Initial Clinical Experience Evaluating Yttrium-90-Chimeric T84.66 Anticarcinoembryonic Antigen Antibody and Autologous Hematopoietic Stem Cell Support in Patients with Carcinoembryonic Antigen-producing Metastatic Breast Cancer

Jeffrey Y. C. Wong,^2 George Somlo, Tamara Odom-Maryon, Lawrence E. Williams, An Liu, Dave Yamauchi, Anna M. Wu, Paul Yazaki, Sharon Wilczynski, John E. Shively, Stephen Forman, James H. Doroshow, and Andrew A. Raubitschek

Divisions of Radiation Oncology and Radiation Research [JYCW, AL, AAR], Radioimmunotherapy [J. Y. C. W., A. L., A. A. R.], Medical Oncology and Experimental Therapeutics [G. S., S. F., J. H. D.], Biostatistics [T. O.-M.], Diagnostic Radiology [L. E. W., D. Y.], Biology [A. M. W., P. Y.], Pathology [S. W.], Immunology [J. E. S.], and Hematology and Bone Marrow Transplantation [G. S., S. F., J. H. D.], City of Hope National Medical Center and Beckman Research Institute, Duarte, California 91010

Abstract

cT84.66 is a human/murine IgG1 antibody with high affinity and specificity for carcinoembryonic antigen (CEA). An earlier Phase I trial defined the maximum tolerated dose for ^90^Y-diethylene-triaminepentaacetic acid (DTPA)-cT84.66 at 22 mCi/m^2^, dose-limiting toxicities were reversible leukopenia and thrombocytopenia. The purpose of this Phase I trial was to evaluate the feasibility and toxicities of administering higher activities of ^90^Y-DTPA-cT84.66 with stem cell support in patients with CEA-producing breast cancer. Patients with CEA-producing breast cancer refractory to standard therapies underwent peripheral stem cell collection followed by infusion of ^11^In-DTPA-cT84.66. Those patients demonstrating tumor targeting received a single therapy dose of ^90^Y-DTPA-cT84.66, followed by Ca-DTPA infusion for 72 h posttherapy. Stem cells were reinfused following a divided schedule. To date, seven patients have been accrued to this trial. Each patient received an imaging dose of ^11^In-cT84.66. Six patients demonstrated tumor imaging and received a single cycle of ^90^Y-cT84.66 at 15 mCi/m^2^ (three patients) and 22.5 mCi/m^2^ (three patients). One patient did not demonstrate tumor imaging and was not treated. At these administered activities, ^90^Y-cT84.66 was well tolerated. No dose-limiting toxicities have been observed. All patients demonstrated hematopoietic recovery after stem cell infusion. One patient demonstrated stable disease for 4 months; one patient had stable disease and reduction of bone pain for 3 months; and a third patient experienced >50% reduction of an ovarian metastasis, resolution of malignant pleural effusion, stable pleural metastases, and stable bone scan for 14 months. Preliminary results from this ongoing Phase I trial are promising and demonstrate the feasibility and potential for antitumor effects of stem cell supported ^90^Y-cT84.66 therapy in patients with CEA-producing breast cancers.

Introduction
cT84.66^3^ is a human/murine chimeric IgG1 monoclonal antibody developed at the City of Hope with high affinity (K_d = 1.16 × 10^11^ M^-1^) and specificity to CEA (1). cT84.66 was initially evaluated, conjugated to isothiocyanatobenzyl DTPA, and radiolabeled with ^11^In in a pilot biodistribution trial that entered patients with metastatic CEA-producing malignancies of various histologies (2). That study demonstrated targeting to CEA-producing metastatic sites, imaging sensitivity comparable to other intact anti-CEA monoclonals, no allergic reactions, and decreased immunogenicity compared to murine monoclonals after a single 5 mCi/5 mg administration. ^11^In-DTPA-cT84.66 was further evaluated in an antibody protein dose escalation trial in 15 patients with colorectal cancer (3) and demonstrated no clinically significant changes in biodistribution or tumor targeting with escalation of antibody protein doses from 5 to 105 mg. Recently, ^90^Y-DTPA-cT84.66 was evaluated in a Phase I therapy trial entering patients with metastatic CEA-producing malignancies. This trial determined a maximum tolerated dose of 22 mCi/m^2^, dose-limiting toxicities were reversible thrombocytopenia and leukopenia (4).

Although commonly associated with gastrointestinal malignancies, CEA is expressed in approximately 50-60% of breast carcinomas with serum levels elevated in approximately 40-50% of patients with metastatic disease (5). In addition, ^90^Y-DTPA-cT84.66 has shown antitumor activity in mouse models bearing breast cancer xenografts (6). Therefore, the

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^2^ To whom requests for reprints should be addressed, at the Division of Radiation Oncology and Radiation Research; City of Hope National Medical Center; 1500 East Duarte Road, Duarte, CA 91010. Phone: 626-301-8247; Fax: 626-930-5334.

^3^ The abbreviations used are: cT84.66, chimeric T84.66; CEA, carcinoembryonic antigen; ANC, absolute neutrophil count; DTPA, diethylene-triaminepentaacetic acid; G-CSF, granulocyte colony-stimulating factor; HACA, human antichimeric antibody; RIT, radioimmunotherapy.
purpose of this Phase I trial was to evaluate $^{90}$Y-DTPA-cT84.66 RIT further in patients with metastatic CEA-producing breast cancer, using autologous stem cell support to diminish the anticipated hematological toxicities.

Patients and Methods

**Antibody Production and Conjugation.** Human/murine cT84.66 is an anti-CEA intact IgG1, with high affinity ($K_\text{d} = 1.16 \times 10^{-11}$ M$^{-1}$) and specificity to CEA. Details of its production, characterization, purification, conjugation, and radiolabeling have been reported previously (1, 2, 7–9). 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 nCi to 1 mg and $^{90}$Y at a ratio of 10 nCi 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 vialated lot of purified conjugated antibody met standards set by the Food and Drug Administration. An Investigational New Drug application for $^{111}$In-DTPA-cT84.66 is currently on file with the Food and Drug Administration.

**Clinical Trial Design.** Patients entered on this trial were 18 years of age or older, with metastatic breast cancer refractory to standard therapies. All patients demonstrated evidence of CEA-producing cancer based on an elevated serum CEA or positive staining on CEA immunohistochemistry of previous frozen tumor biopsies. Eligibility criteria included Karnofsky performance status of ≥60% and estimated survival of at least 6 months; any prior radiotherapy, immunotherapy, or chemotherapy completed at least 4 weeks prior to patient entry on study; hemoglobin ≥9 g %, absolute granulocyte count ≥1500/μl, and platelets ≥100,000/μl; serum creatinine ≤1.3 mg/dl and creatinine clearance ≥60 ml/min; and bilirubin ≤1.5, aspartate aminotransferase and alanine aminotransferase no greater than 2 times the upper limits of normal, no previous history of clinically significant liver dysfunction, and ≤25% of the normal liver replaced by metastatic disease. Other entry criteria included lung diffusion capacity ≥50% of predicted, forced expiratory volume at one second ≥70% of predicted, room air pO$_2$ ≥75 mm Hg, and room air pCO$_2$ ≤45 mm Hg; negative serum anti-antibody testing (if the patient had previously received murine or chimeric antibody); negative serum HIV and hepatitis B and C antigen testing; cardiac ejection fraction of ≥50%; and ≥20% of bone marrow involved by tumor on bone marrow biopsy performed just prior to protocol entry. Patients with brain or leptomeningeal involvement by tumor, a history of whole pelvis radiation therapy, or a history of radiation to greater than 40% of the bone marrow were ineligible. All radiological studies and bone marrow biopsies were performed within 8 weeks of trial entry, and all blood studies were performed within 2 weeks of anticipated antibody infusion.

Patients meeting eligibility criteria received 5 μ/kg G-CSF s.c. twice a day (10) for 1 week followed by autologous stem cell collection with continued G-CSF priming. A minimum of $1.6 \times 10^7$ CD34$^+$ cells/kg and $6 \times 10^8$ mononuclear cells/kg was collected. After obtaining the required number of stem cells, blood counts were allowed to recover for at least 1 week or until the absolute granulocyte count exceeded 800/μl.

Patients then received a 5 mCi/5 mg imaging infusion of $^{111}$In-DTPA-cT84.66. A 100-μg anaphylaxis test dose of antibody was first administered i.v. This was followed 15 min later by administration of the remainder of the imaging dose. Spot planar and whole body imaging studies were performed at 2, 6, 24, 48, 72, and 96–168 h after antibody administration using a Toshiba 901 camera with single-photon emission computed tomography capability. Single-photon emission computed tomography scans were performed at 48–72 and 96–120 h. Blood samples were taken at 30 min and 1, 2, and 6 h and at each scan time. Twenty-four h urine collections were performed daily for five consecutive days.

Patients demonstrating imaging of at least one known tumor site received a therapy infusion of $^{90}$Y-DTPA-cT84.66 (co-administered with 5mCi of $^{111}$In-DTPA-cT84.66) 1 week after the imaging infusion. Total protein dose was kept constant at 5 mg. This was followed by i.v. administration of Ca-DTPA at 125 mg/m$^2$ every 12 h by bolus infusion for 72 h. Nuclear scans, blood samples, and 24 urine collections were again performed as with the imaging infusion.

At 7 days posttherapy, a marrow biopsy of the iliac crest was performed to evaluate remaining activity in marrow. Bone marrow samples were weighed and processed. The $^{90}$Y radioactivity was measured using Cerenkov counting (11) with quench correction. The remaining marrow radiation dose was estimated assuming the physical decay of $^{90}$Y and an average biological decay. The biological clearance (average half-life of 421 h) was estimated from a lumbar spine region of interest as defined from planar nuclear medicine images. The time at which the remaining integral radiation dose to the marrow was ≤5 cGy was then estimated.

Stem cells were reinfused according to a divided schedule, based on earlier experience from this institution demonstrating more rapid recovery of blood counts with a divided schedule of reinfusion. (10). For patients entered at dose level 1, 25% of stem cells were reinfused at 5 days posttherapy infusion, with the remaining 75% reinfused at the time point at which the estimated remaining cumulative marrow dose was ≤5 cGy, as determined by bone marrow biopsy at day 7. The trial was then modified to reinfuse the stem cells closer to the anticipated nadir. Patients entered on dose level 2 therefore received 25% of their stem cells at the time point at which the remaining cumulative marrow dose was ≤5 cGy, with the remaining 75% infused when the absolute granulocyte count was <1000/μl.

Patients were followed at least weekly and more frequently during periods of significant blood count depression. G-CSF at 5 μ/kg s.c. twice per day was instituted if the granulocyte count fell below 500/μl and was continued for three days past recovery of granulocyte count >1000/μl Platelet transfusions were given to maintain a platelet count of >20,000/μl, or as clinically indicated. Toxicities were assessed using standard Southwest Oncology Group toxicity criteria with the exception of hematological toxicities, which were graded based on modified criteria suggested by the City of Hope National Medical Center transplant committee at the time of study conception for patients undergoing stem cell support high-dose chemo/radiation therapy. Hence, engraftment failure, conventionally agreed upon as lack of granulocyte and/or platelet engraftment within 28 days posttransplant constituted grade 3 hematological toxicity.
These criteria are further outlined as follows. Grade 1: neutropenia present but $>500/\mu l$ and/or thrombocytopenia present but $>10,000/\mu l$. Grade 2: neutrophils $<500/\mu l$ and/or platelets $<10,000/\mu l$ for a duration of up to 4 weeks. Grade 3: neutrophils $<500/\mu l$ and/or platelets $<10,000/\mu l$ for a duration of 4–8 weeks. Grade 4: neutrophils $<500/\mu l$ and/or platelets $<10,000/\mu l$ for a duration of $>8$ weeks. Grade 5: death due to bacterial or fungal infection or hemorrhage associated with neutrophils $<500/\mu l$ or platelets $<10,000/\mu l$ more than 8 weeks after marrow transplantation.

Restaging studies were performed in all patients at 6–8 weeks posttherapy, with subsequent restaging studies performed as clinically indicated.

**HACA Response.** Serum HACA response to cT84.66 and cT84.66-DTPA was assayed prior to infusion and at approximately 2 weeks and 1, 3, and 6 months postinfusion using a double capture solid phase quantitative RIA as described previously (2). Serum samples incubated with $^{111}$In-DTPAcT84.66 were also examined by size exclusion HPLC using two tandem Superose 6 columns to detect possible immune responses not found by RIA.

**Pharmacokinetic Analysis and Dosimetry 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. 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 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, kidney, and whole body. Details of this compartmental model have been published previously (12). $^{90}$Y radiation doses to normal organs based on biodistribution of $^{111}$In-cT84.66 were estimated with the Medical Internal Radiation Dose (MIRD) method (13) using the MIRDDOSE3 program (14). As reported previously, $^{90}$Y-DTPA-cT84.66 and $^{111}$In-DTPA-cT84.66 biodistributions were comparable in the mouse model (15). Red marrow radiation dose estimates were performed using the American Association of Physicists in Medicine (AAPM) algorithm (16) based on blood residence times determined from the five-compartment model.

**Results**

Seven patients have been entered on this trial. One patient with bone metastases did not demonstrate tumor targeting of antibody after $^{111}$In-DTPA-cT84.66 administration and therefore did not receive the therapy infusion (patient 4). Six patients did demonstrate targeting (Figs. 1 and 2) and received therapy. Table 1 summarizes all six patients. All six patients had significant tumor burden; five patients had bone metastases, three had...
pleural-based or chest wall metastases, and two had bone marrow involvement. Prior to therapy, all six patients demonstrated elevated serum CEA levels ranging from 16 to 110 ng/ml.

Each patient had been heavily pretreated; five patients had received external beam radiotherapy, four patients had failed 3–5 chemotherapy regimens, and four had failed high-dose, stem-supported chemotherapy. Despite heavy pretreatment, the required number of stem cells were collected after G-CSF priming in six of seven patients entered on study. The required number of cells could not be collected in patient 7 after 2 weeks. Following an alternative priming regimen reported previously, she received a single i.v. dose of cyclophosphamide (2 gram/m²) and paclitaxel (175 mg/m²), which resulted in the successful collection of the required number of stem cells. cT84.66 was then infused 1 month after chemotherapy priming.

An earlier Phase I trial established a maximum tolerated dose of 22 mCi/m² in patients with CEA-producing malignancies, the majority of patients with metastatic colorectal cancer (4). Patients entered on the current trial were more heavily pretreated, and therefore an initial dose level of 15 mCi/m² was chosen. Three patients were treated at dose level 1 (15 mCi/m²), and three were treated at dose level 2 (22.5 mCi/m²). Administered activity ranged from 24.3 to 46.0 mCi. Toxicities were primarily hematological and not dose-limiting (Table 1 and Fig. 3). As anticipated, at the higher dose level, the degree of blood count depression was greater, and the time point at which the nadir occurred was earlier. All patients demonstrated evidence of hematological recovery after stem cell reinfusion. For patients at dose level 1, stem cells were reinfused at day 5, and at the time point at which remaining marrow dose was estimated to be ≤5 cGy. This occurred at days 13–14 for all three patients. For patients at dose level 2, 25% of collected stem cells were reinfused at the time point at which remaining marrow dose was ≤5 cGy, which occurred at days 13–18. The remaining 75% of stem cells were reinfused when the ANC was <1000/µl, which occurred at days 16–24. The time point at which the ANC was <1000/µl occurred prior to the time point of the ≤5-cGy marrow dose in patient 7; it was therefore decided to reinfuse 50% of collected stem cells at each time point.

In addition to the hematological toxicities outlined above, patient 1 developed grade 2 nausea and vomiting during the first week posttherapy, requiring i.v. hydration, and patient 3 reported grade 1 arthralgias during the second week after the therapy infusion. These symptoms were controlled with analgesics. To date, no other organ toxicities have been observed.

Dose estimates in cGy to normal organs, as determined from imaging and therapy infusions, are displayed in Table 2. As expected, doses to normal organs were uniformly higher for patients at the higher dose level. Radiation doses to marrow ranged from 76 to 103.9 cGy at the 15 mCi/m² dose level, compared to 134.8–177.1 cGy at the 22.5 mCi/m² level. Similar differences were observed for other organs.

As in an earlier trial (9), an increase in excretion of a radioactive 5-kDa urinary metabolite was observed by HPLC with the administration of DTPA after therapy. Cumulative fraction of injected dose in urine at 144 h increased with the therapy infusion compared to the imaging infusion for all six treated patients (Table 3). In general, radiation dose estimates to normal organs were lower with the imaging infusion compared to the therapy infusion, particularly for liver, marrow, and total body (Table 2). For example, a 0.2–30.6% reduction in marrow radiation dose and a 3.2–41.4% reduction in liver radiation dose

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**Fig. 2** Anterior spot view of the chest (patient 3) at 120 h demonstrating antibody localization to right pleural metastases.
Table 1  Patient characteristics and hematologic toxicities

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
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<tbody>
<tr>
<td>Disease extent</td>
<td>Bone metastases</td>
<td>Chest wall recurrence</td>
<td>Pleural metastases</td>
<td>Bone metastases</td>
<td>Pleural metastases</td>
<td>Bone metastases</td>
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<tr>
<td></td>
<td></td>
<td>Bone metastases</td>
<td>Malignant pleural effusion</td>
<td>Marrow involvement</td>
<td>Malignant pleural effusion</td>
<td>Marrow involvement</td>
</tr>
<tr>
<td>Previous therapy</td>
<td>3 chemotherapy regimens</td>
<td>5 chemotherapy regimens</td>
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<td>3 chemotherapy regimens</td>
<td>1 chemotherapy regimen</td>
</tr>
<tr>
<td></td>
<td>3 radiotherapy courses</td>
<td>1 BMT regimen</td>
<td>1 BMT regimen</td>
<td>2 radiotherapy courses</td>
<td>2 radiotherapy courses</td>
<td>1 BMT regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 BMT regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dose level (mCi/m²)</td>
<td>15</td>
<td>15</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
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<tr>
<td>Amount administered (mCi)</td>
<td>27.0</td>
<td>24.9</td>
<td>46.0</td>
<td>35.5</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 2</td>
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<tr>
<td></td>
<td>Nadir 0.7 at day 31</td>
<td>Nadir 0.6 at day 57</td>
<td>Nadir 0.8 at day 46</td>
<td>Nadir 0.8 at day 33</td>
<td>0.3 at day 30</td>
<td>0.4 at day 25</td>
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<tr>
<td></td>
<td>4 days until &gt;1.0</td>
<td>7 days until &gt;1.0</td>
<td>8 days until &gt;1.0</td>
<td>17 days until &gt;1.0</td>
<td>≥0.5 from days 22 to 34</td>
<td>≥0.5 from days 24 to 26</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>G-CSF given</td>
<td>G-CSF given</td>
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</tr>
<tr>
<td></td>
<td>Nadir 34K at day 29</td>
<td>Nadir 46K at day 43</td>
<td>Nadir 118K at day 28</td>
<td>Grade 1</td>
<td>Grade 1</td>
<td>Grade 1</td>
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<td></td>
<td>6 days until &gt;50K</td>
<td></td>
<td></td>
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<td>Days stem cells reinfused</td>
<td>Day 5</td>
<td>Day 5</td>
<td>Day 5</td>
<td>Day 18 (&lt;5 cGy)</td>
<td>Day 13 (&lt;5 cGy)</td>
<td>Day 13 (&lt;5 cGy)</td>
</tr>
<tr>
<td></td>
<td>Day 13 (&lt;5 cGy)</td>
<td>Day 14 (&lt;5 cGy)</td>
<td>Day 14 (&lt;5 cGy)</td>
<td>Day 24 (ANC &lt;1000)</td>
<td>Day 16 (ANC &lt;1000)</td>
<td>Day 16 (&lt;5 cGy)</td>
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</table>

* BMT, bone marrow transplant.

* Platelets transfused at 54K due to presence of a small arteriovenous malformation seen on pretherapy brain MRI scan.
Fig. 3 Changes in platelet count and neutrophil counts as a function of days posttherapy for patients treated at dose levels 1 and 2. Fluctuations in counts at dose level 2 are secondary to G-CSF and platelet transfusions. Three patients are reported at each dose level. Each line represents data from an individual patient.

Table 2 Dosimetry estimates (cGy) from imaging infusion (I) and therapy infusion (T)

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Marrow</th>
<th>Liver</th>
<th>Kidney</th>
<th>Heart wall</th>
<th>Total body</th>
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</thead>
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<tr>
<td></td>
<td>Dose (I)</td>
<td>Dose (T)</td>
<td>% reduction DTPA</td>
<td>Dose (I)</td>
<td>Dose (T)</td>
</tr>
<tr>
<td>1</td>
<td>114.1</td>
<td>103.9</td>
<td>9.0</td>
<td>888.9</td>
<td>527.4</td>
</tr>
<tr>
<td>2</td>
<td>136.5</td>
<td>97.0</td>
<td>29.0</td>
<td>600.6</td>
<td>443.8</td>
</tr>
<tr>
<td>3</td>
<td>109.5</td>
<td>76.0</td>
<td>30.6</td>
<td>608.2</td>
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</tr>
<tr>
<td>5</td>
<td>183.0</td>
<td>134.8</td>
<td>26.3</td>
<td>1007.4</td>
<td>975.2</td>
</tr>
<tr>
<td>6</td>
<td>161.6</td>
<td>143.8</td>
<td>11.0</td>
<td>935.3</td>
<td>550.9</td>
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<tr>
<td>7</td>
<td>177.5</td>
<td>177.1</td>
<td>0.2</td>
<td>945.0</td>
<td>798.2</td>
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</table>

Table 3 Urine residence times for $^{111}$In (h)

<table>
<thead>
<tr>
<th>Cumulative fraction of injected dose in urine at 144 h</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
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<tbody>
<tr>
<td>Imaging</td>
<td>0.15</td>
<td>0.14</td>
<td>0.13</td>
<td>0.13</td>
<td>0.01</td>
<td>0.11</td>
</tr>
<tr>
<td>Therapy (Ca-DTPA)</td>
<td>0.29</td>
<td>0.29</td>
<td>0.32</td>
<td>0.34</td>
<td>0.25</td>
<td>0.25</td>
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</table>

was observed with the therapy infusion compared with the imaging infusion. This suggests a favorable influence of DTPA on excretion and normal organ biodistribution of activity with the therapy infusion.

HACA was assayed at 1 month for all six treated patients and at 3 and 5 months for two patients. One patient (patient 6) developed a HACA response by RIA and HPLC at 4 weeks that persisted at 5 months.

Follow-up radiological studies suggested antitumor effects in three patients. Patient 3, with progressive bone and pleural metastases prior to therapy, demonstrated radiologically stable disease for 4 months. Patient 6, with progressive bone and pleural metastases requiring thoracentesis twice in the month prior to therapy, demonstrated stable bone scan findings, stable pleural disease on follow-up CT scans, no reaccumulation of pleural effusion, and 50% reduction of a solid ovarian metastasis for 14 months (Fig. 4). Patient 7, with progressive bone metastases, demonstrated stable disease and reduction of bone pain for 3 months. All other patients had progressive disease on restaging at 6–8 weeks, although patient 5 did have reduction of back pain and narcotic use for approximately 1 month after therapy.

Discussion

RIT of solid tumors remains an active area of investigation. However, solid tumors are less radiosensitive than hematolog-
ical malignancies, resulting in fewer clinical responses before reaching dose-limiting toxicities. Dose-limiting toxicities from RIT have primarily been thrombocytopenia and leukopenia. To further improve on the therapeutic ratio, clinical trials using higher myeloablative doses of RIT with bone marrow transplantation or peripheral stem cell support have recently been explored in patients with B-cell lymphomas (17), myeloid leukemias (18), and breast cancer (19, 20). For solid tumors, some of the most promising results have been in breast cancer. Schier et al. (19) have reported 50% partial responses (four of eight patients) in women with chemotherapy refractory breast cancer with 90Y BrE-3. Richman et al. (20) report responses in one of three patients with advanced breast cancer after high-dose 131I labeled chimeric L6.

Breast cancer also provides an appropriate target for the evaluation of these strategies with anti-CEA radioimmunoconjugates. CEA is commonly expressed in breast cancer, with 50–60% staining positive by immunohistochemistry (5) and with serum CEA elevated in 40–45% of patients with metastatic disease. In addition, an increasing number of investigators have demonstrated successful imaging of primary tumors and lymph node metastases using anti-CEA intact antibody or fragments radiolabeled with 131I, 111In, or 99mTc (21–24), with imaging sensitivities ranging from 79 to 97%.

The objectives of this ongoing trial were to evaluate the feasibility of stem cell supported 90Y-anti-CEA RIT in patients with breast cancer and to determine whether higher activities of radiolabeled antibodies could be administered with stem cell support. Additional objectives included evaluation of any second organ (nonhematological) toxicities and any antitumor effects in this population with disease refractory to standard therapy.

This study demonstrates that cT84.66 anti-CEA does target to CEA-producing breast cancer (Figs. 1 and 2) and that delivery of myeloablative doses of 90Y-cT84.66 anti-CEA with stem cell support is feasible in this heavily pretreated population. All patients demonstrated recovery of blood counts after stem cell reinfusion (Fig. 3). In a recently completed non-stem cell-supported Phase 1 trial in less heavily pretreated patients, a maximum tolerated dose of 22 mCi/m² was reached for 90Y-DTPA-cT84.66. The use of peripheral stem cell reinfusion in this trial allowed for the administration of 22.5 mCi/m² without dose-limiting toxicities, indicating that further escalation of administered activity is possible. To date, no other significant second organ toxicities have been observed.

DTPA was administered for 72 h after the therapy infusion with the expectation that DTPA would bind any 90Y not bound to the antibody, hastening excretion of this activity and potentially reducing radiation doses to normal organs. Results from this trial suggest that this was the case. As observed in an earlier trial (9), an increase in excretion of a radioactive 5-kDa urinary species was observed with the administration of DTPA after therapy. Estimates of cumulative fraction of injected dose in urine at 144 h demonstrate greater urinary excretion of activity after the therapy/DTPA infusion compared with the imaging infusion (Table 3). This may have favorably altered pharmacokinetics and/or biodistribution, resulting in the lowered marrow and liver dose estimates observed after the therapy infusion (Table 2). Other factors may have also been involved. For example, the initial imaging dose of antibody may have resulted in enhanced metabolism and clearance of the subsequent therapy dose administered 1 week later.

Although no objective responses have yet been observed, antitumor effects were documented. Three of six patients with progressive disease refractory to other therapies demonstrated stable disease of 3–14 months duration, with 50% reduction of one metastatic site in one patient (Fig. 4).

In summary, preliminary results from this ongoing Phase I trial are promising and demonstrate the feasibility and potential for antitumor effects of stem cell supported 90Y-cT84.66 therapy in patients with CEA-producing breast cancer.

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References


Initial Clinical Experience Evaluating Yttrium-90-Chimeric T84.66 Anticarcinoembryonic Antigen Antibody and Autologous Hematopoietic Stem Cell Support in Patients with Carcinoembryonic Antigen-producing Metastatic Breast Cancer

Jeffrey Y. C. Wong, George Somlo, Tamara Odom-Maryon, et al.


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