High-Volume Intraperitoneal Chemotherapy with Methotrexate in Patients with Cancer


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ABSTRACT

The use of high-volume i.p. chemotherapy with methotrexate (7.5 to 50 µM methotrexate administered via peritoneal dialysis technique) was studied in four patients with ovarian cancer and one patient with malignant melanoma. All had tumor localized to the peritoneal cavity or liver. Methotrexate concentration in the peritoneum could be maintained 18- to 36-fold higher than corresponding plasma concentrations using this method, plasma levels remaining in the range of 0.2 to 3 µM. While local toxicity was generally limited and manageable, mild aseptic peritoneal irritation was commonly seen, and one episode of bacterial peritonitis did occur. Because of the concentration difference between peritoneum and the systemic circulation, systemic toxicity was moderate with only six of 29 treatment cycles resulting in myelosuppression. No definite therapeutic benefit was seen, but the tumors of four of five patients had demonstrated resistance to a methotrexate-containing chemotherapy regimen prior to this study. Further investigation of this novel treatment modality is warranted.

In addition, this study provides the first measurement of peritoneal methotrexate clearance and the ratio of peritoneal to total body clearance.

INTRODUCTION

Chemotherapy, surgery, and radiation therapy can render certain patients with advanced ovarian carcinoma free of intraabdominal disease, but small volumes of residual tumor frequently remain. Regrowth of this tumor is only infrequently controlled with further therapy (1).

In a study reported recently from the National Cancer Institute, combination chemotherapy with Hexa-CAF2 achieved a 76% response rate but only a 33% complete remission rate in patients with advanced ovarian adenocarcinoma (22). When the 17 patients with partial or complete clinical responses were evaluated following 12 months of therapy, peritoneoscopy or repeat laparotomy documented "minimal residual disease" (no i.p. tumor masses greater than 0.5 cm in diameter) in 5 patients. Further Hexa-CAF treatment failed to achieve a complete remission in 4 of these patients, and considerable dose reductions were routinely required because of myelosuppression.1

During studies of MTX pharmacokinetics in patients with ovarian cancer, Myers et al. (14) observed that the drug concentration in plasma exceeded that in ascites fluid for the first 6 to 12 hr following i.v. administration, after which time the MTX concentration was often higher in ascites than in plasma. This finding suggested that a barrier to MTX exit from the peritoneum exists.

Ovarian cancer is usually localized to a single body cavity, the peritoneum, and frequently exerts its lethal effects there. If MTX were distributed into the peritoneum of these patients and a positive concentration gradient from peritoneum to plasma established, this gradient might allow improved therapeutic results to be achieved with minimal systemic toxicity. Pharmacokinetic modeling based upon known physiological principles of drug exchange across the peritoneal surface predicted that a large i.p. plasma concentration gradient could be attained using MTX administered through a Tenckhoff catheter in high-volume solution (6). Preclinical studies verifying this hypothesis have been described (6, 13).

In the past, when chemotherapeutic agents have been injected directly into ascites, the benefit to patients has been palliative at best (16). Various reasons for lack of success with this technique can be suggested, including failure to expose the entire abdominal contents to ascites fluid and drug, rapid disappearance of drug from ascites (by absorption or metabolism), and poor diffusion of drug through the surface of large tumor masses which often are present.

This report outlines the pharmacological and clinical results of a trial of MTX peritoneal dialysis therapy in five patients.

MATERIALS AND METHODS

Patient Criteria. Four patients with ovarian adenocarcinoma and one patient with melanoma received i.p. MTX. Pertinent pretreatment data are summarized in Table 1. Three ovarian cancer patients were Stage III and one Stage IV prior to initial therapy with Hexa-CAF, and each had received at least 12 monthly cycles of this combination. Reevaluation by peritoneoscopy or laparotomy documented either lack of response or tumor progression on this regimen. Additionally, all tumor masses observed in these patients were less than 0.5 cm in diameter. No tumor could be documented outside the peritoneal cavity or liver following physical examination, routine blood counts and chemistries, radiographs, and lymphangiography. Each patient had a creatinine clearance of at least 65 ml/min. All patients gave informed consent prior to treatment.

Tenckhoff Catheter Placement and Care. The single-cuff Tenckhoff catheter was placed under local anesthesia. This semipermanent silastic catheter has been maintained for as long as 3 years in patients receiving peritoneal dialysis for chronic renal failure (20). Following placement, the catheter

1 To whom requests for reprints should be addressed, at National Cancer Institute, NIH, Building 10, Room 6N104, Bethesda, Md. 20205.
2 The abbreviations used are: Hexa-CAF, hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluorouracil; MTX, methotrexate; SGPT, serum glutamic pyruvic transaminase, SGOT, serum glutamic oxaloacetic-acid transaminase; 5-FUra, 5-fluorouracil.
3 R. C. Young, personal communication.

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was flushed sequentially with 1000 ml of Inpersol (Abbott Laboratories, Chicago, Ill.) containing 1.5% glucose and heparin (1000 units/liter) until the drained fluid was clear. The catheter was flushed in a similar manner once daily for the next 3 days or until the patient was discharged from the hospital. Each patient was instructed in sterile dressing techniques and was required to demonstrate competence in dressing his or her catheter placement site prior to discharge. The patients performed daily dressing changes and inspection for signs of infection while at home. They flushed the catheter on alternate days with 10 ml of sterile 0.9% NaCl solution containing heparin (100 units/ml). After 1 week to allow healing of the catheter site, treatment was begun.

**Treatment Regimen.** The methods used and doses of MTX utilized have been described previously (13). Briefly, each patient received a 48-hr dialysis weekly for 6 weeks unless otherwise indicated. Dialysis fluid was replaced with fresh solution every 6 hr for a total of 8 exchanges. During the first course of dialysis, the volume of 1.5% Inpersol (containing MTX) was increased progressively from 2000 ml to patient tolerance, and the volume was then held constant for the remainder of the 6-week treatment course. The MTX concentration in the dialysis fluid was increased from 15 to 50 μM over ensuing weeks unless toxicity became prohibitive. These concentrations were selected to be at least 15-fold higher than required to inhibit incorporation of deoxyuridine into DNA ovarian tumor cells in vitro (5). Each patient received i.v. folic acid (3.5 mg/kg/hr) as a continuous infusion in the period from 40 to 56 hr after the start of each dialysis treatment. If systemic MTX toxicity was observed or the plasma MTX concentration 6 hr following the dialysis was above 50 nm, the folic acid dose was doubled, and the infusion duration was increased from 16 to 24 hr. A urine flow above 100 ml/hr was maintained in each patient during treatment by appropriate administration of i.v. fluids. Patients were allowed to leave the hospital when each dialysis was complete and when the plasma MTX concentration fell below 50 nm.

**Computerized Axial Tomography of the i.p. Space.** The i.p. space of each patient was evaluated during the first 2 treatment weeks by computerized axial tomography following i.p. instillation of 2000 to 2500 ml of 1.5% Inpersol containing 75 ml of 25% Hypaque (Winthrop Laboratories, New York, N. Y.) per liter of dialysate. The largest volume of dialysate which each patient could tolerate was administered.

**Drug Concentration Determination and Pharmacokinetrical Analysis.** MTX concentrations in plasma, urine, and dialysis fluid were determined by a competitive protein-binding method described previously (15) which uses Lactobacillus casei dihydrofolate reductase. In certain patients, dialysis fluid MTX concentrations were also measured by UV absorbance at 340 nm. During treatment, complete blood counts, routine chemistry profiles, and urinary collections were performed daily. Fluid volume was carefully monitored i.p. Peritoneal fluid samples were cultured for bacteria and fungi daily.

The total body clearance of MTX was defined as

\[
\text{mg MTX absorbed from the peritoneum mg/liter area under the curve mg/min}
\]

where AUC is the area under the plasma MTX concentration versus time curve. It was calculated using the trapezoidal approximation (9)

\[
AUC = \sum_{i=1}^{n} \frac{[C_i + C_{i+1}] \times \Delta t}{2} + C_{i+1} \times (\Delta t)^/ \beta
\]

where \(\beta\) is elimination rate constant from plasma, and \(C_i\) is the concentration at a given time, \(t\). The last term is a correction for the area not measured (from the last sample to infinity).

**RESULTS**

**Clinical Observations.** The toxicities noted with this regimen are outlined in Table 2. Two of 5 patients experienced myelosuppression (WBC < 3,000; hemoglobin < 10.0; platelets < 100,000/cu mm). Patient 4 developed a WBC of 2,880/cu mm during the fifth week of treatment, but her leukopenia resolved by Week 6. Patient 3 developed a WBC of 1,800/cu mm and a platelet count of 53,000/cu mm prior to the second weekly dialysis. This pancytopenia remained essentially un-

![Table 1: Pretreatment clinical data for patients receiving the MTX peritoneal dialysis regimen](image-url)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor type</th>
<th>Pathological stage</th>
<th>Creatinine clearance (ml/min)</th>
<th>Prior chemotherapy</th>
<th>Prior response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ovarian adenocarcinoma</td>
<td>III</td>
<td>65</td>
<td>Hexa-CAF</td>
<td>PR*</td>
</tr>
<tr>
<td>2</td>
<td>Ovarian adenocarcinoma</td>
<td>IV</td>
<td>72</td>
<td>Hexa-CAF</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>Ovarian adenocarcinoma</td>
<td>III</td>
<td>66</td>
<td>Hexa-CAF</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>Ovarian adenocarcinoma</td>
<td>III</td>
<td>91</td>
<td>Hexa-CAF</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>Melanoma</td>
<td>IV</td>
<td>83</td>
<td>None</td>
<td>PR</td>
</tr>
</tbody>
</table>

* The system of the International Federation of Gynecology and Obstetrics was used to classify ovarian cancer patients by stage. A commonly utilized system was used to stage the melanoma patient, who had parenchymal liver metastases.

**PR,** partial response.
changed over the remainder of a full-dose treatment regimen. This latter patient had received extensive prior chemotherapy and had a WBC of 3,100/cu mm and a platelet count of 111,000/cu mm prior to the start of MTX dialysis treatment. She experienced no infectious or bleeding complications. Of note, this same patient developed mild oral mucositis and conjunctivitis during the last 2 weeks of treatment.

Peritoneal irritation was experienced by 3 of 5 patients. Patient 1 developed culture-proven Pseudomonas aeruginosa peritonitis (in addition to asceptic peritoneal irritation during earlier cycles) following completion of the fifth weekly dialysis. Dialysis was discontinued, and the patient was successfully treated with i.v. gentamicin. Patients 1 to 3 complained of abdominal pain, usually localized to the lower quadrants, which routinely improved following each weekly treatment and did not significantly limit activity. Peritoneal fluid cultures were routinely negative in these latter patients except as noted above. No correlation of these local symptoms to MTX dose was detected.

Additionally, Patient 2 developed severe upper quadrant abdominal pain with associated rebound tenderness during her second weekly dialysis cycle (15 μM i.p. MTX concentration). The pain began during the dialysis and worsened for 2 to 4 hr following completion of the treatment. Symptoms were improved when the dialysis period was shortened to 24 hr and when the i.p. MTX concentration was reduced to 7.5 μM. Again, multiple peritoneal fluid cultures were negative. This was the only patient who experienced toxicity which required dose modification.

Two of the 5 patients experienced mild and self-limited nausea and vomiting following certain treatment courses (Table 2). Diarrhea occurred in 3 of 5 patients and was watery and nonbloody. Two patients were noted to have transient SGPT and SGOT elevations (less than 2 times normal) which resolved before the end of the treatment course. Patient 5 experienced a decline in creatinine clearance from 83 to 45 ml/min during treatment. This decline, however, was accompanied by development of a perirenal mass consistent with recurrent melanoma.

There was no clear therapeutic benefit derived from this study. Patients 2, 3, and 5 were noted to have progressive tumor within 1 month following initiation of treatment. Tumor in Patient 4 was unchanged following therapy, and the patient was given systemic chemotherapy following this study. Patient 1 refused restaging evaluation but is well (13 months following MTX dialysis) with no clinically obvious tumor. She had, however, received 2 additional monthly courses of Hexa-CEF while awaiting dialysis and thus is not evaluable for response.

**Pharmacology.** A representative plot of plasma and i.p. MTX concentrations during a 48-hr dialysis is shown in Chart 1. This plot is typical of the plasma i.p. concentration gradient data which were obtained using the high-volume technique. Over each 6-hr dwell period, i.p. MTX concentration fell steadily due to systemic absorption of drug; there was a mean decline in i.p. MTX concentration of 68% during this time. The dialysate was then replaced with fresh solution, causing the "saw-tooth" pattern of the dialysis fluid MTX concentration curve shown in Chart 1. Plasma MTX levels in each patient approached a plateau within 6 to 10 hr of the start of each 48-hr dialysis. A 7.5 to 50 μM i.p. dose range was utilized for this study since 1 μM MTX is required to inhibit deoxyuridine incorporation into DNA of most ovarian cancer cells in vitro. With these doses, plasma MTX levels ranged between 0.2 and 3 μM.

Pharmacokinetic data are summarized in Table 3. Data from Patient 5 were separated for purposes of analysis since i.p.

![Chart 1. Plasma and i.p. MTX concentrations during a typical treatment. ▲: dialysis fluid MTX concentrations; ●: plasma MTX concentrations; †: projected MTX dialysis fluid concentrations (no samples actually taken). Dialysis fluid (2200 ml) containing 35 μM MTX was administered i.p. every 6 hr after draining preexisting dialysis fluid. Vertical lines between dialysis fluid MTX levels represent the difference in MTX concentration between freshly prepared dialysate and dialysate which has remained in the abdomen for 6 hr. Oblique lines represent first-order MTX disappearance from the peritoneum during a 6-hr dwell.](cancerres.aacrjournals.org)
melanoma may not be comparable to ovarian cancer in this analysis. The total body MTX clearance (ml/min) represents the net rate of MTX elimination from the plasma (renal excretion, hepatic clearance, etc.). In analogous fashion, peritoneal permeability area product \([PA \text{ (ml/min)}]\) reflects the rate at which MTX is absorbed from the peritoneal cavity. For a given drug, \(PA\) is an intrinsic property of the peritoneal membrane, associated structures, and exposure of these elements to drug. The 17- to 35-fold difference in rate between these 2 processes is responsible for the MTX concentration differences illustrated in Chart 1.

Table 3 indicates that the total body clearance of MTX for the ovarian cancer patients averages 1.7 times the creatinine clearance, a ratio consistent with earlier reports (11). The mean creatinine clearance of these patients was 74 ml/min. Total body clearance did not vary significantly with i.p. MTX dose by the one-way analysis of variance, \(F\) test.

Two patients experienced no significant changes in peritoneal permeability area product during the treatment course (Patients 3 and 4). Patient 2 demonstrated decreasing peritoneal permeability during the first 3 treatment weeks, but by the end of the 6-week treatment course the permeability increased to starting levels. The \(PA\) of Patient 5 increased during Weeks 1 to 3 and then returned to starting levels. Data from Patient 1 were insufficient for analysis. The mean \(PA\) for Patient 5 (melanoma) was higher than the \(PA\) for the ovarian cancer patients.

Once a steady state was reached, the mean MTX concentration gradient could be approximated by the expression \([C_{\text{in}} + PA \left(\frac{PA}{PA-1}\right)]\) (6). As Table 1 indicates, a 17- to 35-fold i.p. plasma MTX concentration gradient was achieved.

**DISCUSSION**

Our data demonstrate that a large positive concentration difference between the peritoneum and plasma could be established and maintained for the 48-hr treatment periods. This concentration differential should allow i.p. tumor to be exposed to potentially tumoricidal MTX doses while the corresponding plasma MTX levels should result in acceptable toxicity; in fact, only one of 5 patients experienced repeated leukopenia. Additionally, as drug is absorbed, the dialysate can be drained and replaced with fresh solution. This allowed continuous high i.p. drug levels to be achieved (Chart 1) as indicated by the mean decline of i.p. drug concentration of 68% over the 6-hr dwell time in this study.

Local toxicity observed with this regimen was limited and manageable. The single episode of infection was successfully treated, and the incidence of infection (3.5% of all dialyses) in this small series is only slightly higher than that reported in a series of patients receiving peritoneal dialysis for renal failure (4). Aseptic peritoneal irritation was commonly seen but required analgesia in only one patient. MTX dose reduction and p.o. indomethacin were associated with elimination of the pain in this instance. This complication might be analogous to the meningeal irritation often seen following intrathecal to the meningeal irritation often seen following intrathecal administration of MTX for central nervous system prophylaxis in childhood leukemia (3).

The small elevations of SGPT and SGOT noted in 2 of the 5 patients may reflect toxicity of absorption of drug through the portal system with resultant liver toxicity. Minor elevations of SGPT and SGOT are frequently observed following i.v. high-dose MTX administration (12). No delayed hepatic or gastrointestinal toxicity was observed. The mean period of follow-up for these patients was 254 days (range, 124 to 399 days). Thus, the plasma MTX levels of 0.2 to 3 \(\mu M\) produced by this regimen for 48 hr caused only limited systemic toxicity (only 6 of 29 cycles produced myelosuppression, and 5 of these myelotoxic cycles occurred in one patient).

We anticipated that filling the peritoneum to patient tolerance with drug-containing dialysate should provide exposure for i.p. surfaces and tumor nodules. The importance of high volume for total exposure was recently emphasized by Rosenshein et al. (17). When female rhesus monkeys (5 kg) were given i.p. injections of 250 ml of fluid containing \(\text{\textsuperscript{99}}\text{Tc}\)-labeled albumin, rapid exposure of the peritoneal surface was noted. If the same radiopharmaceutical was administered in a 20-ml volume, much of the peritoneum remained unexposed, even following abdominal massage or postural changes. In similar fashion, we administered Inpersol dialysis fluid containing contrast media i.p. to each patient. Computed tomography of the abdomen

<table>
<thead>
<tr>
<th>Patient</th>
<th>(\mu M) dose range</th>
<th>(C_{\text{in}}) ((\text{ml/min}))</th>
<th>(\text{Ch}_{\text{in}}/\text{creatinine clearance})</th>
<th>(\text{PA (ml/min)})</th>
<th>((\text{Ch}_{\text{in}} + \text{PA}) / \text{PA})^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15–35</td>
<td>88 ± 55(^{d})</td>
<td>1.0 ± 0.5</td>
<td>2.5 ± 0.4</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>7.5–15</td>
<td>143 ± 49</td>
<td>3.4 ± 1.1</td>
<td>5.6 ± 3.5</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>15–50</td>
<td>71 ± 21</td>
<td>1.0 ± 0.5</td>
<td>3.3 ± 1.2</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>15–50</td>
<td>127 ± 9</td>
<td>1.6 ± 0.2</td>
<td>6.7 ± 0.7</td>
<td>20</td>
</tr>
<tr>
<td>Totals (ovarian patients)</td>
<td>114 ± 20</td>
<td>1.7 ± 0.3</td>
<td>4.8 ± 0.5</td>
<td>23 ± 4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15–50</td>
<td>135 ± 37</td>
<td>2.1 ± 0.5</td>
<td>7.8 ± 0.7</td>
<td>18</td>
</tr>
</tbody>
</table>

\(\text{Ch}_{\text{in}}\), total-body MTX clearance; \(PA\), peritoneal permeability area product.

\(a\) A mathematically derived expression which is equivalent to the mean plasma i.p. concentration gradient achieved in each patient.

\(b\) Values are expressed as mean ± S.E. where applicable. Samples were collected weekly and analyzed for the entire 6-week treatment course.

\(d\) Patient 1 received only 5 weekly dialyses. Infection prevented the Week 6 treatment.

\(e\) The melanoma patient (Patient 5) is considered separately from the ovarian cancer patients (Patients 1 to 4).
suggested extensive peritoneal exposure in each patient in our series (7).

Little data are available concerning drug penetration into tumor masses in this setting (2). Thus, ovarian cancer patients with tumor masses less than 0.5 cm in diameter were selected for this study as small tumor masses should be more easily penetrated by drug.

Ovarian cancer patients who received a complete remission with Hexa-CAF had a median survival in excess of 30 months, but the 43% of patients who achieved a partial response had a median survival of 16 months. If high-volume i.p. chemotherapy could increase the percentage of patients who achieve a complete remission, overall survival for this disease might be improved.

MTX was selected for this trial for several reasons. It is reported to have activity as a single agent in both ovarian cancer (19) and melanoma (8). Precise drug assay procedures are available (15), allowing pharmacological studies to be performed. Finally, both preclinical studies (21) and pharmacokinetic data in patients undergoing peritoneal dialysis (6, 10) suggested that large i.p. plasma concentration gradients could be maintained using this agent.

The large difference between the peritoneal and total body clearance of drug (Table 2) was responsible for the concentration difference observed in our study. The total body clearance was not dose dependent (Chart 2). The small number of patients involved in this study, however, precluded meaningful correlation between toxicity and pharmacological parameters.

This study represents the first measurement of peritoneal MTX clearance and the ratio of peritoneal to total body clearance. In addition, while the present study was devoted to an examination of i.p. MTX as a therapeutic approach, the pharmacokinetic values obtained provide a rational basis to model "third space" effects on MTX clearance after systemic therapy with this drug by large peritoneal pleural effusions.

Failure to achieve a clear-cut therapeutic effect in this study may reflect (a) the small number of patients available to us with "minimal residual disease," (b) the fact that all the ovarian cancer patients had previously experienced tumor growth while receiving a regimen containing i.v. administered MTX, or (c) that MTX may in fact have less activity in ovarian cancer than reported previously.

It is interesting to compare the results of this trial with our recently published study of 5-FUra used in a Phase I trial of parallel design (18). That trial also confirmed the pharmacokinetics predicted by the analysis of Dedrick et al. (6); the behavior of 5-FUra could, by and large, be predicted knowing its molecular weight and systemic clearance. In contrast with MTX, however, responses were seen during the Phase I 5-FUra trial.

This trial demonstrates that i.p. treatment with MTX is technically feasible, produces manageable toxicity, may be performed with relative safety, and is adequately tolerated by patients. The therapeutic effectiveness of this regimen remains to be defined. Future prospects include utilizing other chemotherapeutic agents using this technique and the use of i.p. chemotherapy in combination with other treatment modalities.

REFERENCES

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