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Dose Escalation and Dosimetry of First-in-Human α Radioimmunotherapy with ^{212}Pb-TCMC-Trastuzumab

Ruby Meredith[1], Julien Torgue[2], Sui Shen[1], Darrell R. Fisher[3], Eileen Banaga[2], Patty Bunch[1], Desiree Morgan[1], Jinda Fan[1], and J. Michael Straughn, Jr.[1]

[1]*Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, Alabama;* [2]*AREVA Med, Bethesda, Maryland; and* [3]*Dade Moeller Health Group, Richland, Washington*

Our purpose was to study the safety, distribution, pharmacokinetics, immunogenicity, and tumor response of intraperitoneal ^{212}Pb-TCMC-trastuzumab (TCMC is S-2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra(2-carbamoylmethyl)cyclododecane) in patients with human epidermal growth factor receptor type 2 (HER-2)–expressing malignancy. **Methods:** In a standard 3 + 3 phase 1 design for dose escalation, ^{212}Pb-TCMC-trastuzumab was delivered intraperitoneally less than 4 h after administration of trastuzumab (4 mg/kg intravenously) to patients with peritoneal carcinomatosis who had failed standard therapies. **Results:** Five dosage levels (7.4, 9.6, 12.6, 16.3, and 21.1 MBq/m^2) showed minimal toxicity at more than 1 y for the first group and more than 4 mo for others. The lack of substantial toxicity was consistent with the dosimetry assessments (mean equivalent dose to marrow, 0.18 mSv/MBq). Radiation dosimetry assessment was performed using pharmacokinetics data obtained in the initial cohort (n = 3). Limited redistribution of radioactivity out of the peritoneal cavity to circulating blood, which cleared via urinary excretion, and no specific uptake in major organs were observed in 24 h. Maximum serum concentration of the radiolabeled antibody was 22.9% at 24 h (decay-corrected to injection time) and 500 Bq/mL (decay-corrected to collection time). Non–decay-corrected cumulative urinary excretion was 6% or less in 24 h (2.3 half-lives). Dose rate measurements performed at 1 m from the patient registered less than 5μSv/h (using portable detectors) in the latest cohort, significantly less than what is normally observed using nuclear medicine imaging agents. Antidrug antibody assays performed on serum from the first 4 cohorts were all negative. **Conclusion:** Five dose levels of intraperitoneal ^{212}Pb-TCMC-trastuzumab treatment of patients with peritoneal carcinomatosis showed little agent-related toxicity, consistent with the dosimetry calculations.

Key Words: radioimmunotherapy; dosimetry; radionuclide; alpha; ^{212}Pb-TCMC-trastuzumab

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The spread of tumor in the peritoneal cavity is an adverse factor and therapeutic challenge for a variety of malignancies. Multiple prior experiences in ovarian cancer have shown that the high failure rate in the peritoneal cavity despite removal of all visible disease followed by adjuvant chemotherapy can be reduced by radionuclide therapy (*1–5*). Most intraperitoneal radionuclide therapies of ovarian cancer have used β-emitter antibody conjugates (radioimmunotherapy) and have resulted in dose-limiting marrow suppression (*1–10*). Less toxicity is projected using radionuclides with shorter half-lives, because less radioactivity would distribute systemically (*11*). Additionally, the application of the more radiobiologically potent α emitters such as the ^{212}Pb/^{212}Bi parent–daughter pair (^{212}Pb half-life, 10.6 h) or ^{211}At (half-life, 7.2 h) should improve efficacy over prior β-emitter radioimmunotherapy while limiting irradiation of neighboring healthy cells (*12*). This first-in-human phase I trial of ^{212}Pb-TCMC-trastuzumab (TCMC is S-2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra(2-carbamoylmethyl)cyclododecane) provided a critical opportunity to assess the safety, toxicity, immunogenicity, serum pharmacokinetics, urinary excretion, imaging, body count biodistribution, dosimetry, and tumor response to this agent. Among other α emitters in clinical trials, dose escalations have been well tolerated, without dose-limiting toxicity (*13*). Intraperitoneal administration of ^{211}At-Mx (Fab′)$_2$ has been under study as treatment of ovarian cancer for several years (*14*). These studies have shown low risk of adverse events through the highest dose level, which was a 24-h dwell of 1.5 L at 200 MBq/L. The low toxicity was predicted by a calculated effective dose of less than 2 Sv (*15*). Although there is no current laboratory or imaging measure of efficacy, the preclinical investigation suggests that dose is adequate for control of targeted microscopic disease clusters (*16*).

MATERIALS AND METHODS

Trial Design

This phase I trial, sponsored by AREVA Med and conducted at a single clinical site (University of Alabama at Birmingham, first 5 cohorts), used a single intraperitoneal injection of the investigational agent, ^{212}Pb-TCMC-trastuzumab, in patients with human epidermal growth factor receptor type 2 (HER-2)–expressing malignancies mainly confined to the peritoneal cavity who had failed standard therapy. The clinical protocol was approved by the Western Institutional Review Board and was conducted under an investigational new drug application. Three patients were to be treated at each level, with expansion to 6 patients if dose-limiting toxicity developed. Dose escalation (radioactivity per m^2 of body surface) was 30% per cohort. HER-2 expression of at least 1+ by immunohistochemistry in more than 10% of the cells was deemed acceptable for gastric cancer. Initially, reactivity in 30% of cells was required for nongastric malignancies but was reduced to 10% or more after patient 10. This trial uses trastuzumab as a targeting agent in the intraperitoneal cavity not

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For correspondence or reprints contact: Ruby Meredith, Department of Radiation Oncology, University of Alabama at Birmingham, 1700 6th Ave. S., Birmingham, AL 35249.
E-mail: lobrown@uabmc.edu
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as a primary therapy where 2+ expression is desired for breast cancer patients. The less stringent requirement of 1+ is consistent with expression of 100,000 receptors per cell, which may be approximately 100 times higher than on the normal cells.

Alternatively, elevated HER-2 serum level by enzyme-linked immunosorbent assay (ELISA) was sufficient, and 1 patient was allowed to be treated whose expression value met serum criteria when rounded off to the nearest whole number. Patients needed to have free flow of fluid in the peritoneal cavity and were excluded for serious cardiac dysfunction, left ventricular ejection fraction less than 50%, poor organ function (defined as any of the following: elevated creatinine, total bilirubin greater than 1.5 times normal, aspartate amino transferase and alanine amino transferase greater than 2.5 times normal, absolute neutrophil counts less than 1,500/μL, and platelets less than 100,000/μL), or other conditions that might compromise safety. Other exclusion criteria included Eastern Cooperative Oncology Group performance status greater than 2, pregnancy or breast feeding, evidence of bowel obstruction or transmural involvement, prior radiation to the whole abdomen, prior intraperitoneal radionuclide therapy, stem cell transplant, history of HIV or hepatitis B antibody positivity, or detectable antibody to trastuzumab. Patients were excluded for a history of cumulative anthracycline therapy exceeding 200 mg/m^2 for doxorubicin or a comparable low dose of other anthracyclines.

Eligible, consenting adult patients were housed in a Clinical Research Unit where they received a single intraperitoneal injection of ^{212}Pb-TCMC-trastuzumab in 50 mL less than 4 h after intravenous trastuzumab (4 mg/kg). The standard intravenous loading dose of 4 mg of trastuzumab per kilogram was given to saturate systemic receptors as the tumor targets were in the peritoneal cavity. This procedure was used to minimize the chance of any radioactivity localization to tissues outside the peritoneal cavity, especially the heart, because trastuzumab has been associated with cardiac toxicity. Additional saline was instilled into the peritoneal cavity before and after ^{212}Pb-TCMC-trastuzumab, for a total volume of up to 1,000 mL.

Pharmacokinetics

Posttreatment serum pharmacokinetics, urinary excretion, and biodistribution studies were performed. Blood samples were obtained at 2 and 24 h on all patients. In the first cohort, additional samples were taken immediately after infusion and at 8, 12, 18, and 63 h; complete urine was collected for 24 h. The details of methods have been reported previously (*17*). Whole-body anterior and posterior γ-camera images (peak window at 238.6 keV) were acquired after treatment and repeated at 18–24 h as reported (*17*). The biodistribution of ^{212}Pb-TCMC-trastuzumab was confirmed with probe counts immediately after treatment and at 3 additional times over 24 h. Probe measurements were taken at the axilla, the mid femur, the umbilicus, and over the sternum using the Inspector 1000 portable radiation detector (Canberra Industries).

Radiation Dosimetry

Dosimetry data included measurements of fraction of administered ^{212}Pb activity remaining in the whole body, blood serum, peritoneal cavity (injection site), and urine for various time points after infusion. These data represented the decay-corrected (biologic) retentions. Whole-body imaging did not demonstrate significant radionuclide uptake in any major organ or tissue for separate quantization. The standard MIRD dosimetry approach was used to calculate organ doses, as follows (*18,19*). Uptake and retention in the peritoneal cavity and in the whole body were plotted. Mathematic functions were fit to the effective (not decay-corrected) data. The remainder of the whole-body activity, assumed to be distributed uniformly at low levels in all other organs and tissues, was determined by subtracting activity in the peritoneal cavity from that in the total body. The functions representing the time–activity curves were then integrated to determine the total disintegrations assigned to the major source regions. Corrections were made for patient weight, and then the radiation-absorbed doses to the major organs and the whole body were calculated using the software OLINDA (version 1.1; Vanderbilt University, 2007) (*20*).

The dynamic bladder model was not used; the bladder wall was assumed to be part of the remainder tissues, and only γ cross-organ dose was considered.

Dosimetry Assumptions

Administered activity in the peritoneal fluid lies external to the organs, with radioactivity moving by gradual transfer via blood to the circulatory system and urinary excretion. Blood is a transfer compartment that is uniformly distributed in every organ or tissue and the whole body and does not represent a separate organ or tissue. Therefore, circulating radioactivity imparts a radiation dose to the remainder of the whole body outside the peritoneal cavity before excretion. A second component of dose involves γ radiation to the remainder of the whole body from activity in the peritoneal fluid. We calculated radiation doses for the α, β, and γ components of ^{212}Pb through its complete decay chain. ^{212}Pb resides in equilibrium with its daughters at all time points; daughters include ^{212}Bi, ^{212}Po, and ^{208}Tl (Fig. 1) (*21*). The equilibrium dose constant for ^{212}Pb in equilibrium with daughter products is 18.061 (g-cGy/μCi-hr) or 5.38×10^{-10} kg-Gy/Bq-hr ($=4.96 \times 10^{-8}$ kg-Gy/Bq through complete decay). The radiation dose to the peritoneal fluid was calculated by integrating the total number of radioactive transformations, converting to energy units, and dividing by the mass using standard absorbed dose equations and accounting for all emissions for ^{212}Pb/^{212}Bi and their daughter products through complete decay.

[**Fig. 1**]

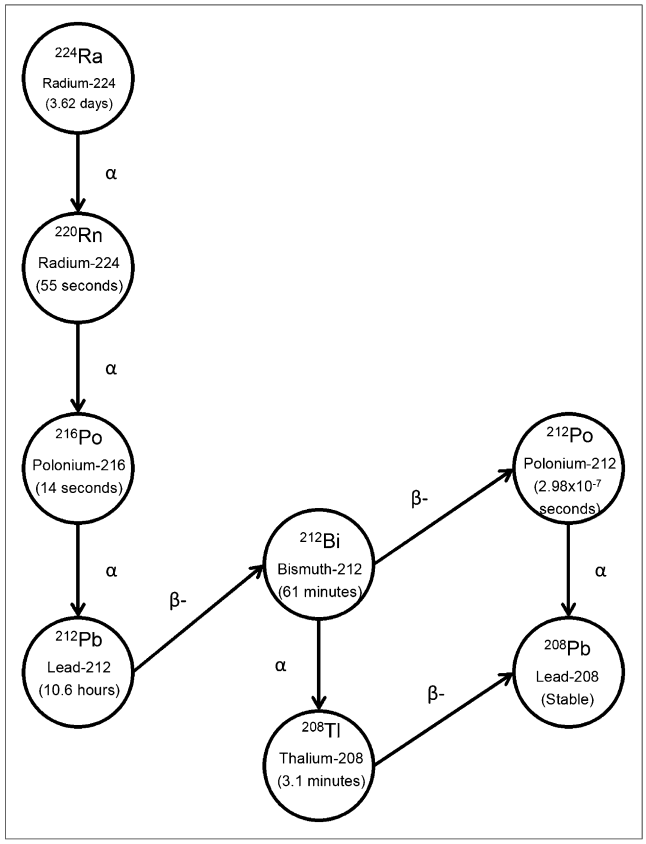

FIGURE 1. Decay scheme of ^{212}Pb includes abundant α emissions of 6.1 and 8.8 MeV, respectively, from its daughters ^{212}Bi and ^{212}Po.

Toxicity Monitoring

The patients were followed for toxicity as defined in the Common Terminology Criteria for Adverse Events (version 4.03; National Cancer Institute). As a precautionary measure (based on prior studies of other α-emitter conjugates), adjuvant medications were initially used. A saturated solution of potassium iodide (SSKI) was initiated the evening before treatment and continued for 3 d. Furosemide (40 mg) was also started the day before ^{212}Pb-TCMC-trastuzumab and used for 10 d then followed by spironolactone (100 mg) daily for 6 mo as renal protective agents. After 10 patients, the SSKI was discontinued and the diuretic use was shortened. ELISA testing of 6-wk serum samples was performed to determine whether there was any evidence of an immune response to TCMC-trastuzumab.

Patient Population

Sixteen patients with HER-2–expressing malignancies who had failed standard therapy were treated at 5 dose levels. Fifteen of the 16 patients were women with recurrent ovarian cancer (or primary peritoneal carcinomatosis), and the only male patient (patient 6) had colon cancer. Patient 15 was African American; all others were Caucasian (age, 46–83 y) and had undergone definitive surgery plus standard adjuvant chemotherapy as initial treatment. After relapse, patients had a variety of other therapies as salvage before ^{212}Pb-TCMC-trastuzumab. All patients met the eligibility criteria as described above (or described as exception below); some had symptomatic ascites, but only 1 had required paracentesis for relief.

Investigational Agent ^{212}Pb-TCMC-Trastuzumab

Trastuzumab is a Food and Drug Administration–approved humanized monoclonal antibody (Genentech), which has therapeutic efficacy by immunologic mechanisms in tumors that overexpress the HER-2 receptor (*22*). TCMC-trastuzumab was provided in a form for further manufacturing of an investigational drug product for human use. Radiolabeling and release testing was performed at University of Alabama at Birmingham. The details of manufacturing and quality assurance have been reported previously (*17*).

RESULTS

Three to 4 patients were treated at each of 5 dose levels (7.4, 9.6, 12.6, 16.3, and 21.1 MBq/m^2) with 30% increase per level. Although there was no toxicity that triggered expansion of any cohort to more than 3 patients, the administered activity for patient 8 fell short of the desired level. Because the administered activity was consistent with that of the prior cohort, she was added as a fourth patient to cohort 2.

Toxicity Profile

The intraperitoneal ^{212}Pb-TCMC-trastuzumab treatment was well tolerated, with most of the adverse events attributed to other medications and conditions rather than the investigational agent. Complaints were considered unrelated if ongoing before therapy and not worsened or if they developed after therapy but were more likely related to other medications and conditions. Most early adverse events not present before therapy were related or attributed to the adjuvant diuretics or intravenous trastuzumab, rather than the investigational agent ^{212}Pb-TCMC-trastuzumab. All patients had placement of a temporary 8 French catheter that was removed less than 1 wk after therapy. One patient had perforation of the bowel at catheter placement; this patient required hospitalization for peritonitis, which delayed her therapy for 1 wk. No sequelae were observed in the subsequent 6 mo.

[**Table 1**] Table 1 lists the grade of each adverse event for individual patients as related, unrelated, or of unknown relationship to study drug and the total percent (%) affected at the right. For example, unrelated grade 1 abdominal pain or tenderness was noted in 3 patients and grade 2 in 1 patient. ^{212}Pb-TCMC-trastuzumab–related grade 1 was noted in 2 patients, for a total of 37.5% affected.

In addition to the adverse events in Table 1, 5 patients developed asymptomatic, transient elevation in one or more liver function tests in the initial 6 wk, whereas patient 14 developed elevation that persisted until drainage of fluid around the liver. These enzyme changes were considered related because no other etiology was judged to be more likely. However, the abnormality occurred with an episode of dehydration in patient 9, with steatosis in patient 11, and cleared in patient 14 after drainage of fluid around the liver. Three others had preexisting enzyme elevations but patient 5 is the only one with continued, progressive abnormalities that coincided with an increase of her liver metastases. Four patients had other laboratory abnormalities including hyper- or hypokalemia, hypomagnesemia, hyponatremia, and elevated creatinine that were judged unrelated to the investigational agent but most were likely related to diuretics and dehydration. One patient also had an unrelated grade 3 coagulopathy.

Initial 6-wk renal monitoring showed transient, increased creatinine to 1.4 mg/dL in an 80-y-old patient and 1.3 in a 74-y-old who became dehydrated. Monitoring renal function up to 1 y for late toxicity revealed 1 patient who had elevation of creatinine to 1.4 mg/dL after prolonged hydronephrosis from renal and ureteral stones; she subsequently had stent placement and creatinine returned to normal. One patient, patient 5, was allowed to be treated despite recently elevated creatinine because she had undergone stent placement for relief of ureteral obstruction. Her creatinine returned to normal by 5 wk after treatment. No proteinuria was observed. Regarding hematologic toxicity, 6 of the 15 women had grade 1–2 anemia before treatment with hemoglobin (9.8–11.9 g/dL). Four of the 6 remained anemic at 6 wk. Overall, most had the same or higher hemoglobin levels at 6 wk.

One patient had a subnormal white blood cell count (WBC) before treatment, and one other patient in cohort 2 developed a transient WBC drop (without neutropenia) to 3,500/μL at week 4. A summary of neutropenia monitoring after treatment is presented in Figure 2 as the mean of all 16 patients, compared with [**Fig. 2**] the upper and lower limits of normal. The neutrophil and total WBC counts showed little variation, and the mean remained within normal limits. Platelet levels were above the lower limits of normal in all patients before treatment and remained such at 6 wk in 15 of the 16 patients. One patient developed a transient grade 1 thrombocytopenia drop to 142,000/μL on day 28, which normalized by day 35. The mean platelet counts for all patients are shown in Figure 2.

To date, follow-up cardiac toxicity monitoring has not shown any arrhythmia on electrocardiogram or decrease in ejection fraction by echocardiography. One patient who had bilateral pleural effusions developed a small pericardial effusion at 12 wk, but ejection fraction did not drop.

No evidence of an immune response to the TCMC-trastuzumab was found in 11 patients at 6 wk after therapy (3 did not have 6-wk samples available and 2 remain to be tested). No patients had signs or symptoms of serum sickness at any time during follow-up.

Pharmacokinetics and Dosimetry

As previously reported, more extensive pharmacokinetics and imaging data were obtained for the first cohort than for the current report (*17*). Whole-body γ-camera images 18–24 h after ^{212}Pb-TCMC-trastuzumab infusion showed no visible redistribution of

TABLE 1
Severity and Relation of Adverse Events to Investigational Agent ^{212}Pb-TCMC-Trastuzumab*

Event	Unrelated	Related	Unknown	% affected
Abdominal pain/tenderness	1, 1, 1, 2	1, 1		37.5
Infection	2, 2, 3, 3, 3			38
Rash or skin burn	1, 1, 2, 2, 3			31
Nausea	1, 1, 1, 2			25
Short of breath	1, 3, 3, 3, 3			31
Fatigue	1, 1, 2			18.75
Short of breath	1, 3, 3			18.75
Small bowel obstruction	3			18.75
Fever/chills	1			12.5
Decreased appetite	1			12.5
Diarrhea	1		1	12.5
Muscle cramps	2			6
Cutaneous fistula	3			6
Thrombosis	2			6
Perforation with peritonitis	3			6
Facial flushing			1	6
Renal stone	3			6
Weight loss	1			6
Sore throat	1			6
Indigestion	1			6
Sinus congestion	2			6

*For patients with small bowel obstruction, associated symptoms including nausea, vomiting, flatus, and abdominal pain are not reported separately unless they occurred at another time.

activity from the peritoneal cavity and no evidence of uptake in any major organ or tissue by direct counting. This observation of prolonged peritoneal cavity localization was confirmed by the serial body counts, which showed the highest external dose rates over the abdomen. Dose-rate measurements performed with hand-held instruments at 1 m over the patient recorded less than 5 μSv/h in the latest cohort, significantly less than what is normally observed with nuclear medicine imaging agents.

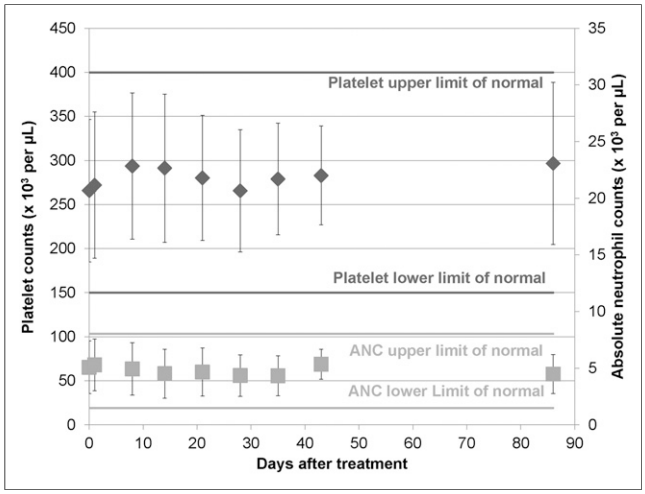

FIGURE 2. Absolute neutrophil counts (ANCs) and platelet counts (mean ± SD) for all patients are compared over time of early follow-up. All means were within reference range.

Multiple posttreatment blood samples were obtained on the first cohort ($n = 3$) up to 63 h (more than 5 half-lives of ^{212}Pb). Serum radioactivity levels for these patients were compared with 2- and 24-h samples from each of the remaining patients in Figure 3. The activity range of all subsequent patients was similar to that of the first cohort. Maximum serum concentration of the radiolabeled antibody was 22.9% at 24 h (decay-corrected to injection time) and 500 Bq/mL (decay-corrected to collection time). The 4 patients with the lowest serum radioactivity levels at 24 h all had ascites. Ascites is usually associated with peritoneal carcinomatosis with tumor obstructing lymphatic channels such that the normal rate of flow from the abdominal cavity is diminished. [Fig. 3]

The whole-body ^{212}Pb retention data fit by linear least-squares analysis to a single exponential showed an effective (not decay-corrected) retention half-time of 9.56–10.4 h and a biologic half-time of 118 h to infinity ($r = 0.999$) for time points within 24 h. The peritoneal cavity ^{212}Pb retention data fit a single exponential having an effective retention half-time of 8.8–10.4 h and a biologic half-time of 60.9 h to infinity ($r = 0.999$). The integrated residence time (normalized number of disintegrations or time-integrated activity coefficient), the input value to OLINDA/EXM in Bq-hr/Bq, was found to be 12.8–15.0 h.

The remainder of body activity was plotted by linear splines and was integrated. The tail of the remainder activity curve was fit to a single exponential having a maximum retention half-time of

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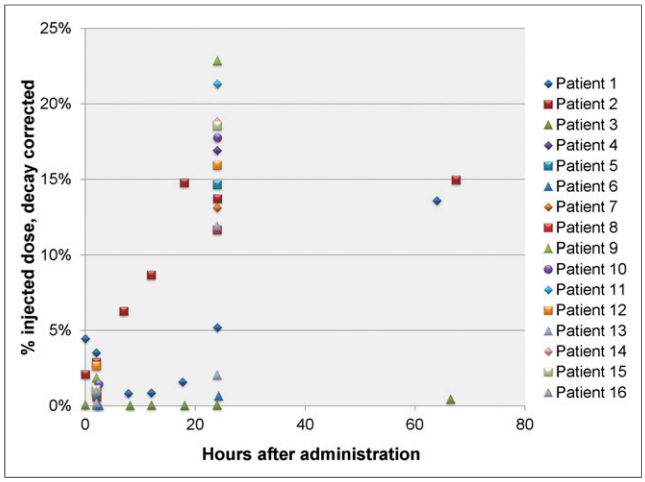

FIGURE 3. Serum levels of radioactivity after intraperitoneal ^{212}Pb-TCMC-trastuzumab are compared as decay-corrected percentage injected dose at 2 and 24 h and up to 63 h for first cohort.

10.6 h (physical half-life of ^{212}Pb), yielding integral area-under-curve residence time values of 0.015–1.323 h.

[**Table 2**] Table 2 provides organ equivalent doses in units of mSv/MBq administered and includes contribution from daughters ^{212}Bi, ^{212}Po, and ^{208}Tl, assuming the use of an α-particle relative biological effectiveness of 3.0.

Because the actual activity per unit volume may be highly variable over time, only dose to a standard reference volume was provided. All values may be multiplied by the administered activity to obtain actual equivalent dose values. All results were rounded to 3 significant figures. The actual patient weight was used, and organ masses were assumed to match those of a standard reference phantom of similar weight.

Response Assessment

Tumor assessment has been followed by serial standard CT scans and tumor markers. Some measurable lesions decreased, but no patient met criteria for a partial response by Response Evaluation Criteria in Solid Tumors at 6 wk. Outcome in consecutive patients is compared with characteristics and details of therapy in Table 3. Tumor assessment by standard CT using [**Table 3**] 5-mm slice thickness has not been ideal to assess response because most patient tumor sizes were less than 15 mm. When pretreatment was compared, week-4 and -6 posttreatment CA125 levels did not correlate with other clinical parameters. Most had increasing CA125 levels despite some having regression of measurable disease. Only 2 patients had a consistent decrease, and their levels fell within normal limits despite one having a large tumor burden and extensive ascites. CA125 decreased by week 12 for 2 patients

TABLE 2
Organ Equivalent Dose (mSv/MBq) for α Relative Biological Effectiveness (Weighting Factor) = 3.0

Target organ	Patient 1	Patient 2	Patient 3	Average
Adrenals	1.13E−01	5.64E−01	1.32E−02	2.30E−01
Brain	1.09E−01	5.58E−01	6.98E−03	2.25E−01
Breasts	1.09E−01	5.59E−01	7.60E−03	2.25E−01
Gallbladder wall	1.32E−01	5.87E−01	3.99E−02	2.53E−01
Lower large intestine wall	1.41E−01	5.99E−01	5.43E−02	2.65E−01
Small intestine	1.14E+00	6.39E−01	1.01E−01	6.27E−01
Stomach wall	1.20E−01	5.73E−01	2.36E−02	2.39E−01
Upper large intestine wall	1.86E−01	6.48E−01	1.12E−01	3.15E−01
Heart wall	1.10E−01	5.60E−01	8.78E−03	2.26E−01
Kidneys	1.20E−01	5.72E−01	2.32E−02	2.38E−01
Liver	1.15E−01	5.66E−01	1.58E−02	2.32E−01
Lungs	1.09E−01	5.59E−01	8.39E−03	2.25E−01
Muscle	1.15E−01	5.65E−01	1.53E−02	2.32E−01
Ovaries	1.59E−01	6.18E−01	7.64E−02	2.84E−01
Pancreas	1.16E−01	5.68E−01	1.82E−02	2.34E−01
Peritoneal fluid	1.89E+02	3.52E+02	2.07E+02	2.49E+02
Red marrow	9.32E−02	4.42E−01	1.79E−02	1.84E−01
Osteogenic cells	3.86E−01	2.08E+00	3.51E−02	8.34E−01
Skin	1.10E−01	5.60E−01	9.31E−03	2.26E−01
Spleen	1.14E−01	5.65E−01	1.51E−02	2.31E−01
Thymus	1.09E−01	5.59E−01	7.50E−03	2.25E−01
Thyroid	1.09E−01	5.58E−01	7.06E−03	2.25E−01
Urinary bladder wall	1.20E−01	5.73E−01	2.43E−02	2.39E−01
Uterus	1.54E−01	6.10E−01	6.78E−02	2.77E−01
Total body	2.54E+00	4.89E+00	5.57E+00	4.33E+00

TABLE 3
Patient Characteristics Are Compared with Outcome

MBq infused	Age (y)	No. of chemotherapy regimens*	Ascites	Largest tumor (cm) (includes nodes)	No. of masses > 1 cm	HER-2 immuno-histochemistry score	ELISA	Response 6 wk	Mo. since treatment
15	46	5	Limited	3.4	5	2+; >30%	10.3	S	9†
11	67	5	Limited	2.8	5	1+; >30%	NA	S	24
11	83	3	Large	4	2	2+; >30%	9.6	P	14†
13	60	3	0	1.8	5	1+; >30%	12.3	S	18
17	62	1	0	2.5	3	2+; >30%	13.7	P	2†
21	77	2	Large	2.9	1	1+; <10%	14.6	P	2†
21	66	9	0	2.6	4	1+; >30%	12.3	S	11†
19	59	4	0	4.3	3	1+; >30%	14.7	S	14
25	80	2	0	7.2	5	1+; >10%	13.7	S	4†
19	71	3	0	ne	0	1+; >30%	12.2	S	11
31	54	8	0	3.9	4	1+; >30%	NA	S	9
28	68	5	0	4.5	2	NA	16.4	P	9
31	72	2	Large	5.1	5	1+; >30%	18.9	S	8
39	59	4	Limited	1.2	3	1+; >30%	15.2	S	5
40	73	2	0	1.5	1	2+; >10%	NA	S	4
38	61	1	0	1.3	2	1+; >30%	9.2	S	4

*Number of chemotherapy cycles ranged from 6 to 64. Most common regimens contained taxane or platinum, followed by anthracycline, gemcitabine, and topotecan as cytotoxic chemotherapy. Intraperitoneal chemotherapy was a component in a few regimens. Some regimens included bevacizumab, other antibody, vaccine, molecularly targeted inhibitor, or adenoviral vector therapy. Hormonal agents were not considered as regimens.

†Deaths.

S = stable; P = disease progression; NA = not applicable.

who had elevated levels at 4 and 6 wk but no intervening additional therapy.

DISCUSSION

This first-in-human phase I trial of intraperitoneal ^{212}Pb-TCMC-trastuzumab provides safety data and extensive analyses of radioimmunoconjugate biodistribution/pharmacokinetics and radiation dosimetry, which are consistent with prior nonhuman model results (*23,24*). We observed limited redistribution of ^{212}Pb-TCMC-trastuzumab out of the peritoneal cavity and minimal toxicity with 5 dose level escalation. Thus, this study validated projected medical application and the feasibility of on-site manufacture for final product using a radionuclide that requires international shipment.

The rate of the conjugate traversing into the systemic circulation from the peritoneal cavity was found to be consistent with that previously demonstrated after intraperitoneal administration of other antibody radionuclide conjugates (*3,9,14,25*). However, because of the quicker decay of ^{212}Pb, the amount of radioactivity arriving in the systemic circulation was much less than that of most other agents. This was expected and was anticipated to result in less hematologic toxicity than that observed previously with β-emitter conjugates (*12*).

In this study, we found no significant myelosuppression; only 1 patient each developed grade 1 leukopenia (nadir WBC, 3,500/μL, without neutropenia) and grade 1 thrombocytopenia (platelet nadir, 142,000/μL).

The absorbed radiation dose per MBq administered for organs reported here is comparable to those of the nonhuman primate study with ^{212}Pb-TCMC-trastuzumab in which tissue samples were available for correlation with the γ scans and body counts (*21*). The relatively low radiation dose reported here from the dosimetry calculations was consistent with the minimal toxicity observed. These data are closely comparable to dosimetry reported after intraperitoneal administration of another α-emitter radionuclide conjugate, ^{211}At-Mx $(Fab')_2$ (*14,15*).

Neither CA125 nor carcinoembryonic antigen was helpful in assessing response. Carcinoembryonic antigen was within normal limits for all 15 ovarian cancer patients. CA125 was abnormal in most of these patients but did not correlate with change in tumor size, which one might hypothesize could have been due to radioimmunotherapy-related peritoneal inflammation because mesothelial cells are known to be a source of CA125 found in ascites fluid (*26,27*). The intraperitoneal radioimmunotherapy may have resulted in sufficient surface disturbance to elevate the CA125 level even if there was a therapeutic effect. In the future, newer markers specific to ovarian cancer may also contribute to efficacy evaluation (*28*).

Two patients had disease progression with bowel obstruction; the remainder maintained or improved their functional status during the initial 6-wk follow-up. The maximum benefit of intraperitoneal α-emitter therapy is expected to be for microscopic disease whereas

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monitoring in this study was limited by measures of gross disease. Efficacy determined by reduction in size of measurable masses and prolonged progression-free outcome should be sufficient to allow additional study to optimize this form of therapy.

The initial patients in this study received thyroid protection with SSKI. This requirement was based on experience of others with the α-emitter ^{211}At for which thyroid uptake without blocking was higher than any normal organ or tumor after intraperitoneal administration (*14*). In the ^{211}At study, the thyroid uptake was not unexpected because of the observed properties of ^{211}At that are consistent with a heavier analog of iodine. The effect of blocking in later patients reduced the uptake of ^{211}At by more than 15-fold, compared with the initial patients who did not receive blocking. Thyroid uptake was not predicted in the current trial because of the basic ^{212}Pb properties and had not been observed in animal studies but was included as a precautionary measure in the initial patients. After γ imaging of the initial patients confirmed no evidence of uptake, and thyroid function showed no change, the adjuvant SSKI was discontinued.

CONCLUSION

Overall, the properties of ^{212}Pb-TCMC-trastuzumab were expected to provide more potent radiation to targeted malignant cells, while limiting radiation exposure to normal tissues as compared with β-emitter conjugates, due to the shorter half-life and path length of ^{212}Pb α radiation. This first-in-human dose escalation study confirmed the predicted dosimetry and low toxicity. These results were consistent with the prior animal model studies and human experience with α-emitter ^{211}At conjugate. Further study plans for dose escalation and evaluation of optimal timing/integration and potential synergy with other treatment modalities.

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DISCLOSURE

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