Phase I and Pharmacological Studies of 5-Fluorouracil Administered Intraperitoneally

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ABSTRACT

A Phase I study was conducted of 5-fluorouracil administered i.p. in a 2-liter volume of 1.5% Inpersol. The drug was administered via Tenckhoff peritoneal dialysis catheters to ten patients with tumors confined to the i.p. space. Dialysis concentrations ranged from 5 μM to 8 mM. Complications of the dialysis procedure alone included mild abdominal discomfort and 2 cases of gram-negative bacterial peritonitis, both easily controlled with antibiotics. 5-Fluorouracil caused the same pattern of toxicity as when administered by other routes. There was no local or central nervous system toxicity. Dose-limiting toxicity included pancytopenia and mucositis at a dialysis concentration of 4.5 to 5 mM administered for eight consecutive 4-hr exchanges. There were two documented responses in eight evaluable patients.

5-Fluorouracil concentrations were measured by high-pressure liquid chromatography. Peritoneal fluid concentrations decline in a first-order fashion with a half-life of 1.6 hr. The mean permeability area product was 14 ml/hr/mm. A mean of 82% of drug was absorbed in 4 hr. Plasma levels rise over the first 30 to 45 min and decline in a nonlinear fashion. Plasma levels are substantially lower than are peritoneal fluid levels. Mean 4-hr peritoneal fluid concentration was 298 times the simultaneously measured plasma levels. Total body clearance ranged from 0.9 to 15 liters/min and declined with increasing dialysate concentration.

We conclude the i.p. route is a relatively safe way to deliver high concentrations and large amounts of drug to the i.p. cavity with a significant pharmacological advantage over conventional routes of administration.

INTRODUCTION

Extensive peritoneal involvement with metastatic tumor is a problem in the management of a variety of human tumors, such as carcinoma of the ovary, breast, stomach, and colon. Ovarian carcinoma spreads locally and, even in advanced (Stage III) disease, is generally confined to the intraabdominal cavity with diffuse peritoneal seeding and peritoneal involvement. This peritoneal involvement leads to gastrointestinal tract involvement and inanition, which is the usual cause of death in these patients.

Achievement of better local control is a problem even in patients in whom progress appears to have been made. Although Stage III patients who achieve complete remission, either through chemotherapy or extensive surgery, have increased survival potential, they are still at high risk for disease recurrence, and many will succumb to their disease. In addition, despite considerable partial responses, patients with minimal residual disease after chemotherapy will uniformly suffer regrowth of their tumor. New approaches are needed. Trials have been conducted in the past of local instillation of chemotherapeutic agents directly into the peritoneal space. Historically, however, drugs have been given either in small volumes, as a single (i.p.) injection, usually without pharmacological monitoring, or only in patients with ascites (4, 13, 19).

A recent theoretical analysis (7) of the pharmacology and kinetic properties of i.v. versus i.p. drug therapy concluded that the latter route has major advantages in drug administration. This analysis predicted slow passage of the drug from the i.p. space to the systemic circulation and thus a substantial difference in peritoneal versus plasma clearance for hydrophilic drugs. This difference in clearance should lead to concentration differences between the peritoneal cavity and plasma if the drug were instilled directly into the abdomen. The peritoneal cavity and i.p. tumor would be exposed to higher drug concentrations than were tissues exposed to the drug through the systemic circulation. In addition, this analysis suggested that i.p. therapy could be optimized by directing therapy at small tumor volumes, in large volumes of fluid, and in the absence of other drugs which might lessen hepatic or renal clearance.

5-FU4 possesses several of the features thought to be of advantage for i.p. chemotherapy, namely (a) small molecular weight and good penetration of tissue spaces and cell membranes (16), properties required for tumor surface penetration, and (b) rapid clearance from the systemic circulation (2–6, 10, 12, 14, 22, 26). It is an established single agent in ovarian (11, 23) and colon (24) cancers as well as in a variety of other cancers (24) and in combination regimens (11, 24). Thus, we initiated a trial of i.p. administration of 5-FU in patients with advanced intraabdominal cancer. The results of this trial are the subject of this report.

MATERIALS AND METHODS

Ten patients from the Medicine and Surgery Branches of the National Cancer Institute were treated (Table 1). All patients had histological proof of malignant disease confined to the intraabdominal space. All patients had failed conventional therapy, except for one patient with colon cancer metastatic to liver at time of diagnosis and 2 patients with resected Dukes C colon cancer who were treated as part of a separate adjuvant study. Informed consent was obtained from all patients. Tumor size was assessed by physical examination, direct observation.

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5-FU: Fluorouracil; C₉, peritoneal fluid concentration; PA, permeability area product; Cl, apparent total body clearance; AUC, area under the curve; C₉, concentration in plasma.

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at laparotomy or peritoneoscopy, diagnostic ultrasound, or computerized axial tomography. The sensitivity of computerized axial tomography was improved by scanning with a solution of Hypaque dye (Winthrop Laboratories, New York, N. Y.) in dialysate solution in the abdomen, as reported elsewhere (8).

Tenckhoff flexible Silastic peritoneal dialysis catheters were surgically implanted into the abdominal cavity via a s.c. tunnel with a single Dacron felt cuff. Patients maintained the dressing and care of their catheters in the hospital after appropriate instruction by the nursing staff.

Catheter function was assessed by checking for free flow of fluid in and out of the abdomen and by observing the distribution of Hypaque in the dialysate by computerized axial tomography. Patients were treated with 5-FU (Hoffman-La Roche Inc., Nutley, N. J.) in 2 liters of Inpersol (Abbot Laboratories, North Chicago, Ill.) containing 1.5% dextrose to which were added 1000 units of sodium heparin and 8 mEq of KCl. Fifty mEq of NaHCO₃ were also added to adjust the pH from 4.5 to 8.4 to increase the solubility of 5-FU and to prevent potential peritoneal irritation. All dialysis bottles were warmed to 37°C prior to instillation. Two treatment schedules were used: (a) 8 consecutive 2-liter exchanges, each of 4 hr duration for a total of 36 hr, including time for instillation and drainage; and (b) one daily instillation of 2 liters of Inpersol with drug for a 3- to 5-day course without drainage. Treatment courses were repeated every 2 weeks. The concentration of 5-FU in the dialysate ranged from 5 μM to 8 mM (1.3 to 2080 mg/2 liters). 5-FU concentration was escalated in each patient in each successive course until toxicity was reached or until tumor growth determined that patients with progression be removed from the study. Dose escalations were carried out in successive courses in the same patient since cumulative toxicity was not expected.

**Determination of 5-FU Levels**

5-FU was assayed by high-pressure liquid chromatography according to the method of Buckpitt et al. (1) as described elsewhere. Samples were either plasma, peritoneal fluid, or an aliquot of the dialysate. All plasma samples were first centrifuged for 30 min at 10,000 × g in a Sorvall RC 2 centrifuge (DuPont Instruments, Wilmington, Del.), and the plasma was separated. A 2-ml aliquot was used for each determination. When less than 2 ml was available, the plasma aliquot was measured and brought to 2 ml with normal plasma, and a correction factor was determined. A standard curve for 5-FU in plasma was prepared by the addition of drug concentrations to normal plasma. One hundred μl of [3H]-5-FU (Amersham/Searle Corp., Arlington Heights, Ill.) were added to standards and unknown samples to serve as an internal standard. The final concentration of [3H]-5-FU was <10⁻⁸ M. All standards and samples were adjusted to pH 10 with 5 N KOH and brought to a final volume of 5 ml with water.

A 2-stage clean-up procedure was followed. First, samples were passed over separate anion-exchange columns made up to disposable 10-ml glass pipets. The column was packed with 5 ml of Dowex AG 1-X2 acetate anion-exchange resin (200 to 400 mesh; Bio-Rad Laboratories, Richmond, Calif.) which had been prepared by multiple washings in distilled water. After sample application, each column was first washed with 30 ml of H₂O and 4 ml of 1 N acetic acid, which were discarded, and then eluted with 4 ml of 1 N acetic acid. Eluates were reduced to dryness under nitrogen and the residue was resuspended in 500 μl of 0.05 M KH₂PO₄ buffer, pH 6.8. An organic extraction was then carried out by adding 7 ml of spectral-quality ethyl acetate (Matheson Coleman and Bell, Norwood, Ohio) to the samples and shaking vigorously for 10 min in glass-stoppered centrifuge tubes. Samples were centrifuged for 10 min at 2000 × g, the aqueous phase was discarded, and the organic phase was reduced to dryness under N₂.

For analysis, the samples were resuspended in 100 μl of 0.01 M KH₂PO₄ buffer. One hundred-μl samples were analyzed on a Waters high-pressure liquid chromatograph (Waters Instruments, Milford, Mass.) fitted with a Waters Model 440 UV

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**Table 1**

Patients treated with 5-FU i.p. and incidence of bacterial peritonitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor</th>
<th>Tumor location</th>
<th>Maximum 5-FU dose* (mm)</th>
<th>Frequency of exchange</th>
<th>No. of courses</th>
<th>No. of connections and disconnections*</th>
<th>Bacterial peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. W.</td>
<td>Ovary</td>
<td>Bulky pelvic</td>
<td>5</td>
<td>q4h</td>
<td>11</td>
<td>110</td>
<td>+ (1)</td>
</tr>
<tr>
<td>A. B.</td>
<td>Ovary</td>
<td>Peritoneal studding and pelvic mass</td>
<td>4.5</td>
<td>q4h</td>
<td>3</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>B. S.</td>
<td>Ovary</td>
<td>Small diffuse peritoneal studding</td>
<td>4.25</td>
<td>q4h</td>
<td>5</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>G. M.</td>
<td>Colon</td>
<td>Hepatic metastases</td>
<td>3</td>
<td>q4h</td>
<td>3</td>
<td>34</td>
<td>-</td>
</tr>
<tr>
<td>C. K.</td>
<td>Colon</td>
<td>Hepatic metastases</td>
<td>5</td>
<td>q4h</td>
<td>5</td>
<td>47</td>
<td>+ (1)</td>
</tr>
<tr>
<td>J. B.</td>
<td>Colon</td>
<td>Hepatic metastases and pelvic mass</td>
<td>5</td>
<td>q4h</td>
<td>9</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>D. W.</td>
<td>Ovary</td>
<td>Bulky abdominal-pelvic</td>
<td>2</td>
<td>Daily for 5 days</td>
<td>2</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>M. P.</td>
<td>Ovary</td>
<td>Positive washings</td>
<td>8</td>
<td>Daily for 3 days</td>
<td>13</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>N. S.</td>
<td>Colon*</td>
<td>Resected</td>
<td>5.5</td>
<td>Daily for 5 days</td>
<td>5</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>L. S.</td>
<td>Colon*</td>
<td>Resected</td>
<td>5.5</td>
<td>Daily for 5 days</td>
<td>2</td>
<td>17</td>
<td>-</td>
</tr>
</tbody>
</table>

* Concentration/2 liters Inpersol.
* Numbers in parentheses, number of episodes.
* Patient being treated as part of protocol-adjuvant therapy of resected Dukes C carcinoma of the colon.
absorbance detector with a 254 nm filter, a Waters U6K Injector, and a Varian Aerograph recorder (Varian Instruments, Walnut Creek, Calif.). Samples were run at a flow rate of 2 ml/min in a 0.01 M KH$_2$PO$_4$ solvent over a C$_18$-Bondapak column (inside diameter, 3.9 mm x 30 cm) (Waters Instruments). The 5-FU peaks occurred regularly at 12 min (Chart 1). The contents of each peak were collected in a liquid scintillation vial. Fifteen ml of Aquasol (New England Nuclear, Boston, Mass.) were added, and the amount of $^3$H was determined in a liquid scintillation counter.

Because the 5-FU peaks were without significant tailing, the peak heights rather than the peak areas could be used for quantitation. Therefore, a standard curve was constructed in which the ratio of peak height to dpm of internal standard was plotted as a function of known 5-FU concentration by linear regression. The peak height/dpm ratio of the samples was calculated, and 5-FU concentration was determined from the standard curve. Correlation coefficients for standard curves were greater than 0.98. The assay was sensitive to $5 \times 10^{-8}$ M 5-FU.

**Pharmacokinetic Calculations**

**Peritoneal Permeability.** First-order absorption of 5-FU from the peritoneum was observed. Peritoneal clearance expressed as the permeability area product was obtained from the slope of the logarithm of peritoneal fluid concentration versus time (e.g., Chart 2):

$$\ln C_p(t) = \ln C_p(0) - \frac{PAt}{V_o}$$

where $t$ is time and $V_o$ is the volume of peritoneal fluid (2 liters). For most exchanges, only a single peritoneal fluid concentration was obtained at 4 hr, and PA was calculated from a rearrangement of Equation A:

$$PA = -\ln \left[ \frac{C_p(4 \text{ hr})}{C_p(0)} \right] \times 2 \text{ liters/4 hr}$$

**Cl.** Clearance, a pharmacokinetic parameter used to assess the body’s overall ability to eliminate drug (a generalization of the renal clearance concept), is calculated as:

$$Cl = \frac{\text{dose absorbed}}{AUC}$$

AUC is an expression of concentration x time or total amount of drug measured in the plasma. It is determined by the trapezoidal rule from time 0 to the last plasma point and then by first-order extrapolation to infinite time (usually less than 10% of total area). This formula is valid for any linear kinetic model, regardless of the number of compartments. If Cl varies with dose, then the drug kinetics are nonlinear.

**RESULTS**

Ten patients were treated with 1 to 11 courses for a total of 55 courses of treatment (Table 1). The data from all 10 patients were pooled to examine drug pharmacology and catheter tolerance. Drug toxicity was interpreted for each of the 2 schedules of administration.

In both dialysis schedules, serum Na$^+$, K$^+$, Cl$^-$, PO$_4^{2-}$, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, bilirubin, glucose, creatinine, and blood urea nitrogen remained normal during the dialysis and during the period between dialyses. All patients had mild elevations of serum HCO$_3^-$ associated with the high concentration of NaHCO$_3$ in the dialysate, which resolved within 24 hr.
All patients tolerated their catheters well and did not experience difficulty in dressing the catheter or resuming daily functions, including bathing. Four of 10 patients experienced mild discomfort in the location of the catheter tip, which was associated with vigorous exercise or during the dialysis procedure. All patients tolerated the dialysis procedure well with only mild discomfort from abdominal fullness. All were able to ambulate during the periods when fluid was in the abdomen.

There were 2 episodes of catheter-related sepsis. In one, shortly after catheter placement, the patient developed Escherichia coli peritonitis, associated with an E. coli urinary tract infection. This was successfully treated with i.v. and i.p. gentamicin, and i.p. 5-FU treatment was resumed without incident. In a second patient, a Klebsiella peritonitis was associated with obstruction of the catheter and required both antibiotic therapy and removal of the catheter with replacement before i.p. 5-FU therapy could be resumed.

Drug Toxicity

Thirty-six-hr Schedule. Six patients were treated for 35 courses of treatment. Three had ovarian carcinoma, and 3 had colon carcinoma (2 males and 1 female). Dose-limiting toxicity consisted of myelosuppression, thrombocytopenia, and mucositis (Table 3). These were observed in 3 of 3 patients at a dialysate concentration of 5 mM and in 1 patient at 4.5 mM. Four of 6 patients experienced some nausea up to 24 hr after the cessation of dialysis (severe in 1 patient). It was associated only with 5-FU concentrations greater than 3 mM. Mucositis occurred in 4 of 6 patients (4 of 4 of those who developed hematological toxicity), and alopecia was observed in 2 of 6 patients. Four patients have been treated safely at a 4 μM concentration by this schedule.

Daily Schedule. Four patients were treated for 20 courses of treatment. In 2 patients with ovarian tumors, the catheter functioned well only for instillation of fluid but not for drainage. These patients were treated with a single 2-liter instillation once a day. In addition, 2 patients (1 male and 1 female) are included who received a single 2-liter instillation daily for 5 days, as part of an adjuvant protocol for the treatment of resected Dukes C colon carcinoma. Patients treated with this regimen experienced no difficulty with the instillation of 2 liters/day without subsequent drainage. They were frequently treated as outpatients.

Treatments in these patients lasted 1 day and then were escalated to either a 3- or 5-day schedule with subsequent dosage escalations in increments of 0.5 to 1.0 mM with each new course. Dose-limiting toxicity was reached in 1 patient (M. P.). At a concentration of 8 mM for 3 days, she developed pancytopenia, sepsis, mucositis, nausea, vomiting, and alopecia. An additional patient developed myelosuppression to 3300 WBC/cu mm on Day 9 at 5.5 mM concentration for 5 days after having no change in WBC at 5 mM for 5 days. Two of 4 patients developed nausea and vomiting. In one of these, it was associated with the presence of fluid in the peritoneum and was thought to be vagal in origin. Insufficient patients have been treated by this schedule to draw accurate conclusions about the toxic dose.

Pharmacological Studies

Drug concentration i.p. declined to a mean 4-hr value that was 17.6 ± 7.9% (S.D.) of instilled concentration, corresponding to a mean absorption half-life of 1.6 hr and a mean PA of 14 ml/min. In selected patients, multiple determinations of peritoneal fluid drug concentration versus time indicated that this decline was a first-order function with respect to time. Plasma 5-FU levels initially rose after i.p. drug administration, peaked at 30 to 60 min, and then declined with a 2-phase disappearance (Chart 2). Mean 4-hr peritoneal fluid levels were 298 (range, 111 to 698) times greater than were the simultaneously measured plasma levels. For the purpose of comparison, we have included the 5-FU values typical of i.v. bolus administration of 15 mg/kg (2–6, 10, 12, 14, 22, 26) and continuous i.v. infusion of 30 mg/kg (4, 15).

Cl ranged from 0.9 to 15 (mean, 4.5) liters/min. Clearance appeared to decrease with increasing doses. In patients where studies of plasma concentration versus time were carried out at increasing concentrations of dialysate, there was a clear trend toward increasing AUC per dose or decreasing Cl. While this trend was somewhat obscured in most patients by a narrow range of dose escalation (10 to 20%), Patient M. P. was studied over a wide concentration range and at a higher concentration than was any other patient (5 to 8 mM). Clearance declined with each successive 1 mM rise in peritoneal dialysate concentration, leading to a disproportional increase in systemic exposure to drug (AUC) (Table 2).

Response Data

There were 2 responses in 6 patients with ovarian cancer. One patient (B. S.) achieved complete remission after 5 courses of 5-FU i.p. at concentrations ranging from 4.0 to 4.25 mM. She had previously been treated with l-phenylalanine mustard and radiation to the pelvis and paraaortic lymphatics to the level of the diaphragm. At restaging laparotomy, she was free of disease although thick fibrotic adhesions made complete examination difficult. A second patient (E. W.) achieved apparent partial remission. This 50-year-old female had been treated previously with hexamethylmelamine, Cytoxan, methotrexate, 5-FU i.v. (27), Cytembena, and cis-dichlorodiammine-platinum. After i.p. treatment with 5 mM 5-FU, her bulky pelvic mass shrank from 6 x 5 to 3 x 4 cm in 2 months, as documented by physical examination and computerized axial tomography. The remaining 4 ovarian patients and the 3 colon patients all had disease progression. The 2 patients with colon cancer who received adjuvant treatment remain free of disease.

DISCUSSION

The pharmacokinetic basis for i.p. chemotherapy is the observation that absorption (clearance) of many drugs from the peritoneum is a much slower process than is the elimination of

<table>
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<tr>
<th>Table 2</th>
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<tr>
<td><strong>Nonlinear plasma pharmacokinetics exhibited by Patient M. P.</strong></td>
</tr>
<tr>
<td>Toxicity was encountered at C&lt;sub&gt;50&lt;/sub&gt; = 8 mM.</td>
</tr>
<tr>
<td>c&lt;sub&gt;50&lt;/sub&gt; (mM)</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7*</td>
</tr>
<tr>
<td>8</td>
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</table>

* Mean of 3 exchanges at 7 mM.
the drug from the body. The expectation is that tumor tissue will be exposed to high drug concentrations, while lower systemic concentrations are present. Quantitatively, the ratio of peritoneal concentration to \( C_p \) may be expressed (at steady state) as:

\[
\frac{C_o}{C_p} = \frac{CI}{PA} + 1
\]  

The maximum i.p. level achieved is about 10 times higher than is the highest systemic level seen after systemic administration, and i.p. levels decline more slowly, with a 12 of 1.6 hr versus the drug from the body. The expectation is that tumor tissue is the highest plasma bevel seen after systemic administration, values derived from the literature of 1 to 6 liters/mm (4, 9, 12, after systemic doses. In these studies, mean 4-hr 5-FU penito end of 4 hr, i.p. bevels exceed maximum plasma levels achieved temic concentrations are present. Quantitatively, the ratio of will be exposed to high drug concentrations, while lower sys temic concentrations are present. The toxicities seen with i.p. 5-FU are the same as those reported (19) for other methods of administration of the drug (nausea, vomiting, mucositis, pancytopenia, skin rashes, and alopecia). The clinical toxicity data demonstrate a steep dose/toxicity relationship for i.p. 5-FU, which is consistent with nonlinear saturation of the clearance mechanism. Of the patients who experienced toxicity at 5 mM for 36 hr, 2 of 3 were treated previously at 4 mM and experienced only nausea. When they were retreated at 4 and 4.5 mM, respectively, after the toxic episode, they again experienced only mild side effects. In addition, Patient A. B. experienced no side effects at 4 mM for 36 hr, but at 4.25 mM, the patient had soreness in her gums and clinical results for methotrexate.5

In this study, CI decreased with each increasing dose (Table 3). This indicates nonlinearity of 5-FU plasma pharmacokinetics since, if kinetics are linear, clearance should remain constant for a given route of administration no matter what the dose. Also, the qualitative changes of the plasma concentration versus time curve as peritoneal 5-FU concentration is increased (later peak time and longer time to decline) are not predicted by any linear model. Variable rates of 5-FU clearance have also been reported or can be calculated from the literature [1 to 2 liters/min after i.v. bolus administration (9, 22) and 3 to 7 liters/min for continuous infusion (4, 9, 22)].

The toxicities seen with i.p. 5-FU are the same as those reported (19) for other methods of administration of the drug (nausea, vomiting, mucositis, pancytopenia, skin rashes, and alopecia). The clinical toxicity data demonstrate a steep dose/toxicity relationship for i.p. 5-FU, which is consistent with nonlinear saturation of the clearance mechanism. Of the patients who demonstrated clinical toxicity, mean 4-hr plasma bevels were 3.43 \( \mu \)M, and mean peak plasma bevels were 63 \( \mu \)M. From the present data, we cannot state a single cutoff point for drug toxicity.

Clinically, apparent drug-induced peritonitis was not a prob-
problem in this trial, although it was observed in an earlier Phase I trial with i.p. methotrexate. Subclinical damage or alteration in the peritoneal surface, if it were to occur, might be expected to result in a changing peritoneal clearance during a 36-hr dialysis. However, there was no clear trend observed in the peritoneal fluid levels from the first to the eighth exchanges in a single course of therapy. At restaging laparotomy, Patient B. S. had a generalized dense fibrotic reaction causing multiple adhesions. No refractile bodies indicative of starch were found, nor was there tumor present. While this appears most likely to be a complication of her prior radiotherapy treatment, we cannot rule out either a direct reaction to 5-FU or a combined effect of 5-FU and radiation therapy.

A major complication of this procedure was bacterial peritonitis. Popovich et al. (25), reporting on 9 renal dialysis patients treated for 138 weeks, found 1 episode per 10 dialysis weeks or a 0.3% incidence per catheter connection-disconnection procedure. We currently have an incidence of 2 episodes in 10 patients with a total of greater than 100 weeks of experience and approximately 450 connection-disconnection procedures, for an incidence of 0.4%. The number of infections is in part a function of the number of invasions of catheter integrity. The problem, however, can be minimized by scrupulous attention to sterile technique in the care and handling of the catheter. Neither episode of peritonitis in this series required a cessation of therapy for more than 4 weeks.

In both the current trial and an earlier Phase I study with methotrexate, we have observed mild but tolerable abdominal discomfort associated with the instillation of non-drug-containing dialysate. This was frequently localized to the area of the catheter tip or in the right and left upper quadrants of the abdomen. With 5-FU, patients uniformly lack any physical signs of peritonitis, and analgesia was required in only one patient. A cautionary note, however, must be added because this is a limited number of patients, and drugs with direct cytotoxicity may not be without local side effects.

In summary, our results suggest that: (a) i.p. 5-FU therapy is a feasible means of administering drug to localized intraabdominal disease; (b) therapy is limited by systemic toxicity and is relatively nontoxic considering the high concentration of drug and the large amount absorbed systemically (more than 6 g in 36 hr); (c) plasma concentrations of 5-FU produced by i.p. administration are as high as those which can be safely achieved by continuous i.v. infusion, while the i.p. tumor by this route is bathed in a drug concentration 1 log higher than the highest levels which can be safely achieved by i.v. bolus administration; and (d) 2 responses were seen during the Phase I study, one of them in a patient with bulky ovarian disease who had previously failed systemic 5-FU. Based on these results, we have initiated a Phase II study of 5-FU in patients with ovarian cancer at a starting concentration of 4 mm in 2 liters for 36 hr.

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