Phase I and Pharmacological Studies of Adriamycin
Intraperitoneally to Patients with Ovarian Cancer

Robert F. Ozols,1 Robert C. Young, James L. Speyer, Paul H. Sugarbaker, Raymond Greene, Jean Jenkins, and Charles E. Myers

ABSTRACT

A Phase I study of Adriamycin administered i.p. was performed in 10 ovarian cancer patients who were refractory to systemic chemotherapy. Adriamycin was infused in 2 liters of Inpersol via a semipermanent Tenckhoff dialysis catheter. Adriamycin was administered for a 4-hr dwell every 2 weeks with concentrations ranging from 9 to 54 μM. The dose-limiting toxicity of i.p. Adriamycin was a sterile peritonitis. Severe abdominal pain with ascites and adhesions was observed at concentrations greater than 36 μM. There were three objective responses, and two other patients had a marked reduction in ascites formation while on treatment. The objective responses were in patients who had small volume (<2-cm masses) disease. The clinical activity of i.p. Adriamycin was probably the result of cytotoxicity and not merely a sclerotic effect, since the reduction in ascites was accompanied by a decrease in the number of malignant cells and by a corresponding inability of these cells to form tumor colonies in soft agar.

Adriamycin concentrations were measured by high-pressure liquid chromatography. A mean of 85% of the drug was absorbed over the 4-hr dwell time. The concentrations attained i.p. have been demonstrated previously to be cytotoxic to human ovarian cancer cells from untreated patients or from patients who had relapsed after treatment with a non-Adriamycin combination. Plasma levels peaked within the first hr after i.p. instillation. Plasma levels were markedly lower than corresponding peritoneal concentrations. The maximum pharmacological advantage (peak peritoneal concentration/peak plasma concentration) was 474, while the 4-hr peritoneal level was 166 times higher than the corresponding plasma level after an i.p. dose of 40 mg/2 liters (36 μM). The peak plasma levels after a 60-mg/2 liters (54 μM) dose were 10 times lower than after a 60-mg i.v. dose. The recommended starting dose for a Phase II trial is 27 to 36 μM (30 to 40 mg Adriamycin per 2 liters Inpersol) with a 4-hr dwell every 2 to 3 weeks for six cycles.

INTRODUCTION

The determining factor for the successful treatment of ovarian cancer is the eradication of all intraabdominal disease. The majority of patients with ovarian cancer have Stage III disease at the time of diagnosis (2), and postoperative therapy is directed towards the elimination of any residual disease in the pelvis, mesentery, under the diaphragms, or in the paraaortic lymph nodes. Combination chemotherapy regimens have produced clinical complete responses in 35 to 48% of patients with advanced disease (1, 5, 17–19). However, surgical restaging has demonstrated that pathological complete remissions occur in only 20 to 25% of the patients treated with combination chemotherapy (19). Patients with residual disease following an initial response to chemotherapy are usually refractory to the continued administration of systemic chemotherapy. Furthermore, even those patients with a surgically documented complete response to systemic chemotherapy remain at risk for recurrent i.p. disease (18, 19).

The Division of Cancer Treatment, National Cancer Institute, has been evaluating i.p. chemotherapy as a therapeutic modality in intraabdominal cancers. In contrast to earlier trials of i.p. chemotherapy in which antineoplastic agents were administered i.p. in a small volume, the current trials at the National Cancer Institute have utilized a semipermanent Tenckhoff catheter, which has allowed repeated i.p. administration of chemotherapeutic agents in a large volume. Pharmacological modeling studies had suggested that such an approach would be advantageous in diseases confined to the abdominal cavity (3). Phase I trials in ovarian and colon cancer patients of i.p. methotrexate (9) and 5-fluorouracil (15) have demonstrated that repeated dialysis via a Tenckhoff catheter produces a pharmacological advantage (peak i.p. drug level/peak plasma level) of 36 and 298, respectively.

Adriamycin is an antineoplastic agent that has several features which make it a potentially advantageous drug for i.p. administration in ovarian cancer patients. (a) It is an active agent in ovarian cancer with a 40% response rate in previously untreated patients (4, 20). (b) Its molecular weight and hydrophilic properties suggest a slow peritoneal clearance (10); (c) the i.p. route is curative in 70% of mice with a transplantable murine ovarian cancer, which has a metastatic pattern similar to human ovarian cancer (11, 12). Adriamycin i.v. had no effect on survival. And (d) a dose-response relationship between Adriamycin and in vitro cytotoxicity to human ovarian cancer cells has been demonstrated with a clonogenic assay (13, 14). Ovarian cancer cells obtained from patients who had progressive disease after treatment with a non-Adriamycin-containing chemotherapy regimen demonstrated in vitro resistance to concentrations of Adriamycin achievable by i.v. administration of Adriamycin. Significant in vitro cytotoxicity was, however, observed following exposure of the same cells to a concentration of Adriamycin which, while not achievable by i.v. therapy, could potentially be attained by i.p. administration.

This report describes the clinical and pharmacological results of a Phase I trial of i.p. Adriamycin in 10 patients with advanced ovarian cancer. In addition, the clinical results are compared to the in vitro cytotoxicity of Adriamycin as measured...
in the clonogenic assay with ovarian cancer cells from patients receiving i.p. Adriamycin.

MATERIALS AND METHODS

Patient Characteristics. Ten patients with histologically confirmed ovarian adenocarcinoma were treated with i.p. Adriamycin. All the patients had failed a primary systemic chemotherapy regimen: L-phenylalanine mustard, one patient; hexamethylmelamine, cyclophosphamide, methotrexate, 5-fluorouracil (18), 2 patients; or cyclophosphamide, hexamethylmelamine, cis-platinum, 5-fluorouracil (19), 7 patients. In addition, 9 of 10 patients had been treated with i.p. 5-fluorouracil (15). Four patients had tumor masses less than 2 cm in diameter prior to the administration of i.p. Adriamycin and 6 patients had bulky intraabdominal disease.

Tenckhoff Catheter. Semipermanent Tenckhoff silastic dialysis catheters were implanted surgically into the peritoneal cavity under local anesthesia. The catheter was implanted through a s.c. tunnel and secured with a Dacron felt cuff. The patients were instructed in catheter care as described previously (9, 10, 15, 16).

Dialysis Schedule. Patients were treated with Adriamycin (Adria Laboratories, Columbus, Ohio) in 2 liter of Inpersol (Abbott Laboratories, North Chicago, Ill.) containing 1.5% dextrose. Heparin was not added to the bottles containing Inpersol because of precipitation with Adriamycin. All dialysis bottles were warmed to 37° prior to instillation. Adriamycin levels were measured in the Inpersol dialysate, and only a single peak was detected with high-pressure liquid chromatography (see below).

The patients received a single 4-hr instillation of Adriamycin containing dialysate every 2 weeks unless otherwise indicated. The dialysis procedure consisted of 3 separate exchanges. The first 2-liter bottle containing only Inpersol was instilled and immediately drained. The second 2-liter bottle contained Adriamycin and was allowed to dwell for 4 hr and was then drained. The third 2-liter bottle was plain Inpersol and was immediately drained after instillation.

The Adriamycin concentration of the dialysate was progressively increased with each dialysis course until toxicity became prohibitive. The initial 3 patients were treated at 9 μM Adriamycin (10 mg/2 liters) followed by 3 patients who were started at 18 μM (20 mg/2 liter), 3 patients at 36 μM (40 mg/2 liters), and one patient whose initial dialysate was 54 μM (50 mg/2 liters).

In Vitro Sensitivity of Adriamycin. The in vitro sensitivity to Adriamycin was determined previously for ovarian initially by Hamburger et al. (6, 7). Human ovarian cancer cells were obtained from either malignant ascites or malignant washings collected via the Tenckhoff catheter and exposed for 1 hr to various concentrations of Adriamycin. The effect on tumor colony-forming cells was then compared to untreated controls. In 2 patients, the colony-forming ability of cells collected immediately prior to and immediately after an in vivo exposure to a 4-hr dwell with Adriamycin was compared.

Determination of Adriamycin Levels. Plasma from 5 ml of blood collected in EDTA glass tubes and peritoneal fluid (withdrawn through the Tenckhoff catheter) was frozen at −20° until analysis. The samples were prepared for analysis by adding 50 ng daunomycin as an internal standard and 1.0 ml of 0.1 M sodium borate buffer, pH 9.8, to 1.0 ml of the plasma or peritoneal fluid. Each sample was then extracted with 17 ml of chloroform:methanol (4:1, v/v), and the organic layer was transferred to a conical tube and evaporated to dryness under nitrogen at room temperature. The residue was dissolved in 100 μl methanol and injected into the high-pressure liquid chromatograph. Standards containing 0 to 200 ng/ml of Adriamycin were processed in an identical fashion as the samples of blood or peritoneal fluid.

Drug levels were measured on a high-pressure liquid chromatographic system with fluorescent detection using a phenyl reverse-phase column (9). Quantitation of drug concentrations was achieved by measuring the peak height ratios of drug internal standards of the samples and comparing them to a standard curve constructed by plotting peak height ratio versus concentration of the known standards using a least-squares plot.

RESULTS

Tenckhoff Catheter. Ten patients with advanced refractory ovarian cancer were treated with a total of 38 courses of i.p. Adriamycin (range, one to 6 cycles/patient). Tenckhoff catheters were well tolerated by the patients. Two of the patients experienced mild abdominal pain, which was positional and probably due to irritation from the catheter tip. There were no instances of bacterial peritonitis during i.p. Adriamycin therapy.

Toxicity. The i.p. administration of Adriamycin in ovarian cancer patients was associated with gastrointestinal toxicity, myelosuppression, and peritoneal irritation (Table 1). The lim-

<table>
<thead>
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<th>Maximum concentration (μM)</th>
<th>Patient</th>
<th>No. of cycles</th>
<th>No. of cycles at maximum concentration</th>
<th>Toxicity at maximum concentration</th>
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<td>1</td>
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<td>3</td>
<td>1</td>
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<td>6</td>
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<tr>
<td></td>
<td>10</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Two liters of dialysate for a 4-hr dwell every 2 weeks.
  
* Suppression of WBC to less than 3500/cu mm.
  
* Count less than 100,000/cu mm.
  
* +, persisting for 24 hr; ++, > 24 hr.
  
* +, persisting for <24 hr; ++, persisting for 1 to 3 days requiring mild analgesia; ++++, persisting for 3 to 8 days requiring codeine analgesia.
  
* Adhesions observed at autopsy or after a second-look procedure.
ting toxicity of i.p. Adriamycin was a dose-dependent peritoneal irritation (Table 2). At a concentration of 9 μM (10 mg/2 liters) with a 4-hr dwell, only 1 of 3 cycles produced mild abdominal discomfort lasting less than 24 hr (1+ peritoneal toxicity). In contrast, at a concentration of 54 μM (60 mg/2 liters), 2 of 6 courses were associated with pain lasting from 1 to 3 days requiring mild analgesics (2+ toxicity), and 4 of 6 courses at this dose resulted in persistent abdominal pain lasting 3 to 10 days requiring codeine analgesia (3+ peritoneal toxicity). The development of 2+ and 3+ peritoneal toxicity led us to increase the interval between dialysis from 2 to 3 weeks at the higher concentrations of Adriamycin (≥36 μM). The higher doses of i.p. Adriamycin also resulted in the formation of sterile ascites in 2 patients, which persisted for 1 and 3 months. There were no instances of drug-induced intestinal obstruction, although 2 patients also had an increase in asymptomatic abdominal adhesions after i.p. Adriamycin, noted at a second-look laparotomy and a restaging peritoneoscopy. All 3 patients who had 3+ peritoneal irritation at 54 μM had decreased abdominal pain when the concentration was decreased to 36 μM.

The peritoneal toxicity did not appear to increase with an increased number of cycles of i.p. Adriamycin. Nine patients received more than one cycle of dialysis with 4 patients receiving either 5 or 6 cycles of i.p. Adriamycin. The peritoneal toxicity was correlated with the highest concentration of i.p. Adriamycin. As noted above, as the concentration of a subsequent cycle was decreased in these patients, the severity of the peritoneal toxicity also decreased. The recommended starting dose with acceptable peritoneal toxicity in a Phase II study of i.p. Adriamycin would be 27 to 36 μM administered in 2 liters with a 4-hr dwell every 2 to 3 weeks for a total of 6 cycles.

Less frequent and less severe toxicities included nausea and vomiting and myelosuppression. Only one patient had nausea and vomiting lasting longer than 24 hr. However, this patient also had a tumor-related partial small bowel obstruction. Three patients had myelosuppression with WBC nadirs of 3.6/cu mm, 2.7/cu mm, and 1.4/cu mm, which developed after a concentration of 36 μM. One patient also developed thrombocytopenia of 17,000/cu mm, which was a preterminal event developing 21 days after a dose of 36 μM (40 mg/2 liters).

Pharmacological Studies. The mean 4-hr i.p. Adriamycin level was 15% of the instilled drug concentration. The mean disappearance half-life (sum of absorption and binding to i.p. tissues) of Adriamycin from the peritoneal dialysate was 1.6 hr. The plasma levels of Adriamycin peaked within 30 min of i.p. administration and then gradually declined over 24 h (Chart 1). The plasma levels following an i.p. dose of 60 mg/2 liters (54 μM) are compared to the plasma levels observed in 2 different patients who received the same dose i.v. The peak plasma level following the i.v. bolus was 10 times greater than the peak plasma levels observed after i.p. administration. Except for the difference in the peak plasma levels, the pharmacokinetics of Adriamycin clearance from the blood was similar for the first 24 hr after i.p. and i.v. administration, although the absence of Adriamycin levels 24 to 72 hr after i.p. administration did not allow for an exact comparison of i.p. versus i.v. area under the curve values. Adriamycin metabolites were detected in the plasma after i.p. administration of 36 to 54 μM Adriamycin.

The i.p. administration of Adriamycin produced a marked pharmacological advantage with the mean peak peritoneal fluid level being 474 times greater than the mean peak plasma level after an i.p. dose of 40 mg/2 liters (36 μM) (Table 3). The mean peritoneal level at the completion of the 4-hr dwell was 166 times greater than the corresponding plasma level. Similar ratios of peritoneal fluid Adriamycin levels to plasma levels were observed after an i.p. dose of 60 mg/2 liters (54 μM) (Table 3).

Response Data. There were 3 responses in the 10 patients with refractory ovarian cancer who received i.p. Adriamycin. One patient had a negative peritoneoscopy after 6 cycles of i.p. Adriamycin [peak dose, 60 mg/2 liters (54 μM)]. She was not treated for 18 months until a subsequent peritoneoscopy revealed malignant cells in the peritoneal washings. Another patient had multiple small peritoneal tumor nodules prior to i.p. Adriamycin. At the completion of 6 cycles of i.p. Adriamycin [maximum dose, 50 mg/2 liters (45 μM)], a single focus of

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**Table 2**

Peritoneal irritation of i.p. Adriamycin

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>No. of cycles</th>
<th>Pain</th>
<th>Ascites</th>
<th>Adhesions</th>
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<td>6</td>
<td>2/6</td>
<td>4/6</td>
<td>1/6</td>
</tr>
</tbody>
</table>

*See Table 1.*
malignant cells was found in the omentum. A third patient whose only evidence for ovarian cancer was cytologically malignant peritoneal washings developed negative washings which persisted for 4 months. Two other patients had marked reduction in ascites production while receiving i.p. Adriamycin. Instead of 3 to 5 liters of ascites production per week requiring frequent paracentesis, both patients did not require therapeutic paracentesis after the initial cycle of i.p. Adriamycin. In addition, the number of cells in the ascites decreased from 50 to 100 x 10^6 cells/liter to 5 to 10 x 10^6 cells/liter. Both of these patients, however, developed progressive disease outside the peritoneum.

In vitro cytotoxicity to Adriamycin was evaluated using the human tumor stem cell assay (Table 4). Ovarian cancer colony formation was observed in 8 of 10 specimens; however, only 4 specimens (40%) had sufficient colony formation to evaluate in vitro cytotoxicity. Of these 4 specimens, 3 demonstrated sensitivity to Adriamycin (>70% colony reduction) following a 1-hr exposure to Adriamycin at 10 μg/ml (18 μM). Two of the specimens were obtained from patients who had a marked reduction in ascites production while on i.p. Adriamycin. Tumor cells from both patients collected immediately after a 4-hr dwell at 18 μM. Either no colony growth or insufficient colonies (<30/plate) to perform drug testing upon. In vitro sensitivity to Adriamycin

<table>
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<tr>
<th>Patient</th>
<th>Specimen</th>
<th>Colony growth</th>
<th>&gt;30 colonies/plate</th>
<th>Sensitivity to Adriamycin</th>
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<td>1</td>
<td>Washings (+)</td>
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<td>Yes</td>
<td>Untestable</td>
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<tr>
<td>2</td>
<td>Ascites Posttreatment washings (+)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>3</td>
<td>Ascites Posttreatment washings (+)</td>
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<td>Yes</td>
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<tr>
<td>4</td>
<td>Washings (+)</td>
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</tr>
<tr>
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<td>10</td>
<td>Washings (+)</td>
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</tbody>
</table>

Five or more colonies/500,000 nucleated cells.

Greater than 70% reduction in colony survival following a 1-hr exposure to Adriamycin at 10 μg/ml (18 μM).

Cells collected from the Tenckhoff catheter following a 4-hr dwell at 18 μM.

DISCUSSION

The results of this trial have demonstrated that i.p. Adriamycin can be administered safely to refractory ovarian cancer patients. The rationale for this trial was based on pharmacological modeling studies (3) and experimental studies in murine ovarian cancer (11, 12) and with human ovarian cancer cells in a short-term soft-agar culture (13, 14). The pharmacokinetic basis for i.p. therapy is the slower absorption (clearance) of many drugs from the peritoneum compared to the rate of elimination from the rest of the body. Consequently, tumors confined to the abdomen will be exposed to a higher concentration of cytotoxic drugs than systemic levels. The administration of drugs in a large volume (2 liters of dialysate) through a semipermanent Tenckhoff catheter helps ensure uniform distribution of drug throughout the peritoneal cavity and allows for repeated drug administration to maintain a constant high level of i.p. drug. In theory, the greatest antitumor effect would be achieved with an i.p.-administered drug, which resulted in cytotoxic levels i.p. as well as in the systemic circulation.

The experimental rationale for i.p. Adriamycin in ovarian cancer patients was based on studies in murine ovarian cancer and with human ovarian cancer cells. In the murine model, it was demonstrated that i.p. Adriamycin was more beneficial than i.v. Adriamycin because of higher intracellular Adriamycin levels with a resultant increased suppression of DNA synthesis (11) in tumor cells. In vitro dose-response studies in human ovarian cancer cells, either from malignant effusions or cytologically malignant peritoneal washings, demonstrated 3 sep-
arate patterns of Adriamycin sensitivity using colony survival in soft agar (13, 14). The greatest degree of sensitivity was observed in cells from previously untreated patients whereas cells from patients who had relapsed after therapy with systemic Adriamycin demonstrated marked in vitro resistance. Even after a 1-hr exposure to 18 μM Adriamycin, a concentration 10 times greater than the peak level after i.v. administration, the mean inhibition of colony formation was only 20%. In contrast, cells obtained from patients who had relapsed after therapy with a non-Adriamycin combination had a dose-dependent survival of colony formation. After exposure to Adriamycin at the peak levels achievable by i.v. administration, there was no significant inhibition of colony formation, but at a 18 μM exposure, the mean percentage of colony inhibition was 90%. These results suggest that if the Adriamycin concentration to which human ovarian cancer cells are exposed could be increased to 10-fold the peak plasma level achievable after i.v. therapy, then clinical benefit may be obtained for that group of patients who became refractory to non-Adriamycin combinations. Patients who have relapsed after therapy with systemic Adriamycin are not likely to benefit from such an approach, since Adriamycin resistance in these cells was of such a magnitude in the in vitro studies that significant cytotoxicity was not achieved even by increasing the drug levels to 10 times that achievable by i.v. administration.

The Phase I trial of i.p. Adriamycin demonstrated that the levels of Adriamycin which were required to produce significant in vitro cytotoxicity (in cells from previously untreated patients or after treatment with a non-Adriamycin regimen) could in fact be achieved by administration of Adriamycin via the Tenckhoff catheter. The pharmacological advantage (peak i.p. level/peak plasma level) achieved with Adriamycin was 474. This was greater than that observed with either methotrexate, 36 (7), or 5-fluorouracil, 298 (8). In this small series of patients, the clinical activity of i.p. Adriamycin (3 partial responders) was confined to patients who had a small volume of disease at the initiation of i.p. Adriamycin. These results are in agreement with the experimental observation that Adriamycin does not penetrate deeply into intraabdominal tumor masses. Using the intrinsic fluorescence of Adriamycin, we have demonstrated previously that Adriamycin does not penetrate more than 6 to 8 cell layers into intraabdominal murine ovarian tumors (12).

The major and dose-limiting toxicity of i.p. Adriamycin was peritonitis. Abdominal pain became apparent in all patients with a dose of 18 μM or greater. At higher doses of i.p. Adriamycin, the severity and intensity of the abdominal pain increased. In addition, sterile ascites and peritoneal adhesions also resulted after treatment at doses greater than 36 μM. Since 9 of 10 patients in this trial had been treated previously with i.p. 5-fluorouracil, which also can result in peritoneal irritation (8), the peritoneal toxicity of i.p. Adriamycin may have been a result of, in part, an already drug-damaged peritoneum. The clinical activity of i.p. Adriamycin was probably a cytotoxic effect and not due to peritoneal sclerosis because (a) the decrease in volume of ascites following i.p. Adriamycin was associated with a net decrease in concentration of malignant cells in the ascites and (b) ovarian cancer cells obtained from patients immediately following i.p. Adriamycin had a marked decrease in colony formation compared to i.p. Adriamycin.

On the basis of this Phase I trial of i.p. Adriamycin, we have initiated a Phase II trial of i.p. Adriamycin in refractory ovarian cancer patients who have not received systemic Adriamycin and who have residual masses less than 2 cm in diameter.

REFERENCES

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