Pharmacokinetics and Imaging of ^{212}Pb -TCMC-Trastuzumab After Intraperitoneal Administration in Ovarian Cancer Patients

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Abstract

Purpose: Study distribution, pharmacokinetics, and safety of intraperitoneal (IP) ^{212}Pb -TCMC-trastuzumab in patients with HER-2-expressing malignancy.

Experimental Design: IP ^{212}Pb -TCMC-trastuzumab was delivered, after 4 mg/kg intravenous (IV) trastuzumab, to 3 patients with HER-2-expressing cancer who had failed standard therapies. Patients were monitored for toxicity and pharmacokinetics/dosimetry parameters.

Results: Imaging studies after 0.2 mCi/m^2 (7.4 MBq/m^2) show little redistribution out of the peritoneal cavity and no significant uptake in major organs. Peak blood level of the radiolabeled antibody, determined by decay corrected counts, was $<23\%$ injected dose at 63 hours; maximum blood radioactivity concentration was 6.3 nCi/mL at 18 hours. Cumulative urinary excretion was $\leq 6\%$ in 2.3 half-lives. The maximum external exposure rate immediately post-infusion at skin contact over the abdomen averaged 7.67 mR/h and dropped to 0.67 mR/h by 24 hours. The exposure rates at the other positions monitored (axilla, chest, and femur) decreased as a function of distance from the abdomen. The data points correlate closely with ^{212}Pb physical decay ($T_{1/2} = 10.6$ hours). Follow-up >6 months showed no evidence of agent-related toxicity.

Conclusions: Pharmacokinetics and imaging after 0.2 mCi/m^2 IP ^{212}Pb -TCMC-trastuzumab in patients with HER-2-expressing malignancy showed minimal distribution outside the peritoneal cavity, $\leq 6\%$ urinary excretion, and good tolerance.

Key words: antibody immunotherapy, cancer, intraperitoneal, ovarian, ^{212}Pb -TCMC-trastuzumab

Introduction

The majority of patients with ovarian cancer are diagnosed after the disease has spread through the abdominal cavity. Although complete responses are common with optimal surgery and standard adjuvant chemotherapy, about half will experience recurrence that is usually confined to the abdominal cavity. Intensification of treatment by intraperitoneal (IP) chemotherapy and/or radionuclides has shown therapeutic efficacy, and some Phase III studies have documented im-

proved survival and/or decreased abdominal failure rate.^{1,2} Much work remains to optimize the agents and their integration with other modalities to achieve improved outcome. Prior experience with IP radionuclide conjugate therapy suggests that a radionuclide with shorter half-life than the 2.7 days of ^{90}Y and less γ emissions than ^{131}I or ^{177}Lu would allow dose escalation without excess toxicity.³

The potential for therapeutic targeted delivery of α -emitters has been recognized for many years as their cytotoxicity efficacy is $\sim 1000\times$ that of β particles.^{4–10} Although

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the intense radiation and considerably shorter path length features of α -particles make them attractive, and may be optimal for radioimmunotherapy, their development/implementation has been challenging due to lack of availability, and poor stability of radiolabeled conjugates using chelators that were developed for β -emitters.^{11,12} The use of ^{212}Pb (10.6 hours half-life) provides clinical feasibility. ^{212}Pb itself is not an α -emitter, but its physical decay results in the emission of two short-lived α -particles with potent therapeutic efficacy to cellular nuclei. ^{212}Pb decays to ^{212}Bi via β emission. ^{212}Bi , with a 60-minute half-life, has a split decay chain and emits an α particle at 36% frequency at an average of 6.1 MeV; ^{212}Bi decays to ^{212}Po the remaining 64% via β emission. The ^{212}Po decays to stable ^{208}Pb in microseconds by emission of an 8.8 MeV α particle. Betas are of low energy and/or frequency such that they are not expected to contribute significantly to toxicity or efficacy. Cumulative energy from the γ emissions is <12% of those from the α s, but the 238.6 keV γ ray with a 43% yield can be exploited for imaging.

The synthesis of the 2-(4-isothiocyantobenzyl)-1, 4, 7, 10-tetraaza-1, 4, 7, 10-tetra-(2-carbamonyl methyl)-cyclododecane, or TCMC, chelator has overcome the problem that ^{212}Pb was not stable with prior β -conjugate chelators. This has allowed extensive *in vitro* and animal model testing of ^{212}Pb -TCMC-trastuzumab prior to this human trial. IP administration of ^{212}Pb -TCMC-trastuzumab in a preclinical setting has demonstrated therapeutic activity against a variety of human tumor xenografts, and has allowed assessment of redistribution from the peritoneal cavity.^{13–17} Those studies provided the information required to progress to this initial clinical trial of IP ^{212}Pb -TCMC-trastuzumab.

Materials and Methods

Patient population

Three patients with ovarian cancer who had progressed after multiple therapies were treated in the initial imaging/pharmacokinetics cohort of a Phase I trial. At the time of trial entry they had no evidence of significant compromise of normal organ function or other major illnesses. All had ascites but none had required paracentesis.

Trial design

The trial design included delivery of the investigational agent, ^{212}Pb -TCMC-trastuzumab, as a single IP injection in patients with HER-2-expressing malignancies mainly confined to the peritoneal cavity who had failed standard therapy. The study was approved by the Western Institutional Review Board and was authorized by the food and drug administration (FDA). HER-2 expression of at least 1+ by immunohistochemistry in >10% of the cells was acceptable for gastric cancer; 30% was required for other diseases. Alternatively, HER-2 serum levels >15 ng/mL by enzyme-linked immunosorbent assay (ELISA) were allowed. Patients had to have free flow of fluid in the peritoneal cavity and were excluded for serious cardiac dysfunction, left ventricular ejection fraction <50%, poor organ function (defined as any of the following: elevated creatinine, total bilirubin >1.5 $\times$ normal, aspartate transaminase (AST) and alanine aminotransferase (ALT) >2.5 $\times$ normal, absolute neutrophil counts <1.5 $\times 10^3/\mu\text{L}$, or platelets <100 $\times 10^3/\mu\text{L}$), or other

conditions that might compromise safety. Other exclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status >2, pregnancy or breast feeding, evidence of bowel obstruction or transmural involvement, prior radiation to the whole abdomen, prior IP radionuclide therapy, stem cell transplant, history of human immunodeficiency virus (HIV) or Hepatitis A antibody positivity, or detectable antibody to trastuzumab.

Eligible, consenting, adult patients were housed in a Clinical Research Unit where they received a single IP injection of 0.2 mCi/m² (7.4 MBq/m²) ^{212}Pb -TCMC-trastuzumab in 50 mL <4 hours following 4 mg/kg IV trastuzumab. Additional saline was instilled into the peritoneal cavity before and after ^{212}Pb -TCMC-trastuzumab, for a total volume of ≤ 1000 mL. Post-treatment blood pharmacokinetics, urinary excretion, and biodistribution studies were performed. Blood samples were obtained immediately post-infusion and at 2, 8, 12, 18, 24, and 63 hours; urine was collected for 24 hours. Each void was collected, the volume was determined, and then 1 mL was counted. Blood samples were allowed to clot and spun, and a 1 mL aliquot of serum was counted. The well counter was operated with the window open to include 238.6 keV γ detection. Counts were corrected for decay between the time of collection and measurement. Simultaneous whole-body anterior and posterior γ images were obtained post-treatment and were repeated at 18–24 hours using a dual-headed Phillips Skylight Camera. These used a peak-energy window of 238.6 keV, which corresponds to a ^{212}Pb γ emission. Images were obtained with a medium-energy general-purpose collimator at 12 cm/min, and high-resolution matrix settings. Dosimetry data were obtained with radiation detector counts immediately post-treatment and at 3 additional times over 24 hours. Probe measurements were taken at the axilla, the mid femur, the umbilicus, and over the sternum using the Inspector 1000 portable radiation detector (Canberra). The patients were followed for toxicity as defined in the Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03). As a precautionary measure (based on prior studies of other α -emitter conjugates) adjuvant medications were used. A saturated solution of potassium iodide (SSKI) was initiated the evening before treatment and it was continued for 3 days. Furosemide (40 mg) was also started the day before ^{212}Pb -TCMC-trastuzumab and it was used for 10 days, and then followed by 100 mg spironolactone daily for 6 months as renal protective agents.

Investigational agent ^{212}Pb -TCMC-trastuzumab

Trastuzumab is an FDA-approved humanized monoclonal antibody (Genentech) which has therapeutic efficacy by immunologic mechanisms in tumors that overexpress the HER-2 receptor.¹⁸ TCMC-trastuzumab was provided in a form for further manufacturing of an investigational drug product for human use, having passed required quality control tests. It was stored in 200- μL vials at a concentration of 5 mg/mL. Labeling was performed at 1 mg of TCMC-trastuzumab per mCi of purified ^{212}Pb eluate. ^{212}Pb generators were provided by AREVA Med and were shipped from Bessines-sur-Gartempes, France. Manufacturing of the final product was at the University of Alabama at Birmingham under good manufacturing practices.¹⁹ Quality control

TABLE 1. PATIENT DEMOGRAPHICS

	Patient		
	No. 1	No. 2	No. 3
Age at ^{212}Pb -TCMC-trastuzumab infusion (years)	46	67	83
Months after surgery to first relapse	28	15	52
Months after surgery to ^{212}Pb -TCMC-trastuzumab	40	27	71
No. of prior chemotherapy courses	16	>23	>20
No. of prior chemotherapy regimens	2	4	3

testing included instant thin layer chromatography (ITLC), endotoxin, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS PAGE), visual inspection, and quantification. The ^{212}Pb -TCMC-trastuzumab was administered within 5 hours after passing all quality control measures. Sterility testing and radioimmunoassay were also performed post-infusion. Radioimmunoassay was used to test the affinity of the ^{212}Pb -TCMC-trastuzumab product to HER-2.

Results

Three patients with ovarian cancer entered this Phase I trial after they had failed multiple prior therapies. Initially, the 3 patients had CA125 values of 748–115,000 at the time of diagnosis of Stage Ic–IIIC disease. Their CA125 values normalized after debulking surgery and initial six cycles of chemotherapy. All received at least six cycles of carboplatin plus another agent. Two received the standard of a taxane but patient No. 1 had difficulty with the first cycle of taxane and received gemcitabine as the second agent for the remaining five cycles. Patient No. 2 received bevacizumab in addition to the standard chemotherapy doublet and contin-

ued to receive bevacizumab until relapse at 15 months. Patients No. 1 and No. 3 did not receive additional therapy until they relapsed at 28 and 52 months, respectively. None had additional surgery for recurrence but all had computed tomography (CT) evidence of widespread disease in the peritoneal cavity. Table 1 provides a summary of information on these patients pre- ^{212}Pb -TCMC-trastuzumab.

The patients had placement of an IP catheter 1–2 days prior to therapy. All demonstrated free flow of fluid in the peritoneal cavity by serial $^{99\text{m}}\text{Tc}$ scans that were performed on the day of catheter placement. None had evidence of significant leakage from the cavity with the second scan 2 hours later. The patients tolerated therapy at the 0.2 mCi/m^2 level with no more than mild acute discomfort associated with phlebotomy and catheter removal. Later adverse events were mild, and attributed to adjuvant medications rather than the experimental agent. Patient No. 3 had Grade 1 nausea and dizziness associated with SSKI. Subsequently, she developed an allergic reaction to spironolactone that resolved with discontinuation. Patient No. 1 had Grade 1 fatigue and increased muscle cramps. These were felt to be related to mild dehydration associated with the renal protective agents. There was no evidence of marrow suppression, new laboratory abnormalities, electrocardiogram (ECG), or echocardiography changes within 6 weeks post-treatment. No late toxicity attributed to the investigational agent has been noted at 6 months.

Gamma camera imaging studies after IP ^{212}Pb -TCMC-trastuzumab showed no distribution of radioactivity out of the peritoneal cavity or normal organ uptake. As shown in Figure 1 even the delayed, repeat scan the day after therapy did not show activity outside the peritoneal cavity such that a shoulder marker plus a standard at the ankle were needed as anatomic indicators of body regions. The day-2 images illustrate the shift to more uniform anterior/posterior

FIG. 1. The immediate anterior and posterior whole-body scan images after IP ^{212}Pb -TCMC-trastuzumab (left) are compared with the repeat scan the next day. $^{99\text{m}}\text{Tc}$ marker at the right shoulder (arrow) plus the ^{212}Pb standard adjacent to the right ankle provide anatomic locations outside the abdominal area as does the transmission scan (right) that displays body anatomy.

TABLE 2. % INJECTED DOSE IN BLOOD DETERMINED BY DECAY CORRECTION

	Hours post-infusion		
	2 hours	24 hours	63 hours
Patient No. 1	4.9	7.2	18.8
Patient No. 2	4.4	21.0	22.9
Patient No. 3	0.1	0.1	0.7

abdominal distribution over 18 hours and the loss of intensity due to radioactive decay compared with the early post-treatment images. The camera-measured drop in radioactivity from the abdomen in day 2 was similar to that of the other body regions that showed no evidence of accumulation and all were consistent with the physical decay half-life of ^{212}Pb .

Despite the lack of visualization of activity outside the peritoneal cavity, slow absorption/distribution occurred based on detectable radioactivity in the blood and urinary loss.

Peak blood conjugate level activity was <23% injected dose at the last time point of 63 hours as determined with decay correction (Table 2). The maximum blood concentration of 6 nCi/mL occurred at 18 hours (patient No. 2). Although this patient had a higher percent injected dose at 63 hours, the concentration was less then due to ensuing radioactivity decay. As shown in Table 2, the range of peak blood concentration was <1%–22.9%, since patient No. 3 had only 0.1 nCi/mL at the time of peak activity. Cumulative urinary loss ranged from 0.3% to 6% in 24 hours among the 3 patients. Patient No. 3, who had the lowest blood concentration, also had the lowest urinary loss.

Detector-measured exposure rates at four body sites were monitored over 24 hours. The maximum dose rate immediately post-infusion over the abdomen averaged 7.67 mR/h and dropped to 0.67 (range 0.55–0.8) by 24 hours. The rate at the other sites monitored (axilla, chest, and femur) decreased as a function of their distance from the abdomen. The ratio of the average exposure rates at the abdomen over other sites was 2–12.8 post-infusion and changed to 1.3–5.9 by 24 hours. These changes over time were consistent with a very small amount of redistributed activity from the abdomen. The data points correlate closely with theoretic curves (Fig. 2), even without adjustment for urinary excretion of radioactivity.

Discussion

Targeted IP therapy using a radionuclide with 10.6 hours of half-life and predominance of α emissions has potential for improved efficacy and decreased toxicity compared to β emitters used in treatment of malignancy that has spread throughout the peritoneal cavity. This first-in-human experience with IP ^{212}Pb -TCMC-trastuzumab confirms its medical potential and feasibility.

The data obtained are consistent with those of prior non-human studies in showing prolonged retention of the ^{212}Pb -TCMC-trastuzumab within the peritoneal cavity and no evidence for localization to normal organs on planar images.^{13–17} The starting dose level for this first cohort in a Phase I trial was low compared to theoretical tolerance and

FIG. 2. Data points represent mean exposure rate of radioactivity at 4 time points in the initial 24 hours after IP ^{212}Pb -TCMC-trastuzumab. Measurements over the abdomen are compared with those at the chest, axilla, and femur. The actual data points (mean $\pm$ one standard deviation) are shown along with theoretical curves of physical radioactive decay. There was no adjustment for urinary excretion of radioactivity.

experience in other species but was consistent with the starting dose for another α particle radioimmunotherapy trial using ^{211}At .²⁰ This dose allowed monitoring of blood, urine, and imaging with minimal exposure to laboratory personnel. Subsequent dose groups will also be followed for toxicity but will have less quantitative pharmacokinetics/dosimetry data collection.

Some low-frequency and mainly low-energy γ -emissions from the decay path, plus bremsstrahlung radiations, allowed detection of gross biodistribution by γ -camera imaging. This was helpful to rule out targeted localization to normal organs such as the heart, thyroid, or kidneys. Given the relatively low activity administered, whole-body imaging of ^{212}Pb was quite sensitive. After administration of 0.4 mCi, the anterior or posterior counts were 4.7 and 4.5 million counts, respectively, and 10 μCi of ^{212}Pb in the counting standard at the patient's ankle was very clear in the image. The inability to distinguish anatomy outside the abdomen despite evidence of limited redistribution is influenced by scatter from ^{212}Pb in the abdomen that affects contrast of body areas with background. Serial quantitative monitoring of spectral distribution at four body sites also confirmed the modest level of redistribution from the peritoneal cavity. The amount of radioactivity detected in the blood and urinary loss is consistent with that of other radiolabeled antibody conjugates.^{9,10,20–22} As a precaution to possible localization to organs/tissues outside the peritoneal cavity that might have HER-2 expression, a standard loading dose of 4 mg/kg trastuzumab was given intravenously within 4 hours prior to the IP injection of ^{212}Pb -TCMC-trastuzumab.

^{212}Pb -TCMC-trastuzumab is being developed to improve upon results with other radionuclides that have been proposed or evaluated for IP therapy such as ^{90}Y and ^{177}Lu by providing more potent radiation to targeted malignant cells while limiting radiation exposure to normal tissues.³ ^{212}Pb has a shorter half-life and path length (range of α radiation) compared with radionuclides that predominantly

emit β particles.^{6–10,22} IP therapy using another α -emitting conjugate, ²¹¹At-MX35F(ab')₂, has shown promise as an adjuvant therapy for ovarian cancer in patients with no evidence of gross disease.²⁰ Based on clinical experience and preclinical data, it is reasonable to expect that treatment at the time when disease deposits are only microscopic should provide the maximum therapeutic benefit.^{7,8,10,20} ²¹²Pb-TCMC-trastuzumab may have beneficial activity against a number of malignancies that have HER-2 expression. Additional study of ²¹²Pb-TCMC-trastuzumab and other α -emitting agents is warranted.^{10,22–32}

Conclusions

Pharmacokinetics and imaging after IP ²¹²Pb-TCMC-trastuzumab in patients with HER-2-expressing malignancy showed minimal distribution outside the peritoneal cavity, consistent with preclinical studies. This α -emitter radioimmunotherapy has potential for improved therapeutic ratio over β -emitter-targeted conjugate therapy and could add to the overall armamentarium of treatments for patients with HER-2-expressing malignancies. Additional study of this α -emitting radioimmunotherapy is warranted.

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Author Disclosure Statement

The author has no significant financial interests that are related to or would reasonably appear to be affected by the proposed article. All authors involved in the article have been informed of their obligations under federal regulations governing disclosure of significant financial interests and have no conflicts of interest or potential conflicts of interest that have not been disclosed.

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