disease where doses below a certain threshold value have little measurable effect. The authors concluded that a more flexible approach in determining the value of doses $<$ 5000 cGy needs to be adopted.

In addition, a number of clinical trials have demonstrated clinically important antitumor effects with doses in the range of 3000 cGy. In a multicenter trial from Norway, 309 patients with operable rectal cancer (61) were randomized to preoperative pelvic radiation (3150 cGy at 175 cGy/day) and surgery *versus* surgery alone. Radiation resulted in a statistically significant delay in local recurrences compared with surgery alone. Similarly, an European Organization for Research and Treatment of Cancer trial randomized 466 patients with operable rectal cancer to preoperative radiation (3450 cGy at 230 cGy/day) and surgery *versus* surgery alone (62) and demonstrated a statistically significant decrease in local recurrences ($P$ = 0.003) with this dose.

Finally, doses as low as 3000 cGy have been effectively combined with chemotherapy. Franklin *et al.* (63) reported on esophageal cancer patients treated with 3000 cGy (200 cGy/day), continuous infusion 5-FU, and mitomycin-C followed by surgery. Of 18 patients resected with localized disease, 6 were tumor free. Nigro *et al.* (64) from the same institution reported on 28 patients with anal cancer using the identical regimen. Seven of 12 patients achieved a pathological complete response at resection, whereas an additional 14 patients had a clinical complete response and no tumor seen microscopically after excision of the scar. The results were improved over that of chemotherapy alone or 3000 cGy alone (65).

Because the radiobiological effect of a cGy of RIT and a cGy of conventionally fractionated external beam radiation are comparable for a typical solid tumor (66), strategies that have proven successful in optimizing clinical application of external beam radiotherapy should also prove successful with RIT. Future RIT trials should continue to incorporate similar multimodality, consolidative therapy approaches, integrating RIT into established chemotherapy regimens to further improve antitu-

*Table 4* Estimated doses to tumor

| Patient no. | Tumor mass (T)/node (N) | Volume (cc) | cGy/mCi | Total dose (cGy) |
|---|---|---|---|---|
| 1 | T | 20.1 | 126 | 3970 |
| 3 | T | 308 | 6.9 | 213 |
| 5 | T | 25.7 | 23.6 | 651 |
| 6 | T | 3.5 | 212 | 6400 |
| 9 | T | 33.2 | 12.5 | 361 |
| | T | 27.1 | 22.8 | 659 |
| 16 | T | 9.8 | 30.7 | 783 |
| | T | 14.1 | 40.1 | 1020 |
| 20 | T | 7.4 | 49.4 | 1680 |
| | T | 3.2 | 4.4 | 150 |
| | T | 14.5 | 130 | 4410 |
| 21 | T | 123 | 1.0 | 46 |
| 11 | N | 0.5 | 87.9 | 3140 |
| 15 | N | 0.5 | 147 | 4180 |
| 16 | N | 10.8 | 25.0 | 638 |
| 17 | N | 12.5 | 19.1 | 500 |
| | N | 4.3 | 24.4 | 639 |
| 20 | N | 7.4 | 18.3 | 622 |
| 21 | N | 28.2 | 7.0 | 322 |
| | N | 4.1 | 18.4 | 846 |
| 22 | N | 7.6 | 17.9 | 845 |
| | N | 10.1 | 5.4 | 255 |
| 23 | N | 13.8 | 11.8 | 474 |
| | N | 10.8 | 35.3 | 1420 |
| | N | 10.8 | 8.9 | 358 |
| 25 | N | 5.7 | 22.8 | 689 |
| | N | 11.2 | 13.3 | 402 |
| | N | 13.8 | 8.5 | 257 |
| | N | 8.0 | 8.5 | 257 |
| 26 | N | 6.2 | 5.6 | 165 |
| 27 | N | 0.5 | 136 | 4690 |

*Table 5* Radiation dose estimates to tumor from selected nonmyeloablative RIT clinical trials

| Study | Antibody | Tumor type | No. of tumors analyzed | Tumor dose (cGy)/cycle | Objective response rate (%) |
|---|---|---|---|---|---|
| Meredith (11) | $^{131}$I-CC49 | Prostate | 4 | 208–1083 | 0 |
| Juweid (12) | $^{131}$I-NP4 F(ab')$_2$ | Colorectal, lung, pancreas, thyroid | 4 | 511–6476 | 0 |
| DeNardo (13) | $^{131}$I-chL6 | Breast | 7 | 120–3700 (~1300 mean) | 40 |
| Van Zanten-Pryzbysz (14) | $^{131}$I-cMOv18 | Ovary | 3 | 600–3800 | 0 |
| Breitz (15) | $^{186}$Re-NR-CO-2 F(ab')$_2$ | Lung, colorectal, breast, ovary, renal | 5 | 500–2100 | 4 |
| Postema (16) | $^{186}$Re-anti-CD44v66 | Head and neck | NS | 1300 median | 0 |
| DeNardo (17) | $^{90}$Y-BrE-3 | Breast | 16 | 442–1887 | 0 |
| Wong (47; 77)[a] | $^{90}$Y-cT84.66 | CEA+ | 40 | 34–7315 (1148 mean) | |
| Wong (current study) | $^{90}$Y-cT84.66 | Colorectal | 31 | 46–6400 (1320 mean) | 0 |
| Wiseman (78) | $^{90}$Y-2B8 | NHL | 18 | 580–6700 (1700 median) | 67 |
| Vose (79) | $^{131}$I-anti-B1 | NHL | NS | 795 mean | 57 |
| Kaminski (80) | $^{131}$I-anti-B1 | NHL | NS | 141–2584 (925 mean) | 79 |
| Lamborn (81) | $^{131}$I-Lym-1 | NHL | 45 | 16–1485 (241 median) | 54 |
| Vose (82) | $^{131}$I-LL2 | NHL | NS | 166–861 | 33 |

[a] Previous biodistribution/imaging (nontherapy) clinical trials that determined antibody uptake from tumor biopsies obtained at the time of planned surgery. Tumor doses determined assuming 35 mCi administered $^{90}$Y-cT84.66 activity.
[b] NHL, non-Hodgkin's lymphoma; NS, not stated.

mor effects. Preclinical studies (6, 27–32, 42), early trials with radioiodinated polyclonal antibodies (67, 68), and a recently completed Phase I trial (27) have demonstrated the potential of combining RIT with a variety of radiation-enhancing chemotherapy agents.

In the Phase I study reported here, the feasibility of combining continuous infusion 5-FU chemotherapy with RIT was evaluated. RIT was delivered using a $^{90}$Y-labeled anti-CEA chimeric T84.66 monoclonal antibody, previously evaluated as monotherapy in a Phase I trial (18). This trial reached an MTD of 16.6 mCi/m$^2$, with DLTs being reversible thrombocytopenia and leukopenia. No significant nonhematological toxicities were observed.

Given its demonstrated effects in colorectal cancer and its radiation-enhancing properties, continuous infusion 5-FU was combined with $^{90}$Y-cT84.66 in this study. The exact mechanism of 5-FU radioenhancement is not known but may be related to inhibition of thymidylate synthase, inhibition of DNA synthesis, and effects on RNA metabolism (36). Considerable interest has been generated for continuous infusion 5-FU as an alternative dose schedule to bolus administration given comparable or improved response rates (69–74) and reduced hematopoietic toxicity, making it a more attractive alternative in combination with RIT. DLTs with continuous infusion 5-FU are gastrointestinal toxicity, mucositis, and hand-foot syndrome and are therefore nonoverlapping. In addition, continuous infusion 5-FU may provide an improved approach toward 5-FU sensitization of radiation. *In vitro* studies (33, 34) found that sensitization occurred only with prolonged 5-FU exposure postradiation (at least 48 h).

Radiation enhancement is seen with radiation delivered as external beam radiotherapy (33–36) or RIT (37–42). In addition, 5-FU may reduce hematopoietic toxicity of RIT, although the mechanism remains unclear. Thomas *et al.* (75) demonstrated a significant increase in survival with the addition of 5-FU to mice receiving 750 cGy total body irradiation. Examination of the marrow after irradiation, however, revealed no obvious differences with the addition of 5-FU. Chalandon *et al.* (76) found no additional toxicity and a significant increase in peripheral WBCs in mice receiving 5-FU and RIT compared with RIT alone.

This study clearly demonstrated the feasibility of combining $^{90}$Y-cT84.66 RIT with a 5-day continuous infusion schedule of 5-FU. Administered 5-FU drug doses and $^{90}$Y activities achieved were close to what would be the expected MTD for each agent alone. This is related to nonoverlapping DLTs of each agent. DLTs with this combination therapy were hematopoietic but did not appear to be greater compared with $^{90}$Y-cT84.66 alone. This may also be in part because of similar antibody clearance kinetics and estimated marrow radiation doses observed on this study compared with those previously reported for $^{90}$Y-cT84.66 alone (18), suggesting that 5-FU had no appreciable effect on antibody pharmacokinetics. Characteristic toxicities of 5-FU such as mucositis were observed but were also not greater compared with 5-FU alone.

The incidence of HACA was lower compared with our previous study. Five of 19 patients developed HACA, which was significantly less than on a previous Phase I study evaluating $^{90}$Y-cT84.66 alone, suggesting an immunosuppressive effect with the addition of 5-FU. Therefore, combining chemotherapy with RIT may have the additional benefit of reducing

HACA, and it will be of interest to see if other chemotherapy agents in combination with RIT will produce similar findings.

Mean tumor dose was 1320 cGy (46–6400 cGy), which is comparable with that seen in previous Phase I trials evaluating this $^{90}$Y-cT84.66 (18, 47, 77) and with other radiolabeled antibodies (Table 5). Although no objective responses were observed, 11 patients with progressive disease entering the study demonstrated radiological stable disease of 3–8 months duration, and 1 patient demonstrated a mixed response.

In summary, given radiation doses to tumor currently achievable with radiolabeled antibodies, RIT will only have a clinically important impact on solid tumors if combined with established chemotherapy regimens, particularly as consolidative therapy. Results from this trial are encouraging and demonstrate the feasibility and potential advantages of combining RIT with 5-FU. The addition of 5-FU does not appear to significantly enhance hematological toxicities of the radiolabeled antibody. In addition, 5-FU reduces the development of HACA response permitting multicycle therapy in a larger number of patients. From this initial experience, future trials are planned that will integrate radiation therapy delivered by $^{90}$Y-cT84.66 into established 5-FU containing regimens in colorectal cancer.

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