Early Postoperative Intraperitoneal Chemotherapy as an Adjuvant Therapy to Surgery for Peritoneal Carcinomatosis from Gastrointestinal Cancer: Pharmacological Studies

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ABSTRACT

Gastrointestinal malignancy may spread to peritoneal surfaces in the absence of lymphatic or hematogenous metastases. To treat peritoneal carcinomatosis, a uniformly lethal disease process, extensive cytoreductive surgery and i.p. chemotherapy were combined. Early postoperative i.p. chemotherapy was instilled in the first few days after the surgical procedure in an attempt to treat anatomic sites that would be sealed off by postoperative adhesions. Mitomycin C was given on the first postoperative day at two doses, 10 and 12 mg/m2. 5-Fluorouracil was given on postoperative days 2–5 at 15 and 20 mg/kg, respectively. Median area under the curve ratio i.p./i.v. was 117 for 5-fluorouracil and 21.6 for mitomycin C. Elevated intraportal levels of drug were observed for i.p. 5-fluorouracil but not for mitomycin C. The marked pharmacokinetic advantage of postoperative i.p. suggests that this treatment strategy should be considered in a clinical trial in patients at risk for progression of peritoneal carcinomatosis.

INTRODUCTION

Surgery for gastrointestinal cancer is associated with an extremely high local recurrence rate. In a review of autopsy cases at the Roswell Park Memorial Institute, 90% of patients whose gastric cancer had received some type of chemotherapy at the resection site (1). From the report of Tepper et al. (2), recurrence within the pancreas bed should be expected in all patients who fail surgical removal of pancreatic cancer. The majority of patients whose cancer recurred had cancer in the retroperitoneum at the same site from which the primary pancreas malignancy had been removed. Cass et al. (3) found that two-thirds of patients with colorectal malignancy have resection site recurrence. A review of the local failure rates with gastrointestinal malignancy are summarized in Ref. 4. If these clinical data are accurate, then gastrointestinal cancer presents a significantly different natural history from many other tumors. For example, local recurrence is unusual with breast cancer or extremity sarcoma. Sugarbaker et al. (5) hypothesized that the surgical procedure itself contributes substantially to the natural history of gastrointestinal cancer. The mechanism whereby a large proportion of patients have disease recurrence confined to the resection site and peritoneal surfaces is related to traumatic dissemination of tumor emboli within the peritoneal cavity, and the implantation of these tumor emboli within the fibrinoid exudate that accumulates at the resection site and on abraded peritoneal surfaces. Sources for these intraabdominal tumor emboli include severed lymphatic channels, disrupted tissue interstices at the lateral margins of tumor dissection, and tumor emboli within venous blood lost from the tumor specimen (5). By the theory of metastatic inefficiency described by Weiss (6), even a small number of tumor cells dispersed within the raw surfaces of the abdominal cavity would be expected to result in recurrent disease; conversely, large numbers of tumor cells confined to endothelial lined lymphatic or vascular channels with an intact basement membrane would not be expected to result in tumor implantation.

In an attempt to design treatments that would eliminate local tumor spread as a mechanism of gastrointestinal cancer recurrence, we performed pharmacological studies with i.p. chemotherapy early in the postoperative period. The rationale for EPIC7 is: (a) the resection site and abraded peritoneal surfaces are at high risk for tumor cell implantation in the postoperative period; (b) all intraabdominal surfaces are fully exposed to i.p. chemotherapy if the surgeon has been careful to separate all adherent structures and if these treatments are instituted prior to the formation of abdominal adhesions; (c) in the postoperative period the surgical techniques required for i.p. drug delivery are extremely simple. With the abdomen open, insertion of a peritoneal access device is safe and associated with virtually no morbidity; (d) regional chemotherapy may result in markedly increased local responses without compromising systemic effects. Drug delivery to the liver is markedly increased if agents exhibit a "single pass effect" through this organ; (e) the cost to the patient in terms of time and money is minimal since the therapy is instituted and completed within a normal postoperative time frame. The drugs themselves are relatively inexpensive compared to the hospitalization. In order to perform phase I and pharmacological studies, patients with peritoneal carcinomatosis were selected. These patients inevitably have recurrences with surgery alone as a treatment modality. These early studies build a strong pharmacological rationale for the more general applications of EPIC. This management plan may help control early spread of cancer on peritoneal surfaces and the tumor spillage that may occur as a result of surgical trauma. If EPIC can eliminate resection site and peritoneal surface recurrence, these treatments may be associated with a change in the natural history of surgically treated gastrointestinal cancer.

MATERIALS AND METHODS

Patients. For these early studies, patients with advanced primary or recurrent gastrointestinal cancer confined to the abdominal cavity were

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5-fluorouracil but not for mitomycin C. The marked pharmacokinetic advantage of postoperative i.p. suggests that this treatment strategy should be considered in a clinical trial in patients at risk for progression of peritoneal carcinomatosis.
selected for protocol treatments. Diagnoses included recurrent colon cancer (7 patients), perforated appendiceal cancer (16 patients), gall-bladder cancer (1 patient), and biliary tract cancer (1 patient). All patients had biopsy confirmed tumor on peritoneal surfaces. Patients were excluded if they had liver metastases or tumor identified systemically. Altogether, 26 patients underwent an extensive surgical procedure followed by EPIC with MMC and 5-FUra.

Treatments. After completing the cytoreductive surgical procedure and prior to closing the abdominal incision, a Tenckhoff catheter was placed through the abdominal wall. A purse string suture was used at the peritoneal level in order to minimize leakage of peritoneal fluid. After the abdomen was closed abdominal lavage with a 1.5% dextrose dialysate was instituted to remove blood products and tissue debris that resulted from surgery. No heparin or potassium was added to the dialysis fluid. One liter of the fluid was run into the abdominal cavity as rapidly as possible. The liter of fluid was immediately drained by gravity. This procedure was repeated on an hourly basis until the effluent was clear. Abdominal lavage was repeated every 4 h until the i.p. chemotherapy was begun on the first postoperative day. The materials utilized to lavage the abdominal cavity or to deliver i.p. chemotherapy are shown in Fig. 1.

In these early studies MMC and 5-FUra were utilized i.p. For MMC a single dose of 12 mg/m² (7 patients) or 10 mg/m² (16 patients) was utilized. Extensive previous experience with 5-FUra i.p. 6–10 weeks after surgery was available (7, 8). The initial i.p. dose of 5-FUra was 20 mg/kg (7 patients) with a maximum dose of 2 g. To decrease toxicity, the dose of 5-FUra was reduced to 15 mg/kg (16 patients) with a maximum dose of 1800 mg. Three patients with reduced renal or hepatic function were given MMC at one-half the calculated dose. Each drug was administered as a single daily instillation in 1.5% glucose dialysis fluid. Two liters of dialysate fluid were instilled i.p. initially but this was associated with excessive abdominal discomfort. In subsequent patients, 1 liter of dialysate was used. Drugs were allowed to dwell for 23 h and removed by closed suction drains placed in dependent parts of the abdomen. When drainage ceased, another container of i.p. chemotherapy was attached and secured with a sterile clamp to the connection site and infused by gravity as rapidly as possible into the peritoneal cavity. All abdominal drains were clamped during instillation and dwell. On the sixth postoperative day all fluid was drained from the peritoneal cavity and the Tenckhoff catheter was withdrawn from its tract; closed suction drains were removed as surgically indicated. Occasionally, there was a small seepage of fluid during the chemotherapy instillations and for a few days thereafter from the abdominal incision and from the Tenckhoff catheter skin exit site. This was thought to be an inconsequential problem except that it could cause inadvertent exposure of hospital personnel to chemotherapeutic agents.

Monitoring. Sampling of peritoneal fluid and plasma was performed in selected patients. A total of 17 complete pharmacokinetic studies were performed with monitoring for 8–12 h in most patients. In three patients, a portal venous catheter was inserted so that portal levels of MMC or 5-FUra could be determined. These catheters were secured with elastic suture material and were removed upon completion of the pharmacokinetic monitoring without complications (9). Blood, peritoneal fluid, or portal vein samples were drawn into heparinized tubes at 0, 10, 20, 30, 60, 90, 120, 180, 240, 360, 480, and 720 min. The tubes were centrifuged at 150 × g for 10 min and the plasma was stored at −70°C. Samples were assayed in batch format to minimize run to run variation.

Pharmacokinetic Analysis. R-strip, an integrated software program by Micro Math Scientific Software (Salt Lake City, UT), was utilized to determine pharmacokinetic parameter estimates for half-life (t½), AUC, and elimination rate constants (Kₑ). This software package utilizes linear regression equations to determine the pharmacokinetic model which best fits the set of data points. Once the “best fit” model is determined, values are calculated for t½, Kₑ, and AUC (via the trapezoidal rule).

5-FUra Assays by HPLC and Magnetic Resonance Spectroscopy. 5-FUra was assayed by HPLC. Briefly, 5-FUra was quantitated in body fluids and tissue extracts using liquid-liquid extraction and reverse phase chromatography. All organic solvents were HPLC grade. Type 1 water was used in all chromatographic and extraction applications. All other reagents were the highest purity. Five hundred µl of sample (serum, plasma, or peritoneal fluid), 25 µl of internal standard (50 µM 5-chlorouracil in water), and 50 µl 1.0 M potassium phosphate buffer, pH 7.0, was added to a tube and vortexed. The drug was extracted with 8 ml ethyl acetate; the organic phase was recovered and evaporated to dryness. Samples were reconstituted with 150 µl of mobile phase. Mobile phase consisted of 20 mM acetic acid in 1% acetonitrile. Instrumentation included a 510 HPLC pump, a 710-B WISP auto sampler, a RCM100 Radial Compression Module containing a Radial-Pak C₁₈-Bondapak column, a model 481 UV detector, (all from Waters, Inc., Milford, MA), and a C-R6A integrator/recorder (Shimadzu, Columbia, MD). The flow rate was 1.0 ml/min and the detector was set at 266 nm and 0.001 ultraviolet absorbance (AUC). Late eluting peaks were flushed from the system by injection of 300 µl of acetonitrile between each analytical run.

For one patient ¹⁹F MRS was used to determine the levels of 5-FUra and its catabolites in plasma and peritoneal fluid samples, which were frozen and shipped to Heidelberg for analysis at the German Cancer Research Center (10). ¹⁹F nuclear magnetic resonance measurements were performed at 470 MHz (11/7 T) using a Bruker AM-500 FT nuclear magnetic resonance spectrometer and 10-mm sample tubes. Approximately 1.5 ml of the biological fluid were measured directly, without any chemical treatment, at a controlled temperature of 4°C. The techniques used to obtain ¹⁹F MRS spectra, their interpretation, and the quantitative analysis for 5-FUra and catabolites have been described in detail elsewhere (10). Data acquisition times per sample ranged from 1 h (detection level for fluorine-containing metabolites were calculated to be 4 µM) to 8 h (detection level, about 1 µM) (10).

MMC Assays by HPLC. The assays of peripheral blood, portal blood, peritoneal fluid, and urine for MMC were carried out as described by Tjaden et al. (11). Briefly, a fully automated liquid chromatographic system for the bioanalysis of MMC was used. The isolation of MMC from its biological matrix (plasma, peritoneal fluid, or urine) was performed using a continuous flow system equipped with a dialysis membrane in order to remove proteins. By using a reverse phase precolumn, the samples are concentrated and subsequently introduced onto the reverse phase analytical column by applying column switching techniques.

RESULTS

Pharmacological Comparisons of Early versus Delayed i.p. 5-FUra. The studies of Dedrick et al. (12), Collins (13), and Speyer et al. (14) all suggest a marked regional concentration advantage using i.p. chemotherapy administration. We wished

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to see if the same differences in 5-FUra concentration in the plasma and peritoneal fluid compartment existed in the early postoperative period when peritoneal surfaces are extensively traumatized by the cytoreductive surgical procedure. Studies on peritoneal fluid and plasma were performed on the second postoperative day and on the second day of a chemotherapy cycle at 3 months postoperatively in an individual patient. The results for early and delayed i.p. chemotherapy are compared in Fig. 2. These data clearly show a marked regional pharmacological advantage of i.p. chemotherapy of comparable magnitude with both early and delayed i.p. 5-FUra chemotherapy. A comparison of early and delayed i.p. 5-FUra pharmacokinetics was repeated and similar results were obtained (Table 1).

Changes in 5-FUra Pharmacokinetics over a 5-Day Treatment Schedule. In previous studies Sugarbaker et al. (15) showed that the local-regional nature of 5-FUra drug distribution was modified over a 5-day course of treatment. These authors suggested that changes in the peritoneal surfaces were responsible for the increased clearance of drug from the abdominal cavity. In order to determine the pharmacokinetics of a treatment schedule in the early postoperative period, we sampled i.p. 5-FUra on postoperative days 2 and 5. These results are shown in Fig. 3. The differences between 5-FUra concentration obtained in an individual patient (peritoneal fluid versus plasma) on the second postoperative day as compared to the fifth postoperative day are less marked. Similar results were seen in the study of a second patient given EPIC and a patient given delayed i.p. chemotherapy (Table 1). AUC differences were approximately 1.5–3 times greater.

Elevated Intraperitoneal 5-FUra in the Early Postoperative Period. In a single patient blood samples were drawn from the portal vein as well as from the peritoneal fluid and peripheral blood on the second postoperative day. Fig. 4 shows the intraperitoneal levels of 5-FUra to be nearly 10 times that present in the peripheral blood.

Comparison of HPLC Data and MRS Data. On a single patient, blood and peritoneal fluid samples were drawn on the second postoperative day and samples were equally divided. The 5-FUra concentration was determined by HPLC and also by 19F MRS. The data are shown in Fig. 5. The close correlation of time courses observed by the two assay techniques suggests that a high level of accuracy and reproducibility can be achieved for both methods when monitoring 5-FUra (10).

However, MRS analysis offers the advantage of measuring both the parent compound and the catabolites of 5-FUra (10). Dihydrofluorouracil, α-fluoro-β-ureidopropionate, and the final catabolite α-fluoro-β-alanine were present in plasma at levels of 10–20 μM 10 min after treatment. α-Fluoro-β-alanine reached its maximum of approximately 50 μM 2 h after treatment at which point 5-FUra represented only 4% of the circulating fluorine-containing metabolites. The three catabolites of 5-FUra appeared in the peritoneal fluid at detectable levels 30–60 min posttreatment and remained at nearly constant levels (ca. 50 μM total) 2–6 h after treatment. The MRS method also allows the detection of free fluoride anion (F–, often a contaminant in 5-FUra solutions), which was found in both fluids at about 5 μM throughout the monitoring period (data not shown).

AUC and t1/2 with Early Postoperative i.p. 5-FUra. Table 1 summarizes the pharmacokinetic parameter estimates for patients receiving 5-FUra i.p. The AUC and the t1/2 for i.p. and systemic 5-FUra in eight patients are shown. One sees that the median area under the curve ratio for i.p. versus systemic 5-FUra in the early postoperative period was 117/1. The elimination t1/2, calculated from the data sets best described by a one-compartmental model ranges from 33 to 88 min (mean, 65.8) and for simultaneously sampled systemic 5-FUra it ranges from 41.5 to 96 min (mean, 67.4). The magnitude of these differences will varying depending upon the dose of chemotherapy (concentration of drug in dialysate fluid), permeability of the i.p. barrier and the day chemotherapy is administered during the 4- or 5-day treatment cycle.

Assay of Four Body Compartments after Early Postoperative i.p. MMC. In the patient shown in Fig. 6, not only were peritoneal fluid and plasma MMC concentrations determined but also portal blood and urine MMC levels were assayed. Marked concentration differences in peritoneal fluid as compared to systemic blood were seen. The concentration advantage for i.p. MMC (AUCi.p./AUCs) was 21.6. The difference in the

![Fig. 2. Pharmacological studies of early versus delayed i.p. 5-FUra. Peritoneal fluid day 2 postoperatively (○); peritoneal fluid day 2 3 months later (□); plasma day 2 postoperative (△); plasma day 2 of cycle obtained 3 months later (■).](image)

### Table 1 i.p. 5-FUra pharmacokinetic parameter estimates

<table>
<thead>
<tr>
<th>Patient (cycle, day)</th>
<th>Dose (mg)</th>
<th>Plasma^a^ (μg/ml/h)</th>
<th>Peritoneal fluid^a^ (μg/ml/h)</th>
<th>AUC (μg/ml/h)</th>
<th>Correlation coefficient Peritoneal fluid</th>
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<tr>
<td>1 (C1D2)</td>
<td>1,100</td>
<td>58.9</td>
<td>32.6</td>
<td>329.4</td>
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<td>2 (C1D2)</td>
<td>1,600</td>
<td>72.8</td>
<td>88.1</td>
<td>146.4</td>
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<td>3 (C1D2)</td>
<td>1,300</td>
<td>68.5</td>
<td>71.7</td>
<td>415.6</td>
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<td>4 (C1D2)</td>
<td>1,300</td>
<td>67.9</td>
<td>63.2</td>
<td>714.3</td>
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<tr>
<td>5 (C1D2)</td>
<td>1,300</td>
<td>73.7</td>
<td>79.6</td>
<td>181.0</td>
<td>47,891.8</td>
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<tr>
<td>6 (C1D1)</td>
<td>1,800</td>
<td>41.5</td>
<td>13.2</td>
<td>255.8</td>
<td>67,542.5</td>
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<tr>
<td>7 (C1D1)</td>
<td>800</td>
<td>79.2</td>
<td>86.3</td>
<td>73.6</td>
<td>8,674.7</td>
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<tr>
<td>8 (C1D1)</td>
<td>800</td>
<td>66.4</td>
<td>17,789.5</td>
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</tbody>
</table>

^a^All data sets were best described as a one-compartment pharmacokinetic model except the peritoneal fluid data sets for patient 3 (C2D5) and 4 (C1D1) which were described as two and three compartmental, respectively, and as indicated.
the collected plasma on the second postoperative day. Peritoneal fluid (O); urine (A); portal plasma (A).  

The high MMC levels in the urine were related to the smaller molecular weight, smaller dose, and low bioavailability when the drug is slowly absorbed. With rapid absorption, saturation of hepatic catabolic enzymes allows i.p. MMC concentration advantage as compared to 5-FUra to be related to the smaller molecular weight, smaller dose, and increased absorption of MMC across the abdominal cavity membrane. The peripheral blood and portal blood MMC levels are essentially the same after i.p. MMC administration. Contrast this to the differences observed for intraperitoneal versus systemic 5-FUra (Fig. 4). The high levels of MMC in the urine should be noted. Urine samples were obtained through a Foley catheter and a continuous urine output of 120 ml/h was maintained over 12 h. The elevated concentration of MMC in the urine was noted to persist for at least 6 h in a second patient who was studied.  

MMC Area under the Curve and $t_{1/2}$. Table 2 shows the AUC and $t_{1/2}$ estimates for five patients treated on their first postoperative day with i.p. MMC. The median AUC ratio of peritoneal fluid to plasma was 21.6. The median $t_{1/2}$ for the patients whose data indicated a one compartment decay in the peritoneal fluid was 96.5 min and that for plasma was 290.8 min.  

**DISCUSSION**

The major cause for limited effectiveness of cancer chemotherapy may be the development of resistant cells. One strategy for minimizing this mechanism of treatment failure involves dose intensive regimens administered to patients with an absolute minimum tumor burden. In our patients with peritoneal carcinomatosis, we used cytoreductive surgery to reduce the tumor burden. An attempt was made to resect cancer until no macroscopic evidence of disease could be appreciated by the unaided eye. For patients with primary gastric, pancreatic, or colorectal cancer, surgical resection of the primary malignancy represents the optimal cytoreductive procedure. In our patients with peritoneal carcinomatosis and in future patients with primary gastrointestinal cancer, EPIC may be the ultimate in dose intensive chemotherapy. Our studies suggest that this unique timing for i.p. chemotherapy administration presents additional possibilities as an adjuvant to gastrointestinal cancer surgery. High doses of regional chemotherapy over prolonged (120 h) time periods should translate into a high fraction of cell kill and a small likelihood of drug resistance. Portions of the abdominal cavity sealed off by scar formation should now have more adequate exposure to chemotherapy. Even if EPIC does not result in prolonged survival, it may change the natural history of primary gastrointestinal cancer by eliminating resection site and peritoneal surface recurrence.

One may wish to compare the exposure of tumor in vivo when i.p. chemotherapy was used to treat patients postoperatively to the exposure required to kill tumor cells in in vitro tests. Park et al. (16) determined the exposure required to reliably kill colon cancer cell lines in vitro by colorimetric assay in a 96-h time period. The concentration of MMC required was 2.5 $\mu$g/ml. The MMC drug concentration used in these clinical studies was between 12 and 20 $\mu$g/ml. Because of the peritoneal plasma barrier, high drug concentrations were maintained for approximately 12 h. The studies of Jol et al. (17) suggested that there was a linear cell kill even at exposure times of 1 h. The exposure time in our patients compared to Park's in vitro studies was considerably reduced but the initial concentration of MMC was nearly 8 times that required for complete cell kill.

For 5-FUra, peritoneal surfaces were treated for 96 h. The initial dose of drug was 500–1800 $\mu$g/ml. Park found reliable cell kill with 5-FUra at 200 $\mu$g/ml. For this drug, the exposure achieved with i.p. drug therapy should compare favorably with that showing high levels of tumor destruction by chemosensitivity testing.

There is a marked difference in the portal venous and systemic venous concentration of 5-FUra after i.p. drug delivery. The high level of 5-FUra in the portal blood has been related to the first pass effect through the liver. Pharmacokinetic studies with 5-FUra p.o. have shown a high hepatic extraction ratio and low bioavailability when the drug is slowly absorbed. With rapid absorption, saturation of hepatic catabolic enzymes allows...
for a smaller extraction ratio and thus higher systemic concentrations. 5-FUra diffusion i.p. across the peritoneal membrane is thought to be slow because of its low lipid solubility and chemical bulkiness. Therefore, out data support a high liver extraction of 5-FUra. If absorption was increased due to alteration in the peritoneal barrier one might expect to see an enzyme saturation or Michaelis-Menton picture leading to excessive systemic toxicity (18). Our data also indicate that i.p. 5-FUra is preferably taken up by visceral peritoneal surfaces to tumor and normal tissues. Only with these types of investigations can we determine safe regimens that provide maximal drug dosage.

We have begun to do this by instilling the i.p. chemotherapy prior to the surgical procedure and then sampling not only the peritoneal fluid and plasma but also the tissues within the abdominal cavity which are bathed by the chemotherapy. It is quite possible that optimal treatment of gross tumor on peritoneal surfaces should used both i.p. and i.v. drugs.

REFERENCES

Early Postoperative Intraperitoneal Chemotherapy as an Adjuvant Therapy to Surgery for Peritoneal Carcinomatosis from Gastrointestinal Cancer: Pharmacological Studies


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