Targeted Chemoradiation in Metastatic Colorectal Cancer: A Phase I Trial of $^{131}$I-huA33 with Concurrent Capecitabine

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huA33 is a humanized antibody that targets the A33 antigen, which is highly expressed in intestinal epithelium and more than 95% of human colon cancers but not other normal tissues. Previous studies have shown huA33 can target and be retained in a metastatic tumor for 6 wk but eliminated from normal colonocytes within days. This phase I study used radiolabeled huA33 in combination with capecitabine to target chemoradiation to metastatic colorectal cancer. The primary objective was safety and tolerability of the combination of capecitabine and $^{131}$I-huA33. Pharmacokinetics, biodistribution, immunogenicity, and tumor response were also assessed. Methods: Eligibility included measurable metastatic colorectal cancer, adequate hematologic and biochemical function, and informed consent. An outpatient scout $^{131}$I-huA33 dose was followed by a single-therapy infusion 1 wk later, when capecitabine was commenced. Dose escalation occurred over 5 dose levels. Patients were evaluated weekly, with tumor response assessment at the end of the 12-wk trial. Tumor targeting was assessed using a $\gamma$ camera and SPECT imaging. Results: Nineteen eligible patients were enrolled. The most frequently observed toxicity included myelosuppression, gastrointestinal symptoms, and asymptomatic hyperbilirubinemia. Biodistribution analysis demonstrated excellent tumor targeting of the known tumor sites, expected transient bowel uptake, but no other normal tissue uptake. $^{131}$I-huA33 demonstrated a mean terminal half-life and serum clearance suited to radioimmunotherapy ($T_{1/2}$: 100.24 ± 29.92 h, and clearance, 36.72 ± 8.01 mL/h). The mean total tumor dose was 13.8 ± 7.6 Gy (range, 5.1–26.9 Gy). One patient had a partial response, and 10 patients had stable disease. Conclusion: $^{131}$I-huA33 achieves specific targeting of radiotherapy to colorectal cancer metastases and can be safely combined with chemotherapy, providing an opportunity to deliver chemoradiation specifically to metastatic disease in colorectal cancer patients.

Key Words: radioimmunotherapy; chemotherapy; colorectal cancer

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Although the now widespread use of chemotherapeutics such as oxaliplatin and irinotecan, increasingly combined with targeted therapies such as bevacizumab and cetuximab, has led to a significant improvement in prognosis of patients with metastatic colorectal cancer (CRC) there was an estimated 51,690 CRC deaths in the United States in 2012 (1). There remains a need for continued development of new agents with improved tumor-targeting potential and antitumor activity if the prognosis of such patients is to be extended beyond the current 20 mo with combination therapy (2,3).

Although radioimmunotherapy can lead to significant response rates, prolonged responses, and disease stabilization in hematologic malignancies (4,5), it has yet to significantly affect the outcome of patients with solid tumors. The A33 antigen is an ideal target for the development of therapeutic antibodies for the treatment of CRC, because of its widespread and often high expression level on more than 95% of CRC (6–8). It is also expressed on normal colonic epithelial cells but no other normal tissues (6). The humanized IgG1 antibody huA33 has high affinity for its target antigen (9), is internalized on binding, and is safe and tolerable when given to patients alone (10,11), in combination with chemotherapy (12), and when radiolabeled (13). $^{131}$I-huA33 can cause targeted delivery of radiation to colon cancer cells and is retained in the tumor for 6 wk (13). Elimination from normal colonocytes in around 5 d (with basal turnover) minimizes toxicity to normal gut epithelium. The dose of radiation delivered to the tumor by 1.48GBq/m² of $^{131}$I-huA33 is equivalent to approximately 8–10 Gy (13).

Published evidence that chemotherapy, including 5-fluorouracil (5FU), can radiosensitize target tumor cells led to the concept of combining $^{131}$I-huA33 with capecitabine. Neoadjuvant chemoradiation with infusional 5FU is considered standard care for potentially resectable rectal cancer patients with unfavorable features on initial staging to downstage tumors, improve resectability, and significantly reduce the risk of local recurrence (14–16). More recently, capecitabine has shown efficacy similar to infusional 5FU in this setting, with comparable pathologic responses (17). Synergistic antitumor effects when $^{131}$I-huA33 is combined with 5FU have also been shown in CRC xenografts (18), suggesting this potential synergy also exists when 5FU is combined with radioimmunotherapy. This synergy is partly due to upregulation of intratumoral expression of thymidine phosphorylase by radiation, which is likely to increase intratumoral conversion of capecitabine to 5FU.

Combining $^{131}$I-huA33 with concurrent oral capecitabine has significant promise as a method of optimizing radioimmunotherapy
for CRC, and this Phase I trial aimed to characterize the toxicity profile of this combination; determine tolerable potential dose; and identify biodistribution, pharmacokinetics, and immunogenicity of 131I-huA33 when given in this manner.

MATERIALS AND METHODS

Trial Design

After pretreatment assessments, eligible patients received an outpatient scout dose of 131I-huA33. Pre- and postscout infusion pharmacokinetics and human antihuman antibody (HAHA) analysis and postinfusion uptake of 131I-huA33 in the tumor was confirmed, then 7 ± 2 d later it was followed by inpatient administration of a single-therapy infusion of 131I-huA33. Commencing simultaneously with this 131I-huA33 therapy infusion was oral capecitabine given in 2 divided doses per day from day 1 to day 14 of each 21-d period for a total of 4 cycles. Weekly assessments of clinical adverse events, hematology, serum biochemistry, and HAHA were performed. Whole-body γ imaging was performed 1, 2 or 3, and 4 wk after 131I-huA33 therapy infusion. Tumor restaging was performed 12 wk after 131I-huA33 therapy infusion. This study was approved by the Human Research Ethics Committee of the Austin Hospital, and all patients signed a written informed consent form before participation in the trial.

Production and Administration

All doses of 131I-huA33 were administered intravenously in 100 mL of normal saline containing 5% human serum albumin over approximately 60 min. The scout dose of 5 mg of huA33 was conjugated to 185–206 MBq of 131I, and the therapy dose of 131I comprised a constant dose of huA33 (10 mg/m²) (regardless of dose level), with the 131I administered activity determined by the assigned dose level. Potassium iodide oral drops were commenced immediately before scout 131I-huA33 infusion in all patients (10 drops, 3 times daily) and continued for a total of 4 wk. Capecitabine was self-administered at doses of 1,000–1,500 mg/m²/d (depending on assigned dose level) for 14 d per 21-d cycle, commencing on the day of the therapy infusion. Dose escalation was permitted, provided a minimum of 3 patients completed a treatment cycle without dose-limiting toxicity (DLT). After an interim analysis performed after completion of cohorts 1 and 2, a protocol amendment was required to modify subsequent capecitabine doses to allow continued patient accrual at higher 131I-huA33 dose levels. The dose escalation after approval of this amendment is shown in Table 1.

Patient Eligibility

Patients were eligible for enrollment if they were at least 18 y old with histologically proven CRC, measurable metastatic disease (at least 1 lesion ≥ 2-cm diameter on CT), and able to give valid informed consent. Full inclusion and exclusion criteria and the definition of evaluability, DLT, and maximum-tolerated dose are included in the supplemental materials (supplemental materials are available at http://jnm.snmjournals.org).

Radiolabeling of huA33

huA33 was radiolabeled using an established radiolabeling technique (13,19). Antibody preparations equal to or better than 95% isotope bound to protein were used, and binding of 131I-huA33 to A33-positive cells was shown to reduce by only 13% after a 7-d incubation in human serum at 37°C. Purified 131I-huA33 was adjusted to 5% human serum albumin and filtered through a sterile 0.22-μm filter before use.

Biodistribution and Dosimetry

γ-camera imaging with anterior and posterior whole-body scans using conjugate-view methodology was performed 1–4 h after the scout 131I-huA33 infusion and then on day 1, day 2 or 3, day 4 or 5, and continued after therapy 131I-huA33 infusion at week 2, week 3 or 4, and week 5. SPECT imaging of relevant areas of disease was also performed. Image analysis was performed by examination of whole-body and SPECT images by experienced nuclear medicine physicians. Normal biodistribution was confirmed from the scout imaging before the therapy infusion in all patients.

Images were analyzed and dosimetry calculation performed by determining regions of interest (whole body, normal organs, and tumor) and calculation of time–activity curves and organ residence times. Organ radiation dosimetry was calculated from data obtained from the OLINDA software package (20).

Pharmacokinetics

Serum obtained from patients after infusion of 131I-huA33 was aliquoted and counted with appropriate standards in a γ-scintillation counter (Packard Instruments). The results were expressed as percentage injected dose per liter and mg/mL. A 2-compartment intravenous bolus model with macroparameters, no lag time, and first-order elimination (WNL Model 8) was fitted to individual labeled infusions for each subject using unweighted nonlinear, least-squares with WinNonLin version 5.2 (Pharsight Co.).

HAHA Response

Antibody responses against humanized antibodies (HAHA) induced after treatment of patients with huA33 monoclonal antibody were analyzed by surface plasmon resonance technology using a BIAcore 2000 instrument as previously described (21).

Tumor Response Assessment

Tumor response was assessed by CT scanning, according to the Response Evaluation Criteria in Solid Tumors (22). CT was performed before study entry and at the end of study assessment. Patients were evaluable for response once they had completed a full cycle of capecitabine. Serum carcinoembryonic antigen was also assessed at baseline and at the end of study assessment.

Statistical Considerations

Biodistribution, tumor and normal organ dosimetry, and pharmacokinetic parameters were examined quantitatively, and descriptive statistics such as mean, SD, and independent sample t tests were used to analyze these data.

RESULTS

Patient Characteristics

Nineteen patients (mean age, 59 y; range, 41–69 y; 6 women and 13 men) were eligible and enrolled. All patients had progressive metastatic disease at study entry, most commonly lung, liver, or lymph node metastases, but prior oncologic treatment received varied considerably. Patient and disease characteristics and prior treatment are summarized in Table 2.
TABLE 2
Patient Characteristics, Prior Oncologic Therapy, and Trial Outcome

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Cohort</th>
<th>Eastern Cooperative Oncology Group</th>
<th>Primary site</th>
<th>Prior chemotherapy with or without radiotherapy</th>
<th>Sites of disease at study entry</th>
<th>Screening carcinoembryonic antigen</th>
<th>End-of-study carcinoembryonic antigen</th>
<th>Overall response</th>
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<td>Liver, lung, LN</td>
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<td>1.4</td>
<td>PD</td>
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<td>1</td>
<td>0</td>
<td>Colon</td>
<td>FX</td>
<td>LN</td>
<td>3.1</td>
<td>3.7</td>
<td>PD</td>
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<td>Colon</td>
<td>A5FU</td>
<td>LN</td>
<td>258</td>
<td>544</td>
<td>PD</td>
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<td>FX, R, M</td>
<td>Liver, lung, omentum</td>
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<td>NXRT, FX, FI</td>
<td>Liver, lung, LN</td>
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<td>Liver, pelvis</td>
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<td>0</td>
<td>Rectum</td>
<td>NXRT</td>
<td>Lung, omentum, mesentry</td>
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<td>1.6</td>
<td>PD</td>
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<td>108</td>
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<td>16.6</td>
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<td>Lung, liver, psoas, paravertebral mass</td>
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<td>Colon</td>
<td>I, FX</td>
<td>Lung, liver</td>
<td>1,005</td>
<td>1,538.3</td>
<td>PD</td>
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<tr>
<td>114</td>
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<td>0</td>
<td>Colon</td>
<td>FX</td>
<td>Suprapubic mass, abdominal wall, bowel</td>
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<td>20.5</td>
<td>SD</td>
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<tr>
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<td>Colon</td>
<td>FX</td>
<td>Lung, liver</td>
<td>15.2</td>
<td>57.4</td>
<td>PD</td>
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<tr>
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<td>NXRT, I</td>
<td>Lung, liver</td>
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<td>408.2</td>
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<tr>
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<td>Lung</td>
<td>29.1</td>
<td>16.7</td>
<td>SD</td>
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<tr>
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<td>55</td>
<td>5</td>
<td>0</td>
<td>Rectum</td>
<td>FX, R + C + B</td>
<td>Lung, liver, lymph nodes</td>
<td>NA</td>
<td>183.5</td>
<td>SD</td>
</tr>
</tbody>
</table>

NXRT = neoadjuvant chemoradiation (5FU); LN = lymph nodes; FX = FOLFOX; A5FU = adjuvant 5FU; SD = stable disease; RI = FOLFIRI; M = mitomycin; I = irinotecan; C = cetuximab; B = bevacizumab; NA = not assessable.
Of the 19 patients enrolled, 1 withdrew consent to remain on the study after 33 d because of side effects and was not evaluable for response. Of the remaining 18 patients, all were evaluable and 12 completed the full study. Of the 6 patients who did not complete the study, 2 were withdrawn because of progressive disease (PD), 3 because of toxicity, and 1 after diagnosis of a second unrelated malignancy (non-Hodgkin lymphoma).

Toxicity

Three patients were withdrawn as a result of excessive toxicity, 2 of whom had DLT (including patient 105, who had febrile neutropenia and thrombocytopenia, and patient 109, who experienced severe diarrhea). The commonest adverse events deemed related to the combination of 131I-huA33 and capcitabine are detailed in Supplemental Table 1. Myelosuppression (particularly thrombocytopenia) was common, but most patients were asymptomatic. Toxicity relating to the addition of capcitabine was mild and self-limiting, with diarrhea, nausea, and asymptomatic hyperbilirubinemia being most commonly reported. One patient developed cardiotoxicity (grade 3 chest pain associated with ST elevation) secondary to capcitabine, which resolved with treatment. Mild and self-limiting, with diarrhea, nausea, and asymptomatic hyperbilirubinemia being most commonly reported. One patient developed cardiotoxicity (grade 3 chest pain associated with ST elevation) secondary to capcitabine, which resolved with treatment.

Biodistribution and Dosimetry

The pattern of 131I-huA33 biodistribution after the scout infusion was initially consistent with blood-pool activity, with gradual appearance of some bowel uptake, and specific uptake in sites of known metastatic disease over time (Fig. 1). The positron-emission tomography images demonstrated identical distribution and tumor uptake of 131I-huA33 in all patients (Fig. 1). This biodistribution pattern was identical to that seen in prior huA33 trials (10,13). 131I-huA33 tumor uptake was present for up to 5 wk after therapy infusion, with clearance from the blood pool and bowel during this time.

Tumor dosimetry was performed in 10 of 19 patients, with 9 patients having lesions too small or close to the blood-pool areas to allow accurate quantitative analysis. The mean total tumor dose was 13.83 ± 7.61 Gy (range, 5.06–29.64 Gy) (Table 3). The mean specific-absorbed dose for the liver, spleen, kidney, and lung was 0.12 ± 0.03, 0.18 ± 0.06, 0.14 ± 0.05, and 0.09 ± 0.03 cGy/MBq, respectively. The red marrow specific-absorbed dose ranged from 0.041 to 0.078 cGy/MBq.

Pharmacokinetics and HAHA

The following are the mean pharmacokinetic analysis results calculated from the scout dose for 131I-huA33: T1/2a, 15.78 ± 4.68 h; T1/2b, 100.24 ± 20.92 h; clearance, 36.72 ± 8.01 mL/h; and V1 (volume of central compartment), 3,204.26 ± 605.59 mL. A weak, intermittent positive HAHA response was observed by BIACore analysis in 6 of 19 patients (patients 111, 113, 115, 117, 118, and 119). A robust, sustained response of low titer was observed in 1 of 19 patients (patient 112).

Response

Of the 18 patients evaluable for tumor response, there was 1 partial response (PR), 10 stable disease, and 7 PD. Patient 102 had a 31.6% reduction in the sum of his target lesions at the end of study assessment, but as he developed a new sternal metastasis was classified as PD overall. Patient 108 had a PR, which lasted for 15.2 mo. Of the 10 patients who had stable disease, there was a reduction in percentage change in the sum of target lesion diameters in 4 patients (by 9.7%–23.1%). The percentage change in sum of target lesions for the 18 patients evaluable for response is shown in Figure 2. Median progression-free survival for all patients was 5 mo (range, 1.0–48.6 mo). For the 11 of 18 (61%) evaluable patients with stable disease or PR at study completion, the median progression-free survival was 6 mo (range, 4.4–48.6 mo). Five patients were lost to follow-up 7–20 mo after completing the study. The median overall survival for 14 of 19 (73.7%) patients with recorded death date was 28.7 mo (range, 3.2–61.9 mo).

DISCUSSION

The combination of radioimmunotherapy with chemotherapy to induce enhanced antitumor effects has been extensively explored in preclinical models (23–28) and in a small number of phase I/II studies in patients with advanced solid tumors, with a suggestion of antitumor activity in some (29–34). The aim of this approach is to use chemotherapy as a radiosensitizer, so that cancer cell cycle is arrested in the radiosensitive G2/M phase and efficacy is improved. After our previous trial demonstrated that 131I-huA33 could be delivered as a well-tolerated, single infusion to patients with metastatic CRC at doses of up to 1.48 GBq/m2 (13), this study was designed to determine whether this radioimmunotherapeutic could be safely combined with chemotherapy. Preclinical data supporting the ability of chemotherapy to radiosensitize, together with the standard practice for giving neoadjuvant radiation with concurrent infusional 5FU for potentially resectable rectal cancer patients

**FIGURE 1.** Screening 18F-FDG PET (A) and CT (B) scans demonstrate large liver metastasis (white arrowheads). γ-camera imaging (C) after scout (D0–D5) and therapy dose of 131I-huA33 (D14) demonstrate uptake by liver metastasis (white arrowheads) and normal bowel (black arrowhead). D0–D5 = days 0 through 5; D14 = day 14.
with unfavorable features on initial staging (14–16), supported the rationale for combining $^{131}$I-huA33 with capecitabine. Synergistic antitumor effects when $^{131}$I-huA33 is combined with 5FU has also been shown in CRC xenografts (18). The published lower incidence of myelosuppression with capecitabine made it a logical option for combination with radioimmunotherapy, although there was the potential for a higher incidence of gastrointestinal toxicity when combined with an antibody targeting a colon-specific antigen.

The study drug combination was well tolerated, with generally mild gastrointestinal toxicity and 2 probable episodes of cardiac toxicity related to capecitabine, whereas myelosuppression primarily attributable to $^{131}$I-huA33 was predictable and self-limiting. Although DLT was observed early using the initial dose escalation criteria, once an amendment was approved to adjust the capecitabine dose, further escalation of $^{131}$I-huA33 dose was achieved safely. Excellent biodistribution, with tumor targeting in all patients and prolonged intratumoral retention, was consistent with prior huA33 trials (10,13). No definite correlation between percentage change in target lesions and total tumor-absorbed dose was observed, and overall dose delivered to the tumor was modest, ranging from 5.06 to 26.94 Gy. The PR seen in 1 patient and degree of target lesion shrinkage in several other patients demonstrate antitumor activity with this combination that exceeds that documented with $^{131}$I-huA33 alone (13). It is also known that capecitabine has minimal activity in 5FU refractory CRC patients (35), and as all patients in our study had progressed after initial 5FU-based treatment regimes (Table 2), this would indicate that the clinical benefit observed would be unlikely to be due to capecitabine alone. A median progression-free survival of 6 mo and an unexpectedly long-duration median overall survival of 28.7 mo were also observed, supporting a potential synergy and improved efficacy through the addition of capecitabine to $^{131}$I-huA33 radioimmunotherapy.

Although radioimmunotherapy has clearly been established as an effective treatment strategy for patients with lymphoma (36,37) in solid tumors, radioimmunotherapy alone has had modest response rates, and the addition of chemotherapy has emerged as an important strategy to improve response rates (34). The optimization of antibody kinetics (e.g., multistep targeting) and isotopes (e.g., $^{177}$Lu) has also emerged as an important factor in improving response rates (36,38). In view of the impressive results recently reported for $^{177}$Lu and $^{90}$Y peptide receptor therapy in the treatment of neuroendocrine tumors (39,40), it is clear that targeted radiation to tumors has significant potential for therapeutic efficacy, and our study provides further evidence of the potential for this approach.

**CONCLUSION**

This study demonstrated that targeted chemoradiation in the form of $^{131}$I-huA33 combined with capecitabine can be administered safely and effectively to patients with metastatic CRC. Biodistribution, pharmacokinetic, and tumor-targeting properties remained favorable with this combination treatment, and the clinical benefit (PR/stable disease) seen in 11 of 18 (61%) evaluable patients and long median overall survival (28.7 mo) suggest potential synergy and improved efficacy through the addition of capecitabine to $^{131}$I-huA33 radioimmunotherapy. Further investigation of this strategy using multistep targeting or alternate therapeutic radionuclides (e.g., $^{177}$Lu) is warranted.
REFERENCES


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