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High Volume Intraperitoneal Chemotherapy ("Belly Bath") for Ovarian Cancer

Pharmacologic Basis and Early Results

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Summary. *The currently accepted therapies for ovarian cancer have produced only limited numbers of extended complete remissions in advanced-stage disease. Studies of high-volume intraperitoneal chemotherapy have been initiated to define the toxicology, pharmacokinetics, and the therapeutic effectiveness of this treatment modality. This technique has been virtually ignored until recently, because little success has been achieved with it except in one study (Rutledge, 1966), in which large intraperitoneal fluid volumes were used. The general lack of success probably reflects inadequate attention to physiologic and pharmacologic principles of drug distribution and absorption in a space as large as the peritoneal cavity. Biomedical engineers, pharmacologists, and clinicians at the NCI have cooperated in the development of a rational chemotherapy for ovarian cancer. Following mathematical pharmacokinetic modeling and toxicologic studies in rat, a Phase I clinical trial of intraperitoneal methotrexate administered in large volumes of dialysis fluid was initiated. Results in three patients confirm the practicality of this approach, and further investigation is warranted.*

Introduction

In recent years, only limited progress has been achieved in the treatment of ovarian cancer, the most common fatal gynecologic malignancy (Anderson and Young, 1977) and the fourth leading cause of cancer death in women (Silberberg and Holleb, 1971). Ovarian cancer characteristically spreads by local extension through the peritoneal cavity. The most common causes of death in these patients involve intra-abdominal complications of this tumor spread (Clark et al., 1974).

Even though 70% of initially diagnosed ovarian cancer patients present with advanced disease, many bulky tumor masses can be surgically removed (Young and Anderson, 1977). Additionally, recent advances in radiation therapy and single or multi-agent chemotherapy have effected marked reductions of bulky tumor (Young et al., 1976). Paradoxically, the remaining residual tumor often enlarges despite further therapy, and prolonged remissions after therapy of FIGO Stage III or IV ovarian cancer occur in less than 20% of patients. While radiotherapists have long sought to control abdominal disease with extensive radiotherapy to the whole abdomen, using various techniques (Fuks, 1975), progress has been hampered by uneven dose distribution and differential radiosensitivity of vital organs such as the kidney to doses of X-irradiation that are less than tumoricidal for ovarian cancer cells.

In patients with ovarian cancer, tumor usually spreads throughout the peritoneum to involve surfaces remote from the primary cancer. "Second-look" peritoneoscopy following surgery when all tumor was thought to be removed has demonstrated occult tumor nodules on the subdiaphragmatic surfaces (Bagley et al., 1973; Rosenoff et al., 1975), which accounts for significant understaging of these patient's disease. The relatively low 5-year survival rates (39–60%) (Young and Anderson, 1977) following resection of Stage I and II tumors probably also reflect occult tumor spread prior to surgery.

In view of the characteristic intra-abdominal spread and morbidity of this tumor, investigators at the National Cancer Institute (NIH) began a multidisciplinary program to investigate the feasibility of intraperitoneal (regional) chemotherapy for patients having this cancer. While prior studies had explored intraperitoneal drug

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administration, little attention was paid to volume of distribution and intraperitoneal pharmacokinetics. Thus, intraperitoneal therapy has been said to offer no advantage over intravenous therapy (Bagley et al., 1972; Green, 1959). This paper will describe the development of a new program for the administration of intraperitoneal chemotherapy and preclinical and clinical findings generated to date.

Peritoneal Anatomy and Function

The peritoneum has the largest surface area of any serous membrane in the body. In the female, this sac is interrupted only by small openings in the free ends of the uterine tubes. Only fluid under significant pressure will normally pass through these openings. This serous membrane contains all elements of loose connective tissue, namely collagenous and elastic fibers, fibroblasts, macrophages, mast cells, and fat cells, among blood and lymph vessels. That portion of peritoneum covering the mesentery is most richly supplied with blood vessels. This is the most probable site of maximal transperitoneal absorption of drug.

Passage of drugs across this membrane can occur via intercellular pores or transcellularly (Michel, 1969). Permeability of drugs through the intercellular pores is heavily governed by molecular size, whereas transcellular diffusion of drugs is dependent primarily on lipid solubility. It was therefore reasonable to postulate that both molecular size and lipid solubility might represent significant variables governing the absorption of a drug from the peritoneal cavity. A systematic investigation of the pharmacologic characteristics of chemotherapy delivered to the peritoneum was conducted in rats and followed by a Phase I human trial of this treatment.

Materials and Methods

Preclinical Studies

Pharmacokinetic modeling based on known physiologic and anatomic principles, including passive diffusion of drugs across the peritoneal membrane, was studied and has been recently outlined by Dedrick et al. (1978). Equations were derived that allowed prediction of the drug concentration in the peritoneal cavity and in the plasma (or various tissue sites) following intraperitoneal drug administration.

Animal model studies of the toxicology and pharmacology of fluid and drugs administered into the peritoneum were performed in female Spraque-Dawley rats. Procedures and methods of this study are detailed by Torres et al. (in press). Common "marker" molecules, such as inulin and urea, and drugs of known molecular weight, lipid solubility, and pK_a were used to define the physicochemical variables governing peritoneal transport and fluid diffusion characteristics.

Clinical Studies

The ultimate goal of these studies was to employ intraperitoneal chemotherapy in patients whose ovarian cancer volume had been reduced to microscopic amounts by chemotherapy or other means. MTX (Methotrexate) was selected for initial trials because of its relatively low peritoneal absorption, availability of an accurate assay procedure (Myers et al., 1975), its activity against ovarian cancer (Sullivan et al., 1967), and the potential for prevention of toxicity with a known rescue agent, folinic acid. Patients with histologically proven Stage III or IV ovarian adenocarcinoma were treated after informed consent was obtained. Prior to entering this trial, all patients had received at least 1 year of prior chemotherapy at the NCI as part of a random comparison of the effects of either L-phenylalanine mustard or a combination regimen known as Hexa-CAF (hexamethyl-melamine, cyclophosphamide, methotrexate, and 5-fluorouracil (Young et al., 1976). The extent of the patients residual tumor was re-evaluated by means of either peritoneoscopy or a restaging laparotomy. All patients included in this study had tumor restricted to the peritoneal surface. Additionally, all observed tumor masses were required to be less than 0.5 cm in diameter ("minimal residual disease"). Systemic chemotherapy was completed at least 3 weeks prior to the Phase I intraperitoneal MTX study ("belly bath").

The dialysis procedure was performed as follows:

1. A Tenckhoff catheter was implanted under local anesthesia (Tenckhoff, 1968). This flexible silastic catheter is widely used for peritoneal dialysis in patients with renal failure. A dacron cuff bonded to the silastic is placed subcutaneously to provide stabilization by virtue of tissue in-growth and to reduce bacterial invasion. Such catheters have been maintained for years. After 1 week to allow healing of the surgical site, chemotherapy was initiated.

2. Each patient was scheduled to receive a weekly 48-h dialysis for 4—6 weeks. During each dialysis, fluid was exchanged after a 6-h dwell time. After initial instillation of 2,000 ml of dialysis fluid, subsequent exchange volumes were adjusted for patient comfort, utilizing a maximum tolerated volume for all remaining exchanges.

3. The initial MTX concentration in the dialysis fluid (1.5% Impersol, Abbot Laboratories, Chicago, Ill.) was 1×10^{-5} M. The dose over ensuing weeks was also increased 5—7-fold unless systemic toxicity or local peritoneal irritation became prohibitive.

4. Intravenous folinic acid was administered from 8 h prior to the completion of each weekly dialysis to prevent potential systemic toxicity.

5. Following completion of 6 weekly dialysis, the intraperitoneal space was lavaged for cytologic evaluation and the catheter was removed.

Results

Toxicologic and Pharmacologic Studies

Experimental data (Torres et al., in press) confirmed the expectation that molecular weight and lipid solubility of drugs were important variables determining transperitoneal absorption.

When a series of commonly used cancer chemotherapeutic agents was studied in this model, peritoneal clearance (vide infra) was related to molecular weight (Table 1). In the rat model, studies of neutral compounds demonstrated that increasing transperitoneal absorption occurred with decreasing molecular weight.

Table 1. Absorption of intraperitoneally administered antineoplastic agents in the rat[a]

Compound	Mean % absorption	Mol wt	K (heptane)[d]
Asparaginase	9.0	133,000	0.19
Adriamycin	10.9	544	–
Bleomycin	12.7	1,400	0.002
Methotrexate	15.0	472	0.001
Actinomycin D	21.0	1,255	0.23
cis-Diaminedichloro-platinum (II)[b]	24.6	300	< 0.001
Phenylalanine mustard	25.0	323	0.10
Dichloromethotrexate[c]	25.6	540	0.002
5-Fluorouracil	28.4	130	0.09
Cytosine arabinoside	29.5	243	0.005
Cytembena	37.0	307	0.01
Cyclophosphamide	37.0	261	0.20
Chlorambucil	69.2	304	0.01
ThioTEPA	74.4	188	0.21
Hexamethylmelamine	91.7	210	11.20

[a] Methods were as described previously (Torres et al., 1978), where Sprague-Dawley rats were injected with 50 ml of normal saline i.p. in which the antineoplastic agents (combination of radioactive and non-radioactive forms) unless otherwise noted were administered in doses which in most cases were equivalent to their respective acute i.p. LD_{50}s. Values for absorption represent the mean of the percentage of the compound which was absorbed 1 h after i.p. administration to 5 animals/drug

[b] Platinum was assayed by atomic absorption spectroscopy (Litterst et al., 1976)

[c] Dichloromethotrexate was analyzed by competitive binding (Myers, 1975)

[d] Values were determined according to the method of Hogben et al. (1959)

Compounds with a heptane-water partition coefficient indicative of high lipid solubility showed increased absorption relative to less lipid-soluble molecules (Table 1). Additionally, it was noted that the rat peritoneum is capable of buffering 50 ml instilled solutions of pH 3–11 to physiologic pH. A molecule whose pK_a was indicative of significant ionization at physiologic pH was less rapidly absorbed than lipid-soluble molecules of comparable molecular weight. Data from patients with renal failure were available concerning the transperitoneal absorption of various physiologic and marker molecules such as urea, inulin, uric acid, and creatinine (Babb et al., 1973; Popovich et al., 1977). In each case, data from the rat model correlated well with peritoneal absorption in humans (if allowance was made for differences in volume and peritoneal surface area).

Phase I Trial: Procedures and Preliminary Results

A Phase I trial of intraperitoneal chemotherapy has recently been initiated at the NCI, and three patients with ovarian adenocarcinoma have received this therapy. Pharmacokinetic evaluation of intraperitoneal MTX in these patients has verified the predictions of the pharmacokinetic model (Fig. 1), with a 1–1.5 log MTX concentration ratio (10–30-fold concentration difference) between dialysate and plasma being established in each

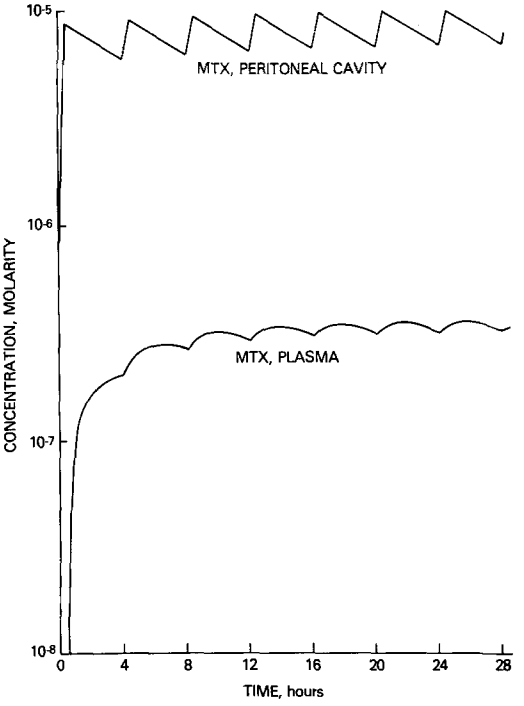

Fig. 1. Simulation of MTX concentrations in peritoneal fluid and plasma administered by repeated peritoneal lavage to a 70-kg human

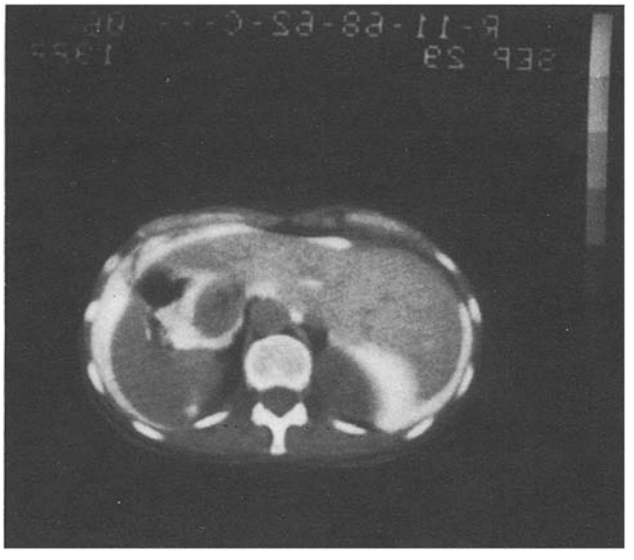

Fig. 2. Intraperitoneally computed tomogram following installation of iodinated contrast media (white)

Table 2. Toxicity of intraperitoneal methotrexate

Type	No. patients affected
Peritonitis, bacterial	1/3
Peritonitis, aseptic	3/3
Myelosuppression	
Platelets < 100,000/cm^2	1/3
WBC < 2,500/cm^2	2/3
Diarrhea	2/3
SGPT elevation	1/3

case. Equilibrium plasma MTX concentration was attained within the first 12 h of the dialysis procedure. Intraperitoneal MTX concentration remained above 7.5×10^{-6} M in two of the three patients studies. Instillation of a dilute Hypaque (Winthrop Laboratories, New York, N.Y.) solution followed by computed tomography of the abdomen has verified extensive distribution of fluid throughout the peritoneal space (Fig. 2).

The toxicity encountered to date is listed in Table 2. All patients have experienced aseptic peritonitis of varying degrees, but pain was disabling in only one patient and was self-limited following each weekly dialysis. Data from one patient suggest that orally administered indomethacin may effectively relieve this pain. The first patient treated developed culture-proven ps. Aerogenosa peritonitis, which was eradicated effectively with i.v. gentamycin. No further infectious episodes have been encountered. Diarrhea has been mild and self-limited, with no rectal blood loss noted. The one patient experiencing severe myelosuppression had previously required extensive dose reductions of intravenous chemotherapy on the basis of poor hematopoietic reserve. This patient also developed transient SGPT elevations (less than twice normal) during intraperitoneal therapy, a complication well documented with intravenous MTX therapy (Jaffe and Traggis, 1975). No other toxic side effects have been noted, and specifically no findings suggestive of bowel obstruction have been documented. One patient experienced tumor progression during this course of therapy.

Discussion

Mathematical models have been developed to predict transperitoneal absorption of anti-tumor agents in man (Dedrick et al., 1978). Absorption of a drug from the peritoneal cavity into other body compartments can be expressed as a peritoneal clearance (C_{perit}). This expression is analogous to renal clearance (C_{renal}). C_{perit} is a function of the product of the peritoneal membrane permeability multiplied by the peritoneal surface area and is expressed in ml/min. Once a drug is absorbed from the peritoneum, it is eliminated from the body by the usual routes (such as renal excretion, metabolism, biliary excretion, etc.). The sum of these latter processes may be termed the total body clearance of drug (C_{body}). In the theoretical design of intraperitoneal chemotherapy, a primary goal is to obtain a tumoricidal drug concentration in the peritoneal cavity while minimizing systemic (extraperitoneal) toxicity. Stated in another fashion, the ideal drug for intraperitoneal use should have a low C_{perit} (i.e., slow transperitoneal drug absorption) but a high C_{body} (i.e., rapid elimination from plasma and other body compartments by excretion or through metabolic degradation when absorbed). Figure 3 illustrates a scheme by which these processes can be visualized.

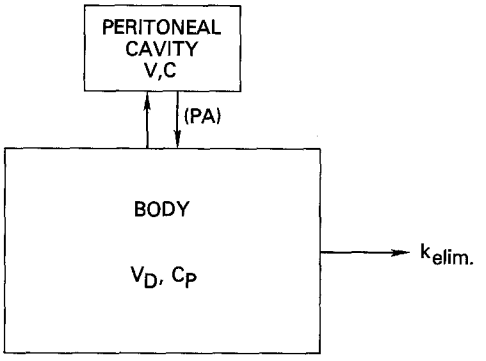

Fig. 3. Schema of the two-compartment open model for peritoneal pharmacokinetics

Studies in the peritoneal dialysis literature would predict a C_{perit} of 8 ml/min for a molecule the size of MTX. A detailed pharmacokinetic model had been developed to simulate the distribution and disposition of MTX in several mammalian species, including man. This model includes a renal clearance of 190 ml/min and was adapted to this work by incorporation of a peritoneal compartment to predict the pharmacologic behavior of MTX when administered into the peritoneal cavity (Dedrick et al., 1975). Figure 1 shows the predicted plasma and intraperitoneal methotrexate concentration if a 4.5-l solution containing 10^{-5} M MTX is infused into the peritoneal cavity and is exchanged with a 4-l volume of fresh solution every 4 h (500 ml residual). The mathematical model predicted a MTX concentration in the plasma 1.5 log lower than in the peritoneum when the plateau plasma concentration was reached. This concentration differential allowed a higher dose of MTX to be delivered to the intraperitoneal tumor with less systemic toxicity than that experienced following routine intravenous administration, provided local gastrointestinal toxicity was not prohibitive.

It has been reported that most of any drug administered into the peritoneal cavity is absorbed via the portal system (Lukas et al., 1971). With an antitumor agent

that undergoes rapid hepatic deactivation, even greater plasma-intraperitoneal concentration gradients should be obtainable. Such an agent might be 5-fluorouracil, whose C_{body} following intraperitoneal administration may be as high as 4,000 ml/min (Clarkson et al., 1964; Garrett et al., 1977). Few reports of C_{perit} for antitumor agents in man are available in the literature. One patient who developed renal failure during intravenous high-dose methotrexate administration was studied by Bleyer (Dedrick et al., 1978). During peritoneal dialysis, the C_{perit} of MTX was measured as 6 ml/min, a value in close agreement with that predicted from the dialysis literature. Hande et al. (1977) reported a similar patient whose C_{perit} of methotrexate was measured as 5 ml/min.

Clinical Studies in Man

Intraperitoneal Drug Distribution. A critical determinant for a successful intraperitoneal chemotherapy program is complete accessibility of drug to all tumor-bearing areas. To achieve wide distribution, one would predict that a drug should be administered in a large volume of fluid so that all surfaces might be adequately exposed. If drug were simply injected into pre-existing ascites fluid, variables such as speed of diffusion and dose distribution might preclude a successful therapeutic result. Rosenshein et al. (in press) studied the distribution of ^{99m}Tc albumin infused into the peritoneal space of female rhesus monkeys. When the radiopharmaceutical was administered in a 250-ml volume, rapid distribution throughout the peritoneal space was noted. If an infusion volume of 20 ml was used, however, much of the intraperitoneal space was unexposed to the injected fluid, even following abdominal massage or postural changes.

Because few data are available on drug penetration into tumor masses, it was determined that the initial trial should be performed in patients whose residual tumor masses were less than 0.5 cm in diameter (minimal residual disease), thereby increasing the probability that adequate penetration of the tumor by MTX would occur. Studies of drug penetration into tumor are presently in progress at the NCI.

Initial pharmacokinetic studies of intravenously administered methotrexate (MTX) in patients with ovarian cancer and malignant ascites (Chabner et al., in press) revealed that the MTX concentration in ascites fluid equilibrated slowly with plasma, and in patients with large volumes of ascites the ascites concentration exceeded that of plasma at late time points. This finding indicated that the peritoneal cavity might act as a separate compartment with limited permeability to MTX entry or exit. Inhibition of bone marrow DNA synthesis as measured by deoxyuridine incorporation occurred at drug levels of $2-3 \times 10^{-8}$ M. DNA synthesis in free-floating ascites tumor cells was generally not inhibited by MTX concentrations less than 10^{-6} M. Obviously, tumoricidal MTX doses given by the usual intravenous route would be accompanied by considerable systemic toxicity, which might take the form of myelosuppression, a problem that regional chemotherapy might avoid.

Should further study verify the practicality and effectiveness of this approach to the therapy of Stage III or IV minimal residual disease ovarian cancer, application of this treatment modality to other settings can be considered. Since ovarian cancer patients who attain a complete remission with current therapy have a significant relapse rate, intraperitoneal chemotherapy should arouse great interest in this adjuvant setting. Certain Stage I and Stage II patients whose prognosis after apparent complete surgical resection is poor by virtue of the tumor grade or other variables (Fisher and Young, 1977) may be potential experimental subjects as well. While this approach aimed at eradicating small tumor masses, trials in patients with more bulky disease could be considered, since sequential use with intravenous chemotherapy might reduce bulky tumor.

Other chemotherapeutic agents, such as 5-fluorouracil, are now being administered by us using this approach. Since intraperitoneal drainage occurs through the portal system, we also suggest that intraperitoneal drug administration in high volume by dialysis might afford effective hepatic perfusion when combined with hepatic artery infusion to "bracket" the hepatic blood supply to tumor masses in the liver.

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