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

Jeffrey Y. C. Wong, Stephen Shibata, Lawrence E. Williams, Cheuk S. Kwok, An Liu, David Z. Chu, Dave M. Yamauchi, Sharon Wilczynski, David N. Ikle, Anna M. Wu, Paul J. Yazaki, John E. Shively, James H. Doroshow, and Andrew A. Raubitschek

Divisions of Radiation Oncology, Medical Oncology, Radiology, Surgery, Pathology, Information Sciences, Molecular Biology, and Immunology, Beckman Research Institute and City of Hope National Medical Center and Beckman Research Institute, Duarte, California

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 90Y-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 90Y-cT84.66 anti-carcinoembryonic antigen at 16.6 mCi/m² 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/m²/day. Upon reaching the highest planned dose level of 5-FU, a final cohort received 90Y-cT84.66 at 20.6 mCi/m² and 5-FU at 1000 mg/m²/day.

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/m² 90Y-cT84.66 combined with 1000 mg/m²/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 90Y-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 90Y-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 multicyle 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.
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 led 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-radiolabeled 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 (\(K_A = 1.16 \times 10^{11} \text{ M}^{-1}\)) 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 diolabeling 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-radiolabeled 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.

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 esti-
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 $^{90}$Y-DTPA-cT84.66 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-idiotypic 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 MIRD-DOSE3 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 90Y β radiation (56) using the formula:

\[ \beta \text{ dose} = 2.13 \times E_{\beta} \times \frac{\text{AUC(tumor)}}{\text{absorbed fraction(tumor mass)}} \]

where \( E_{\beta} \) is the mean β energy of 90Y 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 90Y-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 90Y-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 \( \approx 48–72 \) 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/m²/day 5-FU and 20.6 mCi/m² 90Y-cT84.66, with DLTs being grade 4 thrombocytopenia and grade 4 mucositis. The MTD was therefore defined at 1000 mg/m²/day 5-FU and 16.6 mCi/m² 90Y-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 \( \approx 4–6 \) 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/m² 90Y-cT84.66 and 1000 mg/m²/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-idiotypic 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 90Y-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 90Y 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 90Y-cT84.66 alone (18). 111In and 90Y 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 90Y for cycle 1 compared with 1.724 cGy/mCi 90Y 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 90Y-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 90Y activity ranged from 1.0 to 212 cGy/mCi 90Y for each cycle. No correlation was observed between lesion volume and antibody...
uptake as measured by dose/unit administered activity (data not shown), although uptake values ≥ 50 cGy/mCi were only observed in lesions ≥ 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 90Y 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 biodistribut-
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

<table>
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<th>Patient no.</th>
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<th>Marrow dose (cGy)</th>
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<td>Grade 3 fatigue</td>
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* NA, not available.
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 the antibody, antigen target, or tumor type studied, the radiation be delivered by conventional delivery systems. Regardless of brachytherapy systems. However, because of hematopoietic tox-

radiation doses comparable with traditional teletherapy or had hoped that RIT would offer another means of delivering therapy and 5-FU.

result in clinically important antitumor effects in solid tumors, but not in bulky disease. 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 following 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>
<thead>
<tr>
<th>Table 3</th>
<th>Normal organ 90 Y dose estimates</th>
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<td>Organ</td>
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</tr>
<tr>
<td>Red Marrow</td>
<td>2.0 (0.6–5.9)</td>
</tr>
<tr>
<td>Spleen</td>
<td>12.0 (4.0–27.9)</td>
</tr>
<tr>
<td>Total Body</td>
<td>1.8 (1.4–2.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Estimated doses to tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
<td>Tumor mass (T)/node (N)</td>
</tr>
<tr>
<td>1</td>
<td>T</td>
</tr>
<tr>
<td>3</td>
<td>T</td>
</tr>
<tr>
<td>5</td>
<td>T</td>
</tr>
<tr>
<td>6</td>
<td>T</td>
</tr>
<tr>
<td>9</td>
<td>T</td>
</tr>
<tr>
<td>16</td>
<td>T</td>
</tr>
<tr>
<td>20</td>
<td>T</td>
</tr>
<tr>
<td>21</td>
<td>T</td>
</tr>
<tr>
<td>11</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>N</td>
</tr>
<tr>
<td>20</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>N</td>
</tr>
<tr>
<td>22</td>
<td>N</td>
</tr>
<tr>
<td>23</td>
<td>N</td>
</tr>
<tr>
<td>24</td>
<td>N</td>
</tr>
<tr>
<td>25</td>
<td>N</td>
</tr>
<tr>
<td>26</td>
<td>N</td>
</tr>
<tr>
<td>27</td>
<td>N</td>
</tr>
<tr>
<td>28</td>
<td>N</td>
</tr>
<tr>
<td>29</td>
<td>N</td>
</tr>
</tbody>
</table>
morrow effects. Preclinical studies (6, 27–32, 42), early trials with radiiodinated 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/m², 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

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

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

* 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.

* NHL, non-Hodgkin’s lymphoma; NS, not stated.

Clinical Cancer Research 5849
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 90Y-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 multicyle therapy in a larger number of patients. From this initial experience, future trials are planned that will integrate radiation therapy delivered by 90Y-CT84.66 into established 5-FU containing regimens in colorectal cancer.

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References


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

Jeffrey Y. C. Wong, Stephen Shibata, Lawrence E. Williams, et al.


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