

Safety and Outcome Measures of First-in-Human Intraperitoneal α Radioimmunotherapy With ^{212}Pb -TCMC-Trastuzumab

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Purpose: One-year monitoring of patients receiving intraperitoneal (IP) ^{212}Pb -TCMC-trastuzumab to provide long-term safety and outcome data. A secondary objective was to study 7 tumor markers for correlation with outcome.

Methods: Eighteen patients with relapsed intra-abdominal human epidermal growth factor receptor-2 expressing peritoneal metastases were treated with a single IP infusion of ^{212}Pb -TCMC-trastuzumab, delivered <4 h after 4 mg/kg IV trastuzumab. Seven tumor markers were studied for correlation with outcome.

Results: Six dose levels (7.4, 9.6, 12.6, 16.3, 21.1, 27.4 MBq/m²) were well tolerated with early possibly agent-related adverse events being mild, transient, and not dose dependent. These included asymptomatic, abnormal laboratory values. No late renal, liver, cardiac, or other toxicity was noted up to 1 year. There were no clinical signs or symptoms of an immune response to ^{212}Pb -TCMC-trastuzumab, and assays to detect an immune response to this conjugate were negative for all tested. Tumor marker studies in ovarian cancer patients showed a trend of decreasing Cancer antigen 72-4 (CA 72-4) aka tumor-associated glycoprotein 72 (TAG-72) and tumor growth with increasing administered radioactivity. Other tumor markers, including carbohydrate antigen (CA125), human epididymis protein 4 (HE-4), serum amyloid A (SAA), mesothelin, interleukin-6 (IL-6), and carcinoembryonic antigen (CEA) did not correlate with imaging outcome.

Conclusions: IP ^{212}Pb -TCMC-trastuzumab up to 27 MBq/m² seems safe for patients with peritoneal carcinomatosis who have failed standard therapies. Serum TAG-72 levels better correlated to imaging changes in ovarian cancer patients than the more common tumor marker, CA125.

Key Words: Pb-212-radioimmunotherapy, cancer, ovarian, tumor marker, intraperitoneal

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Low toxicity intraperitoneal (IP) treatment continues to be an unmet need for disease that spreads through the cavity such as ovarian and pancreatic cancer. IP chemotherapy has improved survival of ovarian cancer patients but carries risk of life-threatening toxicity, and has not become the standard at most institutions.¹ Radiopharmaceuticals have greater potential than external beam radiation due to dose-limiting tolerance of normal organs. β -emitting radiopharmaceuticals have shown modest impact but have also been used at dose-limiting toxicity levels.^{2–5} Targeted α -emitter radiopharmaceuticals, as implemented in this report, have the potential advantages of improved efficacy with less toxicity than β -emitters.

For targeted radionuclide therapy, the high ionization density of α -particles is attractive but their development/implementation has been challenging compared with the more widely available β -emitters.^{6,7} With the large helium particle emitted, α -decay results in significantly higher energy delivery (linear energy transfer) than β -decay, which results in higher cell-killing effectiveness. Human cell culture studies showed the relative biological effectiveness (RBE) greater for α -particles than that for β -radiation or kilovoltage photons⁸; this has been confirmed in other preclinical as well as early clinical trials but the RBE range has been variable from ~ 1 to 20.⁹ The clinical experience where ^{213}Bi -HuM195 and ^{90}Y -HuM195 therapy could be directly compared in leukemic patients suggested that the RBE of α -emitter therapy will vary with cell type, geometry, and endpoints utilized.¹⁰ Another advantage of α -particles over β -radiation is the limited range of only a few cell diameters. This spares normal tissues but does limit optimal use to selected clinical applications. Appropriate clinical settings for use of high potency α -particles with short half-lives are those where the targeting is very specific and rapid or other conditions, such as into a resection cavity or tumor mass, where there is limited exposure to normal tissues. Because of many hurdles, implementation of systemic administration using antibody targeted α conjugates has been limited to a few studies, mainly in patients with leukemia, lymphoma, and metastatic melanoma.^{7,11–13} Limited experience with nonsystemic administration has included intralesional melanoma sites, intracavity or intralesional for brain tumors, and intraperitoneal infusion.^{14–18} Whereas reports of others show more extensive pharmacokinetics and dosimetry of another α -emitter conjugate administered to the peritoneal cavity (^{211}At -Mx35 F(Ab')₂), our following report is the first therapeutic IP administration where safety was the primary objective posttherapy.^{16,18,19} Targeted α -conjugate therapy has thus far been well tolerated but initial dose levels have been modest to minimize risks to patients undergoing investigational treatment. This first-in-human clinical trial of IP ^{212}Pb -TCMC2-(4-isothiocyanobenzyl)-1,4,7,10-teraza-1,4,7,10-tetra-(2-carbamonyl methyl)-cyclododecane-trastuzumab was initiated after extensive murine and nonhuman

primate investigations provided biodistribution, safety, and anti-tumor efficacy data.²⁰⁻²⁴ In this phase I study, a single IP infusion of ²¹²Pb-TCMC-trastuzumab was escalated over 6 dose levels with toxicity monitoring to confirm the safety of this agent.

This trial, like many other investigations, studied serum tumor markers as indicators of therapeutic efficacy that could be easily and quickly monitored. This is particularly relevant given the limitations inherent in image-based quantification of peritoneal metastatic disease. Seven tumor markers were studied for their correlation to clinical outcome 6 weeks posttherapy. These included carcinoembryonic antigen (CEA), which is used for monitoring patients with gastrointestinal cancer and a minority of patients with other malignancies.²⁵ Carbohydrate antigen (CA125) was monitored in the ovarian cancer patients as this has historically been the standard marker for monitoring of disease response to treatment.²⁶⁻²⁹ Human epididymis protein 4 (HE-4), serum amyloid A (SAA), mesothelin, interleukin-6 (IL-6), and tumor-associated glycoprotein (TAG-72), were also chosen for study based on prior reports of tumor association.³⁰⁻³⁶

METHODS

Details of the trial design and agent preparation have been previously reported.¹⁷ Briefly, this trial provided a single IP ²¹²Pb-TCMC-trastuzumab infusion <4 h after 4 mg/kg IV trastuzumab in patients with human epidermal growth factor receptor-2 (HER-2) expressing malignancy that had failed standard therapies. Modifications were made after patient 10 to allow patients with HER-2 of 1+ in ≥ 10% of cells. Modification was also made to discontinue the saturated solution of potassium iodide as imaging showed no thyroid localization and no abnormal laboratory values had been observed in >1 year for the initial 3 patients. The diuretic regimen was also shortened as there was no evidence of renal localization or toxicity and patients had difficulty with side effects such that most were noncompliant with the entire prescribed regimen. Monitoring over the duration of 1 year included clinical findings, laboratory values, cardiac studies, immunologic assays, serum tumor marker levels, and computed tomographic scans. Patients had clinical and/or laboratory posttherapy evaluations 7 times in the first 6 weeks. If there was no toxicity, scheduled monitoring was extended to 6-, and then to 12-week intervals. Cardiac monitoring used electrocardiogram and echocardiograms. Enzyme linked immunosorbent assay testing of 6-week serum samples was performed to determine if there was any evidence of an immune response to TCMC-trastuzumab. A standard anti-drug antibody assay was developed. Briefly, the anti-Her-2 antibody was both the coat and a biotinylated primary detection antibody. Patient serum or polyclonal antibodies raised against TCMC-trastuzumab was the analyte.

In the presence of bivalent anti TCMC-trastuzumab antibodies, the biotinylated trastuzumab antibody becomes linked to the trastuzumab coat. HRP-streptavidin is then added to develop a signal. Toxicity was defined using Common Terminology Criteria for Adverse Events (version 4.03 National Cancer Institute). Imaging interpretation and lesion measurements from baseline (<4 w pretreatment) and 6-week interval post-treatment CT scans were performed as an independent review by Imaging Endpoints (Scottsdale, AZ). Lesion measurements were compared by pretreatment and posttreatment volumes as a modification from RECIST criteria described in the original study design that uses tumor diameter products.³⁷ Levels of standard tumor markers CA125 and CEA were obtained at institution laboratories; commercially available kits were used for other markers HE-4 (Fujirebio Diagnostics Inc., in vitro diagnostics), Cancer antigen (CA 72-4) (TAG-72) (DRG International, Research Use Only), SAA (Life Technologies, Ruo), Mesothelin (Aviscera Bioscience Inc., Ruo), IL-6 (Abcam, Ruo). Serum for tumor markers was obtained pre-treatment, at 6 weeks, and at additional timepoints for CEA and CA125 in most patients. Statistical analysis used least squares linear regression to fit the data.

RESULTS

Toxicity

Eighteen patients (age 46 to 83) treated at 6 dose levels (7.4, 9.6, 12.6, 16.3, 21.1, 27.4 MBq/m²) were monitored for at least 1 year or until death. Seventeen patients were treated at the University of Alabama at Birmingham, and 1 colon cancer patient was treated at the University of California at San Diego. Sixteen patients were females with ovarian cancer and 2 males had colon cancer. Treatment was well tolerated. Mild acute adverse effects were associated with the investigational agent as previously presented for the initial 16 patients.¹⁸ Other than 2 patients who had transient abdominal pain associated with agent plus saline administration, possibly related adverse events were mainly grade 1, transient, asymptomatic laboratory abnormalities that were not dose related.

The patients are numbered 1 to 18 by the order of treatment. Monitoring of the enzymes lactic dehydrogenase (LDH), alkaline phosphatase (AlkP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ glutamyltransferase (GGT) showed no elevation among patients 2, 3, 7, 8, 12, 15, 16, 17, and 18. Table 1 shows the time and frequency of patients who developed grade 1 liver function test elevations. As shown in Table 1, 4 patients had elevations before treatment and 6 others experienced elevation to grade 1 level after treatment. These minor fluctuations did not appear dose related; all except patient 14 were below dose level 5 and none occurred at the highest dose level.

TABLE 1. Summary of Enzyme Abnormalities by Date

Week After Treatment	Patients With Enzyme Elevations				
	LDH	AlkP	ALT	AST	GGT
Pretreatment	4, 5	1, 10		5	
Week 1	4, 5, 6	1, 9, 14	11	5, 11	5
Week 4	4	1			
Week 6	4	1, 14	14	13, 14	14

Each patient number is used for all times of grade 1 enzyme elevation from pretreatment to week 6.

AlkP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ glutamyltransferase; LDH, lactic dehydrogenase.

Whereas hematologic toxicity has been dose-limiting in prior IP radionuclide conjugate studies, the mean platelet counts, total white blood cell counts, and neutrophil counts remained normal after a mean equivalent dose to marrow of 0.002 to 0.14 cGy/MBq. Only 2 patients had transient decreased counts to grade 1 (platelets 142,000/ μ L, WBC 3500/ μ L without neutropenia). Anemia was not tracked for toxicity as 6 patients were anemic pretreatment with hemoglobin of 9.8 to 11.2 g/dL. The percent change at 6 weeks for these patients was from a loss of 3.8% to a gain of 16.3%. Three of the 6 had improvement to normal hemoglobin levels during that interval.

Four patients experienced periods of grade 1 creatinine elevation (without proteinuria) associated with dehydration or urinary tract obstruction as reported.¹⁸ Reducing the diuretic regimen after patient 10 did not increase the serum levels of radioactivity or result in renal toxicity. No late renal, liver, hematologic (excluding anemia as noted above), cardiac, or other toxicity has been observed with monitoring >1 year despite additional therapy after the investigational agent. Although all patients had disease progression in <8 months and proceeded with additional treatment, none refused continued monitoring. There were no clinical signs or symptoms of an immune response, and assays to detect an immune response to ²¹²Pb-TCMC-trastuzumab were negative for all 15 of 15 tested (3 patients had no sample).

Tumor Marker Changes Compared With Clinical Response

Blood levels of 7 tumor markers were studied and compared with clinical outcome at 6 weeks posttherapy. CEA and CA125 continued to be obtained until progression. CEA increased with disease progression in the 2 colon cancer patients but all the ovarian cancer patients had levels that were within the normal range both pretreatment and posttreatment. Other tumor markers which are often associated with ovarian cancer, including CA125, mesothelin, IL-6, SAA, and HE-4, did not correlate with imaging outcome (Fig. 1). Only a TAG-72 had a pattern similar to that of tumor growth changes. TAG-72 levels covered a wide range from nearly 200% increase to 66% decrease 6 weeks posttherapy. Compared with the imaging changes, the TAG-72 pattern had a

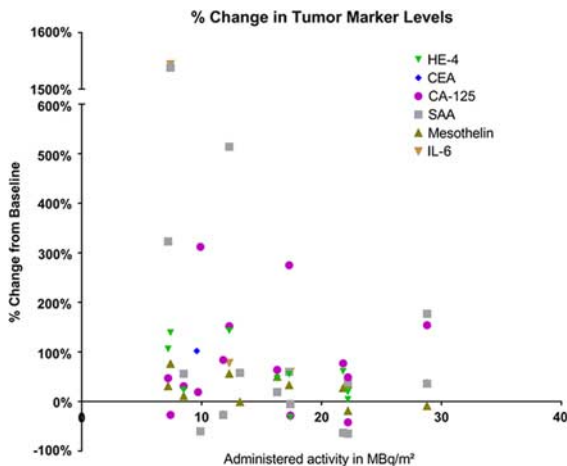


FIGURE 1. Each data point represents the increase or decrease in serum marker as percent change at 6 weeks compared with baseline for individual patients. The change in markers is compared with administered radioactivity in MBq/m². Data points are not shown when values were within normal limits.

steeper slope and higher correlation coefficient with administered level of radioactivity than did tumor growth (R^2 for TAG-72 is 0.73 vs. 0.21 for CT) as shown in Figure 2. Five patients did not have measurable tumor lesions (TL) and are not included in Figure 2. Their clinical outcome is included in Table 2, which shows a trend of less tumor growth, including regression, with increasing administered radioactivity. All patients had progression of disease inside and/or outside of the peritoneal cavity before 8 months but the majority lived >1 year, allowing monitoring for late toxicity.

DISCUSSION

The single IP ²¹²Pb-TCMC-trastuzumab infusion was well tolerated with agent-related toxicities limited to grade 1 and the majority of them were asymptomatic, transient laboratory abnormalities. Although there was no visualization of radioactivity outside of the peritoneal cavity, blood collection showed a rate of <1% to 22.9% transit in 24 hours.¹⁸ The imaging and blood data allowed dosimetry calculations. These found low radiation exposure to normal organs and a mean tumor milieu to marrow ratio of >1000, as most of the radioactivity decay took place in the peritoneal fluid.¹⁷

With >1 year of follow-up in the majority of patients receiving IP ²¹²Pb-TCMC-trastuzumab, no late toxicity has been observed. The paucity of preclinical toxicity data allowed dose escalation for 6 levels, which is the maximum that was planned for this first-in-human study; further increase in dose levels would have soon exceeded preclinical data and required additional nonhuman primate studies.³⁸ On the basis of this initial clinical experience, ²¹²Pb-TCMC-trastuzumab appears safe for further study at the highest dose level tested or even additional dose escalation. As IP α -emitter therapy should be most effective for microscopic disease, the low toxicity should allow it to be further studied in combination with other agents or as an adjuvant after tumor reduction by standard therapies. The transient early toxicities did not appear to be dose related. The grade 1 leukopenia and thrombocytopenia occurred in patients at dose groups 3 and 5. No drops in blood counts to grade 1 were noted in the highest dose group, suggesting

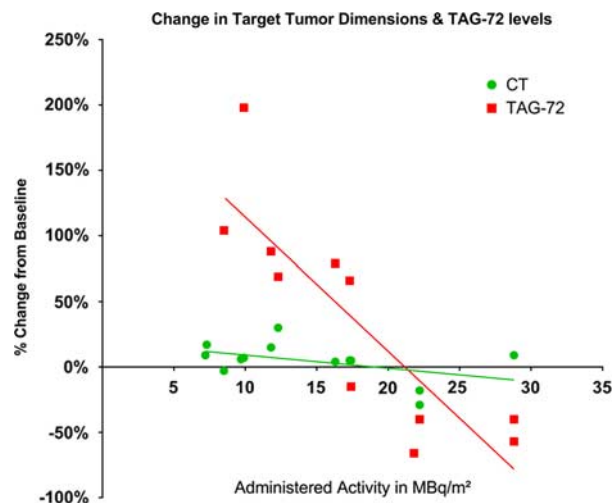


FIGURE 2. Each data point represents a single patient who had measurable lesions and TAG-72 >6 U/mL at baseline. The data points are expressed as percent change from baseline. The lines represent best fit from regression analysis. TAG-72 indicates tumor-associated glycoprotein 72.

TABLE 2. Comparison of Posttreatment Disease Status With Administered ²¹²Pb Dose Level

Patient #	6 wks post-dose	12 wks post-dose	24 wks post-dose	Dose (mCi/m ²)	Comments
1	PD			0.2	PD due to ascites
2	SD	PD		0.2	PD due to non-TLs and ascites
3	PD			0.2	no TLs; PD due to ascites
4	PD			0.26	New ascites
5	PD			0.26	PD due to non-TLs
6	PD			0.26	PD due to ascites at 5wk
8	PD			0.26	new lesion at 6 wks
7	PD			0.34	PD due to non-TLs
9	PD			0.34	PD due to TL and non-TL and ascites
10	SD	PD	PD	0.34	no TLs, new lesion at 12 wks
11	SD/NC+	SD/NC+		0.44	PD at 21 wks
12	SD/NC+	PD		0.44	PD due to TL & non-TLs
13	SD/NC+	PD		0.44	PD due to non-TLs and ascites
14	SD	SD		0.57	PD pleural effusion 12 wk
15	SD/MR	SD/MR	SD	0.57	New TL outside abdomen 30wk
16	SD/MR	SD/MR		0.57	Clinical PD 14 wk
17	SD	SD	PD	0.74	PD at 24 wks due to ascites increase
18	SD/NC+	PD		0.74	Progression in TL

PD	Progressive Disease: Measureable tumor lesions (TL) > 20% increase, new lesions or clinical progression of non TL
SD	Stable Disease: No change (NC) that qualifies as progression or response.
SD/NC-	Stable Disease/ NC-: 0% to 10% reduction
SD/NC+	Stable Disease/ NC+: 0% to 20% increase
SD/MR	Stable Disease/ Minor Response (MR): >20% reduction of TL.
ND	No diagnostic images at that time (ND).

The most current computed tomographic scan measurements were compared with baseline scan measurements using a modified RECIST 1.1.

factors other than radiation dose alone were associated with the count levels posttherapy. Both of the affected patients had pretreatment levels of only 12% above the lower limits of normal such that a modest drop reached grade 1 level. As the radiation dose to marrow was small at 0.002 to 0.14 cGy/MBq, significant hematologic toxicity would not be expected and was not observed.¹⁸ Six of 16 ovarian cancer patients were anemic pretherapy and 3 had improvement to normal levels even during the initial 6 weeks posttherapy. The early post-treatment increase of hemoglobin would not have been expected with higher, marrow-toxic, doses of radiation and suggests incomplete recovery from toxicities of therapy before administration of this investigational agent.

Both methods of index lesion measurement, individual volume versus sum of lesion diameter products, showed a trend of less tumor growth with increasing level of administered radioactivity. The independent review shows more early patients with progression than previously noted when pretreatment and posttreatment comparison used the product of index lesion diameter (Table 2).^{17,37} However, the later independent review

did not necessarily use the same index lesions, which contributed to less than complete concordance of tumor growth results from those previously reported.¹⁷ Although the optimal tumor efficacy with α -emitters is proposed to be for microscopic disease, regression was noted among various sized gross lesions.

Many investigators continue to seek serum tumor markers to facilitate diagnosis and monitoring of therapeutic efficacy. Although CA125 has become the standard marker for monitoring antitumor effects in ovarian cancer, checking this alone has not been rigorous enough to become a standard for diagnostic screening.³⁹ Its use in conjunction with other serum markers, plus additional factors, has been more helpful.^{30,40} Other potential markers under study for ovarian cancer include IL-6, IL-8, kallikrein-10, mesothelin, HE-4, and p53.⁴¹⁻⁴⁴ Also, SAA may be useful in serous subtype of ovarian carcinoma.⁴⁵

In this study, several tumor markers were monitored to determine their potential utility for noninvasive assessment of therapeutic response. Although levels of the standard ovarian cancer tumor marker CA125 did not have a strong relation to outcome, CA125 may have been a better marker had the

pretreatment level been obtained closer to the time to treatment. With the measures of this noncancer specific protein usually 2 to 4 weeks before therapy plus intervening manipulation of the peritoneal cavity with catheter insertion and treatment, the posttreatment levels may have been elevated by factors other than tumor burden. One might expect that elevation related to disruption by catheter placement and therapy would have resolved by 6 weeks but further study would be needed to seek relevant information for this determination.

HE-4 has also been studied as a tumor marker of ovarian cancer. It has been more helpful for diagnosis than for monitoring therapeutic response. HE-4 has most frequently been used in conjunction with CA125 and other factors to distinguish ovarian cancer from a benign abdominal process.^{40,46,47} The mucin-like TAG-72 is generally expressed on adenocarcinomas and less frequently in other types of malignancies.^{48–50} The only normal tissue with notable TAG-72 expression is secretory endometrium, which was not of concern in this study as none of the patients had an intact uterus.^{49,50} Tumor shedding of TAG-72 is common and may allow potential noninvasive monitoring of tumor status via blood levels,⁴⁹ with the assumption that it correlates with tumor burden in an individual patient. TAG-72 had the strongest correlation with CT-monitored tumor changes of the 7 markers reported here. None of the other markers tested showed a good correlation with increasing radioactivity or clinical outcome. Although they have all been associated with ovarian cancer, CA125 is the only marker robust enough to routinely be used and it is not cancer specific. TAG-72 had a relatively robust association with increasing administered radioactivity, having a correlation coefficient of 0.73. On the basis of that, plus its decreasing trend with decreasing tumor growth, a dose/response relation with administered radioactivity is suggested. Additional data are needed to confirm this and to further investigate TAG-72 as a serum marker of response to ²¹²Pb-TCMC-trastuzumab. CEA is a serum marker used as a standard in monitoring response to therapy in colon/rectal cancer. We found it was helpful in the 2 colon cancer patients in this study. CEA may be elevated, and thus is a potential marker for monitoring other gastrointestinal malignancies as well other malignancies of nongastrointestinal origin albeit in a smaller fraction of patients. In this study, all the ovarian cancer patients had normal CEA levels pretreatment and none experienced elevated levels at follow-up, even when disease progression was noted from imaging and other markers (TAG-72).

CONCLUSIONS

IP ²¹²Pb-TCMC-trastuzumab up to 27.4 MBq/m² appears safe for further study and dose escalation. Serum TAG-72 monitoring is recommended as a potential tumor marker for assessing antitumor effects in patients with ovarian cancer.

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