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ORIGINAL ARTICLE

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A pilot phase I trial of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer

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Abstract *Purpose*: Because intraperitoneal (i.p.) therapy may provide a therapeutic advantage and because hyperthermia enhances carboplatin (CBDCA) cytotoxicity, we evaluated the feasibility, toxicity, and pharmacokinetics of CBDCA given via continuous hyperthermic peritoneal perfusion (CHPP) in patients with small-volume residual ovarian cancer. *Patients and Methods*: Six patients underwent optimal cytoreductive procedures (residual disease ≤5 mm) as initial treatment of stages II and III epithelial ovarian adenocarcinoma. All patients received a 90-min CHPP at a CBDCA dose of 800–1200 mg/m^2, with the perfusate being recirculated rapidly from a reservoir through a heat exchanger, resulting in i.p. temperatures of 41–43 °C. Plasma, perfusate, and urine samples were collected and platinum was quantified by flameless atomic absorption spectrophotometry. *Results*: At no time did any patient's core temperature exceed 40 °C. Peak perfusate platinum concentrations were 8- to 15-fold higher than peak ultrafilterable plasma concentrations. The permeability-area product was extremely high and variable (14–90 ml/min), resulting in a regional advantage of 1.9–5.3. The percentage of the dose absorbed ranged widely from 27% to 77%. Dose-limiting hematologic toxicity was observed at a dose of 1200 mg/m^2 and this was associated with a CBDCA AUC in plasma of 11 mg min ml^{-1}. *Conclusions*: CHPP with CBDCA was safely given to three patients at a dose of 800 mg/m^2, and dose-limiting hematologic toxicities observed at 1200 mg/m^2, correlated with the plasma CBDCA exposure established when lower doses of CBDCA are given systemically. The pharmacokinetic data are consistent with the expected effect of vigorous mixing on the exposed peritoneal surface area. Variable drug absorption and clearance make the prediction of systemic exposure highly uncertain. These findings may have important implications for novel therapies given i.p.

Key words Continuous hyperthermic peritoneal perfusion · High-dose CBDCA · Small-volume residual ovarian cancer · Systemic exposure Hepatic toxicity

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Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer and is the fourth most frequently occurring fatal cancer in women in the United States. Each year there are nearly 24,000 newly diagnosed cases and approximately 13,600 deaths from ovarian cancer in the United States [43]. Epithelial ovarian carcinoma is the most common ovarian malignancy and, because patients usually remain asymptomatic until metastases occur, approximately 70% of cases involve advanced (stage III or IV) disease. Because the survival of patients with advanced disease is significantly longer when minimal residual disease remains after initial cytoreductive surgery, aggressive operative intervention has become accepted therapy in the early management of this disease [23, 24]. Following surgical debulking, platinum-based chemotherapy is the standard therapeutic regimen given systemically [53]. Unfortunately, the currently available

modalities for the treatment of epithelial ovarian cancer result only in enhanced disease-free intervals but fail to confer any significant long-term survival benefit. Indeed, even patients with high-grade stage I disease have only a 50% 5-year survivorship [9, 48].

Increasing interest has arisen in the treatment of advanced ovarian cancer patients with surgical debulking followed by adjuvant, dose-intensive chemotherapy and either stem-cell support or autologous bone marrow transplantation, partly because nearly 70% of patients with epithelial ovarian cancer demonstrate an initial clinical response to platinum-based regimens, but the majority relapse and eventually succumb to chemotherapy-refractory disease [20, 35]. In addition, several clinical studies of heavily pretreated patients have shown that the majority of patients respond to high-dose chemotherapy [5, 40–42]. This has led some investigators to assert the recurrences in platinum-responsive patients occur because higher doses are necessary to eradicate relatively less sensitive clones of cells that become resistant to platinum when lower doses are given during initial treatment [32]. As based on in vitro data, cisplatin resistance appears to be a relative as opposed to absolute phenomenon that can be overcome by an increase in the concentration of the drug [4].

The theoretical, experimental, and pharmacokinetic rationale for intraperitoneal drug administration for malignant disease of the ovary has previously been outlined [12, 36, 49]. Water-soluble drugs such as carboplatin (CBDCA) will diffuse out of the peritoneal cavity slowly and generally maintain a significantly higher concentration within the peritoneal space than in the plasma because of rapid clearance from the systemic circulation. In intraperitoneal dose-escalation studies the peak CBDCA concentrations were 18- to 24-fold higher in peritoneal fluid than in plasma, and at 4 h the area under the concentration versus time curve (AUC) was 18-fold higher [13, 15]. Clearly, a substantial regional advantage can be achieved using intraperitoneal perfusion while limiting the systemic toxicities.

The selective lethal effect of supranormal temperatures on neoplastic cells and the additive or synergistic effect of combining hyperthermia with chemotherapy have been well established in laboratory models [8, 22, 28] and have provided the rationale for numerous clinical trials using whole-body hyperthermia combined with systemic chemotherapy for treatment of advanced malignancies [21, 27, 45, 52] This phase I study evaluated the feasibility of continuous hyperthermic peritoneal perfusion (CHPP) with escalating doses of intraperitoneal (CBDCA) in the treatment of patients with stage II or III ovarian cancer.

Patients and methods

Patient eligibility

Patients over 18 years of age with histologically proven epithelial ovarian adenocarcinoma confined to the peritoneal cavity were eligible for this study. Only optimally debulked patients with no residual tumor nodule measuring >5 mm in diameter were eligible for treatment. Eligibility criteria included the following: (1) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (2) no chemotherapy, immunotherapy, or radiotherapy within 30 days; (3) no concomitant medical problem that would preclude their being an operative candidate; and (4) adequate hematopoietic (absolute neutrophil count $>1{,}500/\mu l$ and platelet count $>100{,}000/\mu l$), hepatic (total bilirubin level <1.5 mg/dl), and renal (creatinine <1.5 mg/dl) functions. All patients gave written informed consent according to institutional and federal guidelines.

CHPP technique

Patients underwent tumor debulking and extensive lysis of adhesions followed by CHPP. For patients who had not previously received cytoreductive surgery a debulking operation was performed, which included removal of all disease greater than 5 mm in diameter. In such cases, pathologic confirmation of ovarian adenocarcinoma by frozen section sufficed as histologic evidence of disease. If the patient had undergone primary cytoreductive surgery prior to consideration of protocol eligibility, the operative report was reviewed to confirm that all residual tumor nodules measured ≤ 5 mm in diameter. Some patients required bowel resection as part of optimal tumor debulking efforts, and this was performed when indicated. After tumor debulking and lysis of adhesions, two large-bore catheters (36-Fr Lavacuator tubes; Mallinckrodt, Argyle, N.Y.) were inserted through the abdominal wall, one over the right lobe of the liver and one in the pelvis. The abdominal fascia was closed, and the catheters were connected to a perfusion circuit as schematized in Fig. 1.

The perfusate passed from a venous reservoir (Baxter, Irvine, Calif.) through a roller pump (Cobe Cardiovascular, Inc., Cincinnati, Ohio) and a heat exchanger (Hemotherm, Cincinnati Subzero, Cincinnati, Ohio), and then into the abdominal cavity. Efflux from the other catheter was then recirculated through the reservoir and pump. Influx passed into the abdominal cavity through the catheter

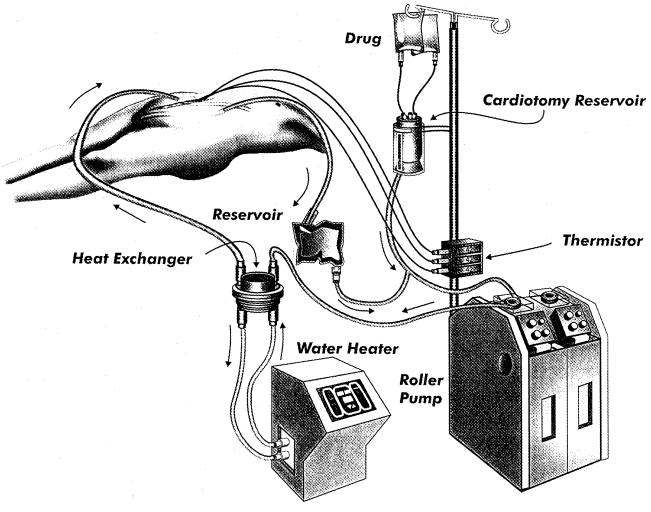

Fig. 1 Schematic drawing of the perfusion apparatus for continuous hyperthemic peritoneal perfusion (CHPP)

overlying the liver, whereas perfusate efflux circulated through the catheter placed in the pelvis. The perfusion flow rate was maintained at 1.5 l/min except in one patient (patient 6), who was limited to 0.5–0.8 l/min due to outflow obstruction. A perfusate volume (4–5) was maintained that moderately distended the abdominal cavity. Once this had been accomplished, the peritoneal cavity was warmed to approximately 41 °C prior to addition of the cytotoxic agents. The abdominal fascia was continuously inspected for leakage of perfusate and, when this was encountered, additional buttressing sutures were placed to correct the fascia leakage. The perfusion was continued for 90 min after addition of the cytotoxic agent. Constant physical manipulation of the abdomen (vigorous manual shaking) was maintained for the entire 90 min to ensure even distribution of the perfusate and uniform peritoneal heating.

The heater coil was maintained at 48 °C. The peritoneal temperature was measured continuously by a Thermistor (Electromedics, Inc., Englewood, Col.) attached to three myocardial needle probes (Electro-medics, Inc) placed immediately beneath the peritoneal surface on either side of the abdomen and in the pelvis. The patient's core temperature was measured with an esophageal probe (this measurement has been found to correlate well with pulmonary artery temperatures; data not shown) and did not exceed 40 °C due to the use of a cooling blanket and ice packs around the legs and head. At the end of the perfusion the abdomen was reopened and the perfusate volume recovered was measured.

Drug administration

The CBDCA (Platinol; Bristol Myers Squibb, Princeton, N.J.) was added to the perfusion circuit via a cardiotomy reservoir (Baxter) after a stable flow rate and temperature had been established. A volume of perfusate equal to the volume of CBDCA to be added was removed from the circuit before addition of the drug. Because of the fluid shifts experienced during a long operation, special attention was paid to maximization of urine output during and after the CBDCA exposure. Patients were hydrated intraoperatively and postoperatively with crystalloid to maintain a urine output of 50–100 ml/h for 12–24 h.

Dosage

Because of the many physiologic and hemodynamic changes associated with major abdominal surgery that may renal drug clearance parameters, CBDCA doses were calculated on the basis of body surface area rather than AUC. The drug dose was escalated from a starting perfusate dose of 800 mg/m^2, a dose that has been tolerated when infused intravenously in conjunction with granulocyte-macrophage colony-stimulating factor [44]. The dose was to be increased by increments of 400 mg/m^2 after three patients had been treated at each level without experiencing dose-limiting toxicity. Toxicities were assessed using the National Cancer Institute's Common Toxicity Criteria [51]. Dose-limiting toxicity was defined as grade IV neutropenia, anemia, or thrombocytopenia or any grade III or IV nonhematologic toxicity, excluding grade III nausea or vomiting, grade III hepatic or pancreatic toxicity that returned to grade I within 2 weeks of treatment, or grade III fever occurring after the treatment.

Pretreatment and follow-up evaluation

Histories, physical examinations, and routine laboratory studies were evaluated before the beginning of the therapy. Patients were monitored in the intensive care unit postoperatively for at least 24 h. The patients underwent routine laboratory screening daily in the postoperative period for the first 5 days, then twice weekly until their discharge from the hospital. All postoperative complications and the time until the patient tolerated a regular diet were recorded. The patients were reevaluated by physical examination and laboratory screening at 4 weeks from the time of surgery. Six cycles of standard first-line systemic chemotherapy consisting of paclitaxel plus either cisplatin or CBDCA were given off-protocol. This systemic therapy began at least 3 weeks but not more than 8 weeks following the CHPP/CBDCA treatment.

Pharmacokinetics studies

Plasma and perfusate concentrations of platinum were determined for five of the six patients. In addition, 24-h urine collections were obtained from three of these five. The sampling schedule for blood, perfusate, and urine was 0, 15, 30, 45, 60, and 90 min after the start of the perfusion, with additional samples of blood and urine being obtained at 3, 6, 12, 18, and 24 h after the start of the perfusion. All samples were placed immediately on ice, plasma was prepared from blood samples by centrifugation, and then all samples were transferred to storage at 70 °C until analysis. Ultrafiltrates were prepared from thawed aliquots of plasma by placement of a portion of that plasma into Amicon Centrifree micropartition devices (Amicon, Beverly, Mass.) and centrifugation of the devices at 2,000 *g* for 20 min at 4 °C in a Sorvall RC-2B centrifuge (DuPont, Wilmington, Del.). Total platinum was measured in all samples, and ultrafilterable platinum was also measured in the plasma, by flameless atomic absorption spectrophotometry as described elsewhere [16]. The amount of CBDCA absorbed from the perfusate was determined from the difference between the amount of drug added to the perfusate and the amount recovered at 90 min (corrected in one patient for leakage). The initial concentration in the

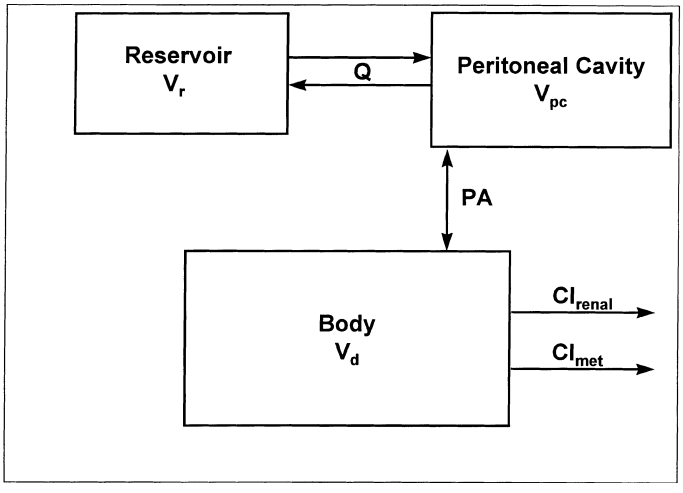

Fig. 2 Compartmental diagram for CHPP of CBDCA. The drug-containing perfusate is recirculated rapidly between the reservoir and the peritoneal cavity. Drug absorbed from the peritoneal cavity into the body is eliminated by renal excretion and by platination of nucleophilic sites in the body with respective clearances CL_{renal} and CL_{met} (V_r Volume of the reservoir and the associated extracorporeal circuit, V_{pc} volume of fluid in the peritoneal cavity, V_d is the volume of distribution of CBDCA in the body, *PA* permeability-area product or mass-transfer coefficient for exchange of CBDCA between the peritoneal cavity and the systemic plasma)

Table 1 Clinical characteristics of patients undergoing CHPP/CBDCA (*BSA* Body surface area)

Patient	Age (years)	Weight (kg)	BSA (m^2)	Prior chemo	Prior surgery	Gross residual disease	Stage	Grade	Histology
1	65	90	21	No	Yes	None	IIIC	3	Papillary serous
2	53	81	1.9	No	No	None	IIIC	3	Transitional cell
3	40	59	1.7	Yes	Yes	None	IIC	3	Papillary serous
4	43	58	1.5	No	Yes	None	IIC	3	Endometrioid
5	50	73	1.8	No	No	None	IIIA	3	Carcinosarcoma
6	67	47	1.4	No	Yes	<5 mm	IIIB	3	Mixed epithelial

perfusate was assumed to equal the dose divided by the initial volume.

The basis of the pharmacokinetic analysis is displayed in Fig. 2. The total perfusate volume (V) is divided between the peritoneal cavity (pc) and the reservoir (r) with its associated extracorporeal circuit. Because the ratio of perfusate volume ($V_r + V_{pc}$) to flow in the circuit, Q, provides a half-time for mixing of about 2 min, these compartments were assumed to have the same concentration, C_{pc}, on the 90-min time scale of the perfusion. The rate of drug absorption from the peritoneal cavity into the systemic circulation is equal to (PA) $(C_{pc} - C_{pl})$, where PA is the permeability-area product or intercompartment mass-transfer coefficient and C_{pl} is the drug concentration in the plasma, assumed to be related to the concentration of ultrafilterable platinum. The value of PA is then determined by division of the amount of platinum absorbed during the 90-min perfusion by the difference between the areas under the peritoneal and plasma platinum concentration curves from 0 to 90 min, $AUC_{pc,0-90}$, and $AUC_{pl,0-90}$. The total body clearance, $CL_{TB,}$ is composed or renal excretion, CL_{renal}, and metabolic clearance, CL_{met}, resulting from platination of nucleophilic sites in the body. The CL_{TB} is obtained by division of the amount of platinum absorbed by the area under the curve for filterable platinum in the plasma from 0 to 24 h (1,440 min), $AUC_{pl,\ 0-1440}$. The regional advantage, R_d, is defined as the ratio of the exposure of the peritoneal cavity to the exposure of the systemic circulation: $(AUC_{pc,0-90} + AUC_{pl,90-1440})|AUC_{pl,0-1440}$. It may also be computed from the equation $R_d = 1 + CL_{TB}|PA$ [10]. The rate constant for platination of plasma proteins, $k_{pl,}$ was calculated by division of the concentration of nonfilterable platinum in the plasma at 24 h by $AUC_{pl,0-1440}$.

Results

Patient's characteristics

Six patients with biopsy-confirmed, epithelial ovarian malignancies were prospectively entered into this phase I clinical trial (Table 1). The median age was 52 years (range 40–67 years). Only one patient had received systemic chemotherapy before enrolling in this study (patient 3, who received four cycles of cisplatin given at 75 mg/m^2 and paclitaxel given at 175 mg/m^2 every 3 weeks). Two patients underwent CHPP immediately following their primary debulking procedures (patients 2 and 5), whereas four patients underwent CHPP at 2–16 weeks following their initial surgical staging operation. All patients underwent optimal cytoreductive procedures such that patients had no gross residual disease and one patient had miliary residual tumor nodules measuring <5 mm in diameter (patient 6). None of the four patients undergoing secondary surgical procedures required further cytoreductive efforts. Two patients had stage II disease and four patients had stage III disease. No retroperitoneal lymph node involvement was identified in the two patients with stage IIIC disease (patients 1 and 2). All patients had one of various histopathologic cell types of epithelia ovarian adenocarcinoma; one patient had a heterologous ovarian carcinosarcoma (malignant mixed mullerian tumor) consisting of a mixed epithelial adenocarcinoma with leiomyosarcomatous and rhabdomyosarcomatous elements (patients 5). Two patients required resection of the rectosigmoid colon as part of their tumor debulking (patients 1 and 2). All patients were capable of completing the 90-min CHPP. The median total operative time was 7 h (range 5.5–9.5 h). All patients survived the operation and treatment.

Maximum tolerated dose

When CBDCA is given systemically, bone marrow suppression is the dose-limiting toxicity [1]. Consistent with this observation, CBDCA-related toxicities encountered during CHPP were exclusively hematologic toxicities and were generally dose-dependent. The toxicities experienced by the patients in this study are listed in Table 2. Of the three patients receiving CBDCA at a dose of 800 mg/m^2, only one experienced any appreciable hematologic toxicity (patient 3). All three patients

Table 2 Dose-limiting toxicities observed in patients receiving CHPP/CBDCA. Toxicities are expressed as roman numerals representing the grade of toxicities on a scale of I to V (see Patients and methods for details)

Patient	CBDCA dose (mg/m^2)	CBDCA dose (mg)	Leukopenia (grade)	Neutropenia (grade)	Thrombocytopenia (grade)
1	800	1,680			
2	800	1,544			
3	800	1,360	III		
4	1,200	1,850	III	IV	IV
5	1,200	2,160	III	IV	
6	1,200	1,680			III

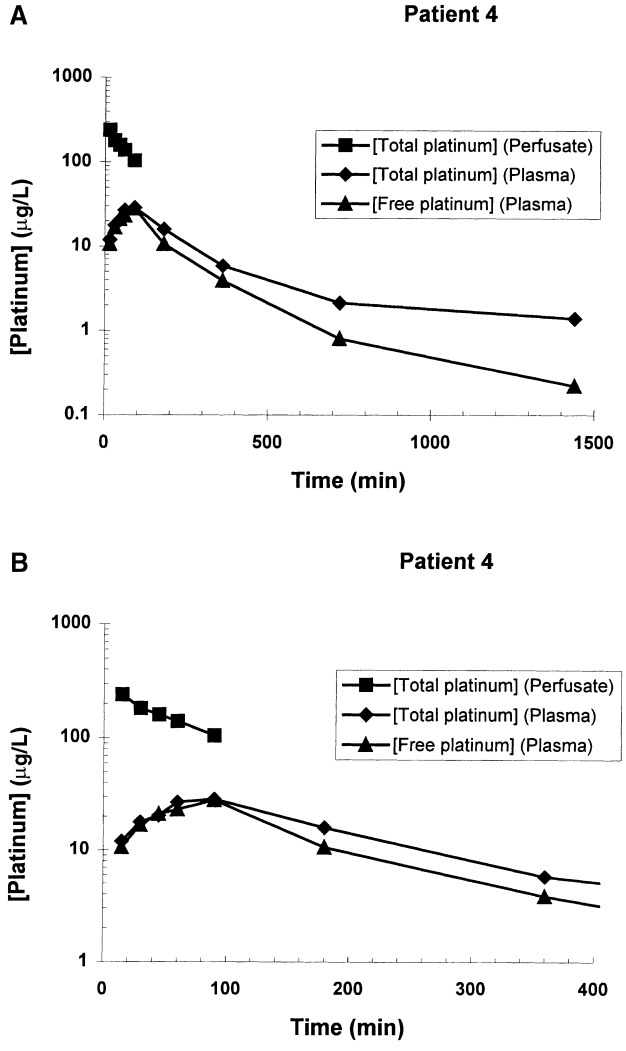

Fig. 3A,B Representative concentration vs time graph generated for patient 4. **a** Platinum concentration in the peritoneal cavity and plasma (ultrafilterable and total) vs time following the beginning of CBDCA perfusion. **b** Expanded scale of the peritoneal and ultrafilterable plasma concentrations

who received the 1,200-mg/m^2 dose experienced significant bone marrow toxicity comprising two grade 4 neutropenic event and one grade 4 thrombocytopenic event. Therefore, the maximum tolerated dose of CBDCA given via CHPP was defined as 800 mg/m^2. No patient developed sepsis or hemorrhagic diathesis as a consequence of the CBDCA-related toxicity. All patients subsequently began systemic chemotherapy regimes at 3–5 weeks following CHPP.

CHPP parameters

The initial perfusate volume ranged from 4 to 5 l. In two cases the perfusate volume had to be supplemented with additional crystalloid to maintain adequate return of the perfusate to the pump. With the water-heating element maintained at 48 °C, the intraperitoneal temperature, as averaged over the three probes and all times was 42 °C (interpatient range 41–43 °C). Patients core temperatures averaged 38 °C, with a maximum of 40 °C being measured in one patient.

Regional complications

There was no notable delay in the return of bowel function (no patient had prolonged postoperative ileus), and no adverse effect on wound healing was observed. The median time before the patients tolerated any enteral feeding was 5.0 days (range 1–7 days) following surgery; patients could tolerate a regular diet at a median of 7.0 days (range 4–8 days) postoperatively. Neither of the two patients who had undergone bowel resection and anastomosis followed by CHPP experienced any anastomotic complication. One patient (patient 6) incurred undetected trauma to the left inferior epigastric artery during the CHPP procedure and required reexploration on postoperative day 1 to correct a subfascial hematoma.

Table 3 Pharmacokinetic results obtained in patients undergoing CHPP/CBDCA. Data are not available for patient 3. CL_{renal} could not be calculated in patient 1 or 2 because urine samples were not collected (AUC_{pl} Area under the concentration vs time curve in plasma for CBDCA, AUC_{pc} area under the concentration vs time curve in the peritoneal cavity for CBDCA, CL_{TB} total body clearance of CBDCA, CL_{cr} creatinine clearance, CL_{renal} renal clearance of CBDCA, PA permeability-area product, R_d regional pharmacokinetic advantage, k_{pl} rate constant for platination of plasma proteins)

	Patient 1	Patient 2	Patient 4	Patient 5	Patient 6
Drug given (mg)	1,680	1,544	1,850	2,160	1,680
Drug absorbed (mg)	1,210	414	1,099	1,408	1,286
Percentage absorbed	72	27	59	65	77
AUC_{pl} (mg min ml^{-1})	6.7	7	11.2	10.7	15.2
AUC_{pc} (mg min ml^{-1})	24.2	36.6	36.9	42.9	29.5
CL_{TB} (ml/min)	182	59	98	132	85
CL_{cr} (ml/min)	133	104	74	97	68
CL_{renal} (ml/min)	–	–	76	86	58
PA (ml/min)	69	14	43	44	90
R_d	3.6	5.2	3.3	4	1.9
k_{pl} (min^{-1} × 10^4)	3.1	1.9	2	1	1.8

Response

The median follow-up period is 15 months. All patients who underwent this procedure are alive, and five remain clinically without evidence of disease.

Pharmacokinetic analysis

Figure 3A illustrates the pharmacokinetic data recorded for one patient over the 24-h period during and following the 90-min perfusion. The total platinum concentration in the plasma differed substantially from the filterable concentration only at later times after discontinuation of the perfusion. Figure 3B shows an expanded time scale to illustrate the log-linear decline in peritoneal concentration of platinum characterized in this patient by a half-life of 70 min. Results recorded for all five patients from whom pharmacokinetic data were obtained are summarized in Table 3.

Discussion

A recently published report of a large clinical trial comparing the effects of chemotherapy delivered either systemically or intraperitoneally for the primary adjuvant treatment of epithelial ovarian cancer has resulted in renewed interest in the use of intraperitoneal chemotherapy to treat this disease [2]. As interest in using high-dose chemotherapy in the primary treatment of ovarian cancer increases, the use of intraperitoneal drug delivery offers an attractive alternative so as to limit systemic toxicities. This phase I study using CHPP to deliver CBDCA to patients with ovarian cancer demonstrates that this surgical approach to drug delivery is safe and results in a relatively small, but possibly clinically significant, regional advantage. This technique also permits the administration of very high doses of CBDCA with relatively minimal systemic toxicity.

The selective lethal effect of supranormal temperatures on human and murine neoplastic cells has been well established in laboratory models [22, 28, 31]. A variety of cell lines, including ovarian carcinoma, have been shown to be sensitive to temperatures ranging from 42° to 45 °C when exposed for a period of 2–4 h, whereas their non-neoplastic parental cell types are largely unaffected by similar therapy. In vivo there is a differential response of normal and tumor microcirculation in response to hyperthermia [14]. Normal (mature granulation) tissue showed a dramatic and temperature-dependent increase in blood flow at temperatures of up to 46 °C. In contrast, blood flow through neoplastic tissue increased to a smaller extent. Stasis occurred in the tumor within 1 h at 41 °C, whereas 47 °C was required to produce stasis in normal tissue. Therefore, there may be two fundamental mechanisms, direct cytotoxic effects and vascular stasis, by which supranormal temperatures can be selectively toxic to neoplastic cells. If vascular stasis occurs, hyperthermia would also favor deeper penetration of drug into the tumor. A significant limitation to the efficacy of peritoneal drug administration is the rather limited penetration of drug into tissue [11]. Therefore, existing evidence strongly indicates that patients with minimal gross residual disease are most likely to derive a therapeutic benefit from CHPP/CBDCA.

Several studies have characterized the cytotoxic effects of hyperthermia in combination with various chemotherapeutic agents in vitro. Both cisplatin (CDDP) and CBDCA have been shown to have additive or synergistic effects with hyperthermia and can shorten the exposure time necessary for cell killing by supranormal temperatures [22, 28]. Both CDDP and CBDCA produce these effects on human ovarian carcinoma cells in vitro. These studies have provided the foundation from which a number of clinical trials employing hyperthermia combined with either CDDP or CBDCA to treat ovarian cancer refractory to conventional therapy have been based [31, 45].

Recently, a phase I trial using CHPP with escalating doses of CDDP in patients with peritoneal malignancies was completed [6]. Treatment with CHPP/CDDP at 41–43 °C for 90 min was extremely well tolerated. Six dose escalations of CDDP were made, and at a dose of 300 mg/m^2 no toxicity was encountered. Although dose-limiting toxicity was not achieved, further dose escalations were abandoned in favor of the addition of tumor necrosis factor to the regimen. Because CBDCA has a toxicity profile different from that of CDDP it has a better therapeutic index than CDDP with substantially less renal toxicity, nausea, and neurotoxicity. Therefore, the intraperitoneal use of CBDCA instead of CDDP obviates the need for the simultaneous systemic administration of neutralizing agents such as sodium thiosulfate to protect against renal toxicity. Systemic thiosulfate has been shown to bind covalently and inactivate CDDP in the systemic circulation and diminish the expected renal toxicities. However, because it is delivered systemically, thiosulfate may also inactive CDDP absorbed by tumor cells and thereby impair the therapeutic effect of CDDP. Moreover, when CBDCA is used instead of CDDP the dose-limiting toxicity becomes myelosuppression rather than nephrotoxicity.

The results shown in Table 3 make several important points concerning intraperitoneal chemotherapy in this setting. Although the results are based on a limited number of patients, they illustrate some of the limitations as well as advantages of the technique.

First, the fraction of the drug absorbed widely from 27% to 77%. When patient 6 is excluded because of apparent outflow obstruction and substantial amounts of volume not recovered, possibly because of absorption by the patient, the range is narrowed only slightly. The variability and unpredictability of the amount of drug absorbed from the peritoneal cavity render the control of patient exposure difficult. Patients 1 and 2 illustrate this point. Both were exposed to 800 mg/m^2 delivered to the extracorporeal circuit; however, there was a 3-fold

difference in the amount of drug actually absorbed by the patients. Probably fortuitously, the rapid absorber was a rapid eliminator (CL_{TB} = 182 ml/min, whereas the slow absorber was a slow eliminator (CL_{TB} = 59 ml/min). The result was that the levels of drug exposure to the patients, defined as the AUC of CBDCA concentration in the plasma (AUC_{pl}) as calculated from filterable platinum, were almost identical and in a reasonable target range [26]. There is a clear need for a method to assess the absorption from the peritoneal cavity during the procedure such that appropriate adjustments could be made if necessary. This might be accomplished by the use of an easily and quickly analyzed indicator molecule.

Second, in all cases except patient 2 the CL_{TB} was reasonably predicted by the creatinine clearance, CL_{cr}, estimated from pretreatment creatinine levels by means of the Cockroft and Gault algorithm and of ideas articulated by Calvert et al. [7] and Newell et al. [38]. In these four patients, CL_{TB} exceeded CL_{cr} by average of 32 ml/min as compared with the value of 25 ml/min suggested by Calvert for pharmacokinetically guided dosing with CBDCA. Furthermore, there was reasonable agreement between CL_{cr} and clearance of ultrafilterable platinum determined by urine collection.

Third, the permeability-area product, PA, greatly exceeds peritoneal clearances obtained during absorption of CBDCA from dialysate simply instilled in the peritoneal cavity. Three groups have reported average clearance values of 8–12 ml/min [13, 15, 37]. The very high values we observed correlate with the extensive mixing that occurs during CHPP. Although we cannot exclude a direct effect of elevated temperature, a number of lines of evidence suggest that there is a large discrepancy between the functional peritoneal surface area under normal dialysis conditions and the anatomic surface area available [11]. These include (1) the relatively small effect on transport obtained by evisceration of animals [19, 46, 47], (2) measurements of intrinsic peritoneal permeabilities of a number of serosal surfaces of the rat combined with anatomic surface areas obtained by dissection, which provided a PA that was 3–4 times the actual measured value [17]; (3) the observation that significant portions of the serosal surfaces of the rat are not stained or poorly stained by Evans blue dye during dialysis [17]; and (4) the increase in PA of about 4 orders of magnitude obtained by vigorous shaking of the rat [33]. Even if we exclude the extraordinarily high value observed in patient 6, likely caused by extensive fluid absorption, the average PA during CHPP was 42 ml/min. This is about 4 times the value expected from the studies cited above. It is unlikely that the increase was caused by the hyperthermia alone. Formenti et al. [18] observed inconsistent effects of regional hyperthermia on the peritoneal AUC in human subjects, with increases being as likely as decreases. One of two patients described as undergoing a "good" hyperthermia session experienced a large decrease in peritoneal AUC, whereas that of the other patient was unchanged. Los et al. [34] did not observe an effect of hyperthermia applied for 60 min to the rat on the rate of decline in the peritoneal platinum concentration during that period.

Another observation concerns the rate constant for platination of plasma proteins. The range in this study was $1.0–3.1 \times 10^{-4}$ min^{-1}, with the average being 2.0×10^{-4} min^{-1}. This is 37-fold lower than the rate constant reported for CDDP [29], confirming the substantially greater platination activity of CDDP as compared with CBDCA.

Because $R_d = 1 + CL_{TB}/PA$, the high PA values obtained during CHPP combined with CL_{TB} in a generally normal range produce low estimates of the regional advantage. This is an unavoidable consequence of procedures designed to provide improved irrigation of the peritoneal surface if PA is proportional to the functional surface area. However, if a large fraction of the peritoneal surface is inadequately exposed under the usual conditions of peritoneal drug administration, then its rationale is weakened and therapeutic results would be expected to be compromised. Whether a 4-fold reduction in R_d would be an acceptable price to pay for greatly improved surface exposure is speculative. A reasonable approach might be to favor drugs with large CL_{TB}, such as CDDP, if their mechanisms of action are consistent with the short period of exposure associated with CHPP.

The results of this study may also have important implications for future studies using intraperitoneal delivery of novel therapeutic agents, such as oligonucleotides, antibodies, immunotoxins, radioimmunoconjugates, and "gene therapy" involving a variety of expression vectors to treat ovarian cancer [3, 50]. The rationale for most of these studies requires that the target tumor cells actually be exposed to the biologic agent. Our data are consistent with the idea that the functional peritoneal surface area is considerably smaller than the potential area accessed with good mixing of fluid in their peritoneal cavity.

It is also noteworthy that none of the six patients in this analysis developed any postoperative wound complication, and there was no complication in either of the two patients who underwent bowel resection with anastomosis. These findings are in agreement with a previous analysis by Kolb et al. [30] in which the incidence of wound complications was not affected by the early postoperative administration of systemic platinum-based chemotherapy. In studies performed in rats a recent investigation demonstrated that intraperitoneal CBDCA did not weaken wound strength, although intraperitoneal paclitaxel was found to weaken wound strength significantly [25]. Therefore, concern for wound-healing complications may not be an important determinant for delaying the administration of adjuvant platinum-based chemotherapy in patients with advanced-stage epithelial ovarian cancer. In the context of data indicating that the mortality rate for patients with ovarian carcinoma rises as the delay in antineoplastic therapy increases [39], these observations provide a rationale for the intraperitoneal administration of a

platinum-based cytotoxic agent in the operating room at the completion of initial cytoreductive surgery, serving as the first "cycle" of primary adjuvant chemotherapy. A clinical trial aimed at assessing the efficacy of this treatment strategy is currently under consideration.

Although the clinical effectiveness of CHPP/CBDCA cannot be determined in a small study of this type, we attempted to assess some of the clinical and pharmacological issues relating to this form of drug delivery. In this analysis the maximum tolerated dose of CBDCA was 800 mg/m^2, a dose that has been tolerated when delivered systemically in the absence of stem-cell supported or bone marrow transplantation [44]. However, in contrast to intravenous administration, none of the three patients receiving this dose via CHPP developed any appreciable toxicity, a finding that is in agreement with Alberts et al.'s [2] recently published study comparing the intravenous versus intraperitoneal administration of CDDP. We believe that patients with advanced-stage epithelial overian cancer are most likely to benefit from CHPP/CBDCA immediately following optimal surgical debulking with minimal gross residual disease and before resistant clones of tumor cells have been selected by surviving systemic chemotherapy. Since this phase I pilot study was performed in patients with small-volume residual disease following initial surgical cytoreduction and was carried out in conjunction with primary adjuvant chemotherapy, data are not available for the assessment of clinical responses. In future clinical analyses a comparison of disease-free survival in optimally debulked patients randomized to receive or not to receive CHPP/CBDCA followed by conventional adjuvant chemotherapy would be necessary for the objective evaluation of the potential role of this modality in the management of advanced-stage ovarian cancer.

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