iodine, the yield of using both imaging modalities in all patients is low. Thallium-201 scintigraphy should be reserved for circumstances in which 131I scintigraphy is negative and when thyroglobulin levels are elevated or recurrent or widespread differentiated thyroid cancer is suspected on a clinical basis.

REFERENCES

Intraperitoneal Radioimmunotherapy of Ovarian Cancer with Lutetium-177-CC49


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Twelve ovarian cancer patients who failed chemotherapy entered a Phase I trial of intraperitoneal 177Lu-CC49 antibody. Methods: Patients had disease confined to the abdominal cavity ± retroperitoneal lymph nodes, adequate organ function and no previous radiation. Results: Side effects included mild discomfort with administration (1/12), delayed transient arthralgia (2/12), and mild narrow suppression (calculated narrow doses of 11–54 cGy). The maximum tolerated dose has not been reached with levels of 10, 18, 25 and 30 mCi/m². Radioimmunoscintigraphy revealed localization consistent with tumor in 11 of 12 patients. One of eight patients with gross disease had >50% tumor reduction after therapy, while six progressed and one went off study with stable disease. Of patients with microscopic or occult disease, one relapsed at 10 mo and three remain without evidence of disease after 18 mo. Conclusion: Intraperitoneal radioimmunotherapy with 177Lu-CC49 is well tolerated and appears to have antitumor activity against chemotherapy-resistant ovarian cancer in the peritoneal cavity.

Key Words: ovarian cancer; radioimmunotherapy; lutetium-177-CC49


Enduction of ovarian cancer implants in the peritoneal cavity has been the major obstacle to disease control in most patients. Although the introduction of platinum-based chemotherapy has increased the response rates of ovarian cancer, there has been only a modest improvement in survival rates (7) and half of the patients who have laparotomy-confirmed complete response will relapse. Since most relapses are confined to the abdominal cavity, improved therapy should be possible with intensification of treatment directed to this area. Some abdominal failures have been successfully treated with external radiation, intraperitoneal or systemic administration of chemotherapy, or a form of radionuclide therapy (2–11).

Positive results have been reported for intraperitoneal delivery of radiolabeled tumor-reactive antibodies to selected patients, but this technology has not yet been fully exploited. Early results from imaging (12) and dosimetry (13) studies of intraperitoneal administration of radiolabeled antibodies have demonstrated selective tumor localization and slow absorption into the bloodstream (14–16). These studies have also shown that the intraperitoneal route is superior to intravenous administration for intraperitoneal implants, while the reverse is true for solid tumor metastases to lymph nodes and areas of hemogenous metastasis (14–16). An early therapeutic trial of intraperitoneal radiolabeled antibody for ovarian cancer, in which patients received >140 mCi 131I-antibody, showed beneficial effects in 9/16 patients with a tumor mass of <2 cm (2). Eight patients in that study with larger tumor masses died of progressive disease within nine months. Similar results are reported for several antibodies using at least three radionuclides (131I, 186Re, 90Y) (4–5,8,10–11). That is, antitumor effects, and in many cases prolonged survival, have been noted when disease volume is small. There is decreasing efficacy, however, with increasing size of tumor nodules (4).

We are conducting a dose-escalating trial of intraperitoneal radioimmunotherapy in ovarian cancer patients with persistent disease using a new agent, 177Lu-CC49, which is linked by the chelator PA-DOTA (17). Lutetium-177 is a rare earth material with a physical half-life of 6.7 days and with beta emissions (Eavg = 133 KeV) that penetrate 0.2 to 0.3 mm in soft tissue. Lutetium-177 also emits two relatively low-abundance, low-energy gamma rays (113 and 208 keV) that allow imaging with a gamma camera, but pose less radiation hazard to health care personnel as compared to 131I.
The monoclonal antibody used, CC49, is a high-affinity murine product that reacts against tumor-associated glycoprotein TAG-72 which is expressed by the majority of common epithelial tumors (18). It has been used by our team and others in several clinical radioimmunotherapy trials, following preclinical studies that showed improved targeting and therapeutic efficacy compared to a related lower affinity antibody (19–22). The current study represents the initial therapeutic intraperitoneal administration of 177Lu-CC49. The only previous clinical experience consists of a National Cancer Institute Phase I intravenous study of nonovarian adenocarcinomas (23).

### TABLE 1
Comparison of Intraperitoneal Tumor Characteristics, Amount of Residual Disease Post-Surgery and Initial Treatment Response to Chemotherapy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Histology</th>
<th>Grade</th>
<th>Stage at diagnosis</th>
<th>Post-op residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Papillary</td>
<td>3–4</td>
<td>3</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>2</td>
<td>Papillary serous</td>
<td>3</td>
<td>1a</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Papillary serous</td>
<td>2</td>
<td>3c</td>
<td>&gt;1 cm</td>
</tr>
<tr>
<td>4</td>
<td>Adenocarcinoma</td>
<td>3</td>
<td>3c</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>5</td>
<td>Serous</td>
<td>3</td>
<td>3b</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>6</td>
<td>Endometrioid</td>
<td>3</td>
<td>3c</td>
<td>&gt;1 cm</td>
</tr>
<tr>
<td>7</td>
<td>Adenosquamous</td>
<td>3</td>
<td>3c</td>
<td>&gt;1 cm</td>
</tr>
<tr>
<td>8</td>
<td>Endometrioid</td>
<td>2</td>
<td>2b</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Adenocarcinoma, extravarian</td>
<td>3</td>
<td>3</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>10</td>
<td>Papillary</td>
<td>3</td>
<td>3c</td>
<td>&gt;1 cm</td>
</tr>
<tr>
<td>11</td>
<td>Adenocarcinoma</td>
<td>2</td>
<td>3c</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>12</td>
<td>Serous cystadenocarcinoma</td>
<td>2</td>
<td>3c</td>
<td>&lt;1 cm</td>
</tr>
</tbody>
</table>

*Disease arising outside ovaries.

### METHODS

#### Study Design

Patients with chemotherapy-resistant ovarian cancer limited to the abdomen have been entered into a dose escalating trial of intraperitoneal 177Lu-CC49 antibody. Monitoring includes toxicity, antitumor effects, pharmacokinetics and immune response after a single intraperitoneal infusion of radiolabeled antibody. Toxicity grading utilizes Cooperative Group Trials Common Toxicity Criteria. This National Cancer Institute coordinated study is approved by the University of Alabama at Birmingham (UAB) Institutional Review Board and all patients gave informed consent after explanation of the nature of the study.

#### Patient Eligibility

Eligibility requirements included: histologically confirmed, TAG-72 reactive ovarian adenocarcinoma or papillary serous carcinoma consistent with ovarian origin; persistent or recurrent disease after a primary platinum-based chemotherapy program; disease confined to the peritoneal cavity ± retroperitoneal lymph nodes and no nodule >5 cm. No history of another invasive malignancy, prior intraperitoneal or antibody treatment or whole-abdomen radiation was allowed. Patients were ≥18 yr old, had a Karnofsky performance status ≥60, adequate organ function and were receiving no concurrent nonstudy chemotherapy, radiation or immunotherapy. Free flow of fluid in the abdomen is tested on the day of planned administration of intraperitoneal therapy. Patients who show loculatation of >15% are not treated.

### CC49 Preparation and Administration

CC49 was radiolabeled using a bifunctional chelator, PAM-DOTA. The final quality control checks and individual dose preparations were performed in the UAB facilities. The radiolabeled product (IND #4427, NSC #647944) is approximately 8 mCi/mg with 88.5%–93.9% immunoreactivity. Unlabeled CC49 (BB IND #3496, NSC #620537) was added to bring each individual dose to a total of 20 mg CC49. Before administration of radiolabeled CC49, the flow of fluid in the peritoneal cavity was studied by infusion of 5 mCi 99mTc-albumin and 500 ml saline through the Tenckhoff catheter which has previously been placed for access into the peritoneal cavity. If loculation, which can be quantitated by camera counts is detected, the patient does not receive radiolabeled antibody. For patients in whom free flow of fluid in the peritoneal cavity was demonstrated, the individually
prepared dose of $^{177}$Lu-CC49 was infused by gravity in a volume of 50 ml, followed immediately by 1 liter of saline. The patient then changed position at least every 15 min for the next 2 hr to facilitate homogeneous distribution. Vital signs were monitored every 15 min during and immediately after treatment.

**Pharmacokinetics**

Pharmacokinetics of radiolabeled antibody are assessed by the radioactivity and protein levels in serial samples as has been done in our previous studies (20).

**Immune Response**

The “double antigen” assay developed and extensively used in our radioimmunotherapy studies is used to detect human antimouse antibodies (HAMA) in patient sera (20).

**Tumor Markers**

CA-125 levels followed although not defined as criteria for disease response. Assays are performed commercially by Dianon using techniques that avoid interference by the presence of HAMA.

**Radioimmunoscintigraphy**

Patients are scanned three or more days after administration of intraperitoneal radiolabeled antibody. Whole-body scans were obtained on each occasion and SPECT of the abdominal cavity on one or more occasions. Three peaks of the $^{177}$Lu spectrum are isolated (51 keV, 113 keV, 207 keV) with windows of 30%, 20% and 20%, respectively. Static spot images were acquired on a 128 × 128 matrix for 400K cts. A 512 matrix was used to acquire whole-body scans. The scan speed was determined by count rate of static images (kcts/sec). The time for each frame of SPECT acquisition was also determined from static image count rate. For SPECT images, a 64 × 64 matrix were used with a step-and-shoot tomography. Scans were interpreted for areas of localization that may correspond to tumor deposits and count data were used for dosimetry calculations. Gamma camera images of localization sites were considered positive for a score of 2–4 based on the following grading: 0 = normal, 1 = probably negative, 2 = suspicious, 3 = positive, 4 = strongly positive.

**Dosimetry**

Radiation doses to the red marrow and the total body are calculated according to the MIRD formalism (24). Total-body activities are derived from total-body probe counting. Marrow activities are calculated from activities in plasma samples, according to the methods developed by the AAPM Bone Marrow Dosimetry task group (25) using a red marrow-to-blood ratio of 0.19 (26). S-values for $^{177}$Lu were computed with the MIRDose computer program (27).

**Statistics**

Linear compartment modeling was conducted to estimate pharmacokinetical parameters. One-compartment and multicompartment models were fitted to the serial sample data. The one-compartment model was chosen to best fit the data parsimoniously and estimates from this were used to present data (28,29). Descriptive statistics were calculated including mean, standard error and standard deviation.

**RESULTS**

Twelve patients (aged 51–77 yr) were treated with intraperitoneal $^{177}$Lu-CC49 between January 1993 and May 1994. Three patients per dose level were treated at dose levels of 10, 18, 25 and 30 mCi/m². All patients had adenocarcinomas; histologic features of each patient’s tumor are summarized in Table 1. Previous treatment is listed in Table 2. Ten of the 12 patients were Stage III at diagnosis and the majority had Grade 3 tumors. CA-125 was elevated at the time of diagnosis in all patients but had returned to normal prior to second-look laparotomy for those who underwent that procedure.

After a single administration of $^{177}$Lu-CC49, HPLC evaluation of blood, and peritoneal fluid samples monitored for 5 days showed the $^{177}$Lu-CC49 complex to be stable (30). The peak concentration reaching the blood occurred at approximately 48 hr after administration (Fig. 1). The pharmacokinetics of radioactivity in peritoneal fluid samples was more variable than that in the blood, as would be expected for nonuniform distribution and variance in the intra-abdominal area of sampling. About 10%–25% of the radioactivity was excreted in the urine during the first 24 hr, with a subsequent decline to about 5% per day with monitoring for the initial 96 hr. Radiolocalization consistent with tumor was observed in all except one of the twelve
patients using serial gamma camera scans beginning 4 days after therapy. No bone marrow uptake was evident. Figure 2 shows areas of localization that may represent tumor nodules.

Mild, transient discomfort with administration in an associated volume of 1500 ml occurred in one patient as the only immediate treatment-related adverse effect. Four other patients had various early nonserious post-treatment problems, including catheter infection (Patient 1), diarrhea \( \times 1 \) (Patient 4), itching and nausea (Patient 7), leakage around catheter (Patient 8) and asymptomatic extravasation into soft tissue (Patient 10). Two additional patients had transient arthralgia at 2 wk which required analgesia. This complaint was accompanied by fever in Patient 6, but no proteinuria or abnormal complement values were observed. There was mild marrow suppression with calculated red marrow radiation doses of 11–54 cGy. Table 3 lists the dose estimates of radiation exposure to the whole body and bone marrow for individual patients. Figure 3 shows platelet nadirs after radioimmunotherapy. Despite Grade 1 toxicity on the scale, none of the 12 patients had a platelet nadir <100,000/mm\(^3\). Figure 4 illustrates the WBC nadirs. There were no bleeding or infectious complications. Thus, substantial marrow suppression has not occurred at current dose levels and dose escalation continues.

All of the patients had evidence of an immune response against the murine antibody. Most patients showed an immune response within 2 wk after treatment. The time and peak anti-CC49 level varied but in general represented high levels of immune response (Fig. 5).

The clinical outcome and comparison of pre- and post-treatment CA-125 levels of the patients is presented in Table 4. As shown, one patient with measurable disease had a partial response. Three patients with microscopic or occult disease remain without evidence of disease at >18–26 mo, and one with microscopic disease showed evidence of progression at 10 mo. One patient with gross disease was taken off the study at 11 wk while stable and six with measurable disease progressed within 6 wk. CA-125 levels did not follow a pattern predictive of tumor status for all patients. It did, however, serve as a reliable indicator for a few patients, including Patient 2, who had an elevated pretreatment level which continued to increase in this patient who rapidly progressed, and it normalized in Patient 4 after therapy but increased a few weeks before recurrence was demonstrated at 10 mo post-treatment. Most patients showed a transient increase, which was present as long as 6 wk after therapy, even if the subsequent trend was for decreasing levels and they remained NED for a prolonged period.

Although most patients had relatively strong reactivity with CC49 by immunoperoxidase assay, this finding did not correlate well with clinical outcome. For example, Patient 8 who had the least reactivity (5% to 10% of cells were 3 to 4+) remains disease-free more than 18 mo post-treatment, while Patients 11 and 12, who had the strongest reactivity (50% of cells were 3 to 4+) and received a higher dose of \(^{177}\)Lu-CC49, had evidence of progression by 6 wk after therapy.

**DISCUSSION**

This dose escalating trial has thus far studied four dose levels with only mild-to-moderate hematologic and nonhematologic side effects. Although hematologic toxicity has been dose limiting in previously reported series of intraperitoneal radioimmunotherapy, nonhematologic toxicity has been more prominent in some intraperitoneal salvage therapies using chemotherapy (6).

Administration of \(^{177}\)Lu-labeled antibody has been easily accomplished with less radiation precautions necessary than with \(^{131}\)I. Although these studies required five days of hospitalization for the convenience of frequent monitoring of blood, urine and peritoneal fluid samples, outpatient treatment will be feasible once these pharmacokinetic parameters have been characterized.

The only previously reported human trial of \(^{177}\)Lu-CC49 is a National Cancer Institute Phase I study of intravenous administration in patients with nonovarian TAG-72 reactive malignancies who had failed conventional therapies (23). In contrast to the National Cancer Institute study, which showed uptake of the radiolabel by the bone marrow that resulted in severe...
hematologic toxicity at 25 mCi/m², our intraperitoneal studies have produced no detectable bone marrow localization and only mild marrow suppression at that same and higher dose levels. The mechanism for the difference in marrow localization that is associated with route of administration remains to be elucidated.

Although designed as a dose-escalating trial, evidence of antitumor effects are noted with a partial response in a patient with measurable disease. It is also encouraging that 3/4 patients with microscopic or occult disease remained disease-free for >18 mo.

These results compare favorably with salvage using intraperitoneal chemotherapy or external beam radiation. For 20 published reports using external beam radiation, about one-third of patients with microscopic disease remained disease-free at 2 yr (3). Although some series show improved survival over this average, involved patients are generally those with better prognostic factors (31,32). Several chemotherapeutic agents used alone or in combination with biologic response modifiers have shown activity. Antitumor activity, however, has essentially been limited to patients with small-volume residual disease (7). This should not be unexpected since studies show that some chemotherapeutic agents only penetrate 1–2 mm into tumor nodules when given intraperitoneally.

Lutetium-177-Lu-CC49 represents a new agent with promising initial results. Our results are similar to previous studies which found that the best chance of prolonged disease-free survival was in patients with small-volume disease, and there was increasing resistance to therapy as tumor volume increased (8). Among the previous ovarian cancer radioimmunotherapy studies, the longest follow-up (median 32 mo; maximum 62 mo) was reported for a group of ovarian cancer patients treated with 90Y-HMFG1 antibody as adjuvant or salvage (4). Since <10% of those patients receiving the radioimmunotherapy as adjuvant have died, the actuarial survival is markedly superior to the >80% mortality of patients receiving alternative adjuvant from the North Thames Ovarian Group by 67 mo.

Patients receiving intraperitoneal administration of CC49 tended to have a stronger HAMA response than in our experience with intravenous administration of this antibody to more than 45 patients (20,33). Although the development of HAMA has been a limitation of repeat intravenous radioimmunotherapy (34), it could work advantageously for intraperitoneal administration by accelerating clearance from the systemic circulation. Stewart et al. (11) have successfully used a related mechanism for removal of the radiolabeled antibody after it was absorbed from the peritoneal cavity. They injected serum from previously treated patients (who had developed HAMA) into the patient being treated with intraperitoneal radioimmunotherapy. More rapid clearance from the blood and thus less radiation exposure to the marrow resulted.

The tendency to have an initial elevation of tumor marker after therapy regardless of subsequent decline and evidence of antitumor effects is similar to a pattern noted with PSA in patients treated for prostate cancer with 131I-CC49 (20). Although the mechanism responsible for this effect has not been established, it may represent release of tumor cell components as tumor cells lyse.

CONCLUSION

Our experience thus far shows intraperitoneal radioimmuno-therapy with 177Lu-CC49 to have antitumor activity at what may be suboptimal doses with mild-to-moderate side effects.

ACKNOWLEDGMENTS

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REFERENCES

There is yet no consensus concerning the appropriate regimen of the application of $^{131}I$iodide iodine (NaI) activities to patients suffering from advanced differentiated thyroid carcinoma. We report on a total of 158 applications of $^{131}I$NaI, including 78 applications of 11.1 GBq. Response to high-activity radioiodine therapy (RIT) is correlated to the course of the disease as well as to the reaction of thyroglobulin and acute/subacute side effects of radiation. **Methods:** Following radioablation of thyroid remnants using 1.85 to 3.7 GBq $^{131}I$NaI, 26 patients with advanced differentiated thyroid carcinoma (follicular, 11; papillary, 4; mixed-cell thyroid carcinoma, 11) were treated with repeated activities of 11.1 GBq $^{131}I$NaI. Initial tumor staging according to UICC showed T4 in 54%, T3 in 19%, T2 in 19% and was not obtained in 8%. Differentiated thyroid carcinoma was multifocal in 23% of patients. Applied accumulated activities ranged from 14.8 to 99.9 GBq with a mean of 55.5 GBq per patient. **Results:** Mean post-diagnostic follow-up was 73 mo, mean follow-up after diagnosis of metastatic spread was 48 mo. Follicular thyroid carcinoma remained as stable disease in 7 of 11 patients, 6 of whom showed metastatic disease after a mean of 20 mo, and only 1 complete remission was achieved using high-dose therapies, with progressive disease in the remaining patients. Overall, 75% of follicular thyroid carcinoma had progressive disease without major response to high-activity RIT. In contrast, only 20% of papillary thyroid carcinoma/mixed-cell thyroid carcinoma showed progressive disease, and complete remission was achieved in 47% of patients. Pulmonary and lymph node metastases in the majority of patients showed good response to therapy, whereas local recurrences and bone metastases showed minor reactions to RIT. After low-activity therapies 8% of patients showed WHO grade I hematotoxic reactions. High-activity therapies, 38% of patients had WHO I, 8% WHO II and one patient had WHO III toxicity (4%). **Conclusion:** Use repetitive high-activity RIT with a maximum of 44.4 GBq applied during 1 yr and a maximum of 99.9 GBq accumulated activity resulted in a significant increase of hematotoxicity. However, during the follow-up period (mean, 4 yr), no clinical symptoms possibly related to low blood counts were seen in patients with advanced differentiated thyroid carcinoma. Initiation of high-activity RIT in reaction to metastatic tumor outspread to achieve complete remission was found to be useful in treating papillary thyroid carcinoma and mixed-cell thyroid carcinoma, but only in a minority of follicular thyroid carcinoma patients.

**Key Words:** advanced differentiated thyroid cancer; high-dose iodine-131-sodium iodide therapy; hematotoxicity


**“High-Dose” Radioiodine Therapy in Advanced Differentiated Thyroid Carcinoma**

Christian Menzel, Frank Grünwald, Axel Schomburg, Holger Palmedo, Hans Bender, Georg Späth and Hans-Jürgen Biersack

Departments of Nuclear Medicine and Surgery, University of Bonn, Bonn, Germany

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Differential thyroid carcinoma clinically follows a relatively benign course, with follicular thyroid carcinoma giving a