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Extremely prolonged continuous intraperitoneal infusion of cytosine arabinoside*

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Summary. Intraperitoneal administration of ara-C produces a peritoneal/plasma concentration ratio of 330 – 1,000: In principle, optimal tumor-cell kill should be obtained when high ara-C concentrations ar maintained in the environment of the tumor for very long periods of time. A phase 1 study was undertaken to determine the maximum tolerated dose of ara-C that could be given as a continuous i. p. infusion for 3 weeks. A total of 14 patients with refractory malignancies were given 28 courses in the outpatient setting. Ara-C infusions were given using a portable programmable pump (Pancreatec Provider Model 2000). No significant side effects were observed in patients receiving 30 mg/m^2 per day (five courses) or 40 mg/m^2 per day $\times$ 21 days (seven courses). However, at a dose of 60 mg/m^2 per day, although 10/16 courses were tolerated for at least 1 week, only 3/16 attempted courses could be continued for the full 3 weeks. The dose-limiting toxicity was chemical peritonitis, which occurred during 7/16 courses at this dose level and required termination of therapy in 4 courses. Myelosuppression was also observed at this dose. There was a large variation in the ara-C and ara-U peritoneal concentrations both within and between patients. The mean peritoneal ara-C concentration increased nonlinearly with ara-C dose whereas the mean ara-U concentration decreased. This study establishes the feasibility and safety of giving a cell-cycle-specific drug intraperitoneally over an extremely prolonged period. For subsequent studies a dose of 40 mg/m^2 per day for 21 days is recommended.

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Introduction

Pharmacokinetic modeling [4] predicts that, under conditions where clearance from the cavity is far lower than that from the systemic circulation, intracavitary administration of drug will result in large differences in drug concentration between the peritoneal cavity and the plasma. Ara-C is an attractive agent for intraperitoneal administration. It is metabolized principally by deamination in the liver [2] and, because compounds given i. p. are absorbed primarily through the portal circulation [11, 12], a significant first-pass effect for ara-C is expected. Using estimates of drug clearance available from the literature, Dedrick and his colleagues [4] predicted that when ara-C is given by repeated peritoneal dialysis, its i. p. concentration could be maintained at a level 3 orders of magnitude higher than that in the plasma. We confirmed this prediction and assessed the clinical efficacy and safety of 60 μM i. p. ara-C (30 mg/2 l) given by q 6 h peritoneal dialysis for a 5-day period every 4 weeks in a group of 10 patients with ovarian cancer who had failed systemic chemotherapy [10]. There was no chemical peritonitis and systemic toxicity was minimal. Two patients were rendered free of disease and are still alive without disease 6+ years after therapy was discontinued, suggesting that ara-C is indeed active against ovarian carcinoma when used in a pharmacologically rational way.

In experimental systems, the biologic effect and toxicity of ara-C are markedly dependent on the schedule of drug administration. Under continuous-exposure conditions, even very low concentrations (0.004–0.018 μM) were sufficient to produce 50% kill of human ovarian carcinoma cell lines, and the dose-response curve was steep such that small increments in drug concentration resulted in substantially greater tumor-cell kill [8]. In a study of in vitro activity against clonogenic ovarian carcinoma cells obtained directly from patients, Von Hoff et al. [15] found that among eight drugs tested, only melphalan and cisplatin produced a steeper dose-response curve. Because of the long doubling times of most solid tumors, prolonged exposure to ara-C, which is a cell-cycle phase-specific agent, should be superior to brief treatment periods. We estimated that we could continuously maintain cytotoxic concentrations of ara-C in the peritoneal cavity under conditions where the plasma concentration of the drug would be too low to cause any significant degree of myelosuppression. The purpose of this study was to test this

Table 1. Patient characteristics

Patients (n)	14
Median age	51 (range 33–66)
Type of tumor:	
Ovarian cancer	13
Colon cancer	1
Prior therapy:	
Chemotherapy, i.v.	12
Chemotherapy, i.p.	12
≥3 regimens	6
Radiotherapy	2
Extent of disease:	
Bulky	7
Minimal	7

Table 2. Toxicities as a function of dose

	Number of courses during which toxicity occurred:		
Dose level	30 mg/m^2	40 mg/m^2	60 mg/m^2
Courses started (n)	5	7	16
Fever	2 (2)[a]	3	13
Abdominal pain	4	3	12 (2)
Nausea, vomiting	1	3	9 (1)
Bacterial peritonitis	0	0	0
Chemical peritonitis	0	2	7 (4)
Hepatotoxicity	0	2	2
Platelets <50,000/mm^3	0	2 (1)	5 (2)
Granulocytes <500/mm^3	0	0	2
Extravasation	0	0	2 (2)

[a] Numbers in parentheses indicate number of cycles during which infusion was stopped due to this toxicity

hypothesis and to determine the maximum tolerated dose of ara-C that could be given by continuous i.p. infusion for 21 days.

Patients and methods

Patients were eligible for this study if they had a histologically confirmed malignancy principally confined to the peritoneal cavity that was refractory to conventional modes of therapy or for which no effective chemotherapy existed. All patients had a performance status of ≤2 (ECOG criteria) and a life expectancy of >2 months. All patients had recovered from the effects of prior therapy and had bilirubin and serum glutamic-oxalic transferase values of <3 times the upper limit of normal. Patients were required to have a white blood count (WBC) of ≥3,000/mm^3 and a platelet count of ≥100,000/mm^3. Written informed consent was obtained from all patients prior to study entry, according to standard guidelines. A complete blood count, determination of serum electrolytes, and hepatic and renal function tests were carried out every week.

All patients had a totally implanted peritoneal access system surgically placed prior to beginning chemotherapy. This consisted of a Porth-a-Cath connected to a Tenckhoff catheter (Pharmacia Deltec, St. Paul, Minn) [14]. A portable, programmable external pump, the Pancreatec Provider IV 2000 (Pancreatec Inc., San Diego) [5], was used to control the infusion rate. This pump is capable of delivering fluid volumes as large as 2 l/24 h. The distribution of i.p. delivered fluid was not routinely assessed, since it has been demonstrated that approximately 70% of patients have adequate fluid distribution throughout the peritoneal cavity [6]. All patients were treated in the outpatient setting. Patients were provided with 1-l bags containing the requisite dose of ara-C and were given instruction on how to change to a fresh bag every 24 h. Patients returned to the clinic twice weekly, at which point the needle was changed; as an added precaution against infection, an iodine-containing cuff was routinely placed on the tubing.

The starting dose of ara-C was 30 mg/m^2 per day in 1.0 l 0.9% NaCl, given as a continuous i.p. infusion for 3 weeks. This was followed by a 3-week rest. Patients received a total of three courses, and a minimum of three patients were treated at each dose level. Dose escalations were carried out both within and between patients until dose-limiting toxicity was reached.

Peritoneal fluid samples were obtained twice weekly for measurement of ara-C and ara-U concentration by high-pressure liquid chromatography using the technique reported by Breithaupt and Schick [1]. Samples were drawn into tubes containing 100 μg tetrahydrouridine/5 ml tube to prevent deamination during sample preparation. Samples were ultrafiltered with a YMT Centrifree filter (Amicon, Danvers, Mass), and the ultrafiltrate was injected into a C18 reverse-phase column and eluted isocratically using 5 m*M* potassium phosphate buffer (pH 7.0) at a flow rate of 2 ml/min. Samples were obtained for measurement of drug levels during 3 courses in 3 patients receiving 30 mg/m^2 per day, during 4 courses in 3 patients receiving 40 mg/m^2 per day, and during 12 courses in 7 patients receiving 60 mg/m^2 per day. In all cases, samples were obtained after steady state had been attained following at least 2 days of constant i.p. infusion. From a total of 19 courses, multiple samples were obtained during 14 and single steady-state samples during 5. Plasma ara-C and ara-U concentrations were not measured in this study.

Results

A total of 14 patients were entered on study and received a total of 28 courses of ara-C. All courses were evaluable for toxicity. The patient characteristics are presented in Table 1. The median age was 51 years, all but one patient had ovarian cancer, and all but one had received extensive prior treatment with both i.v. and i.p. cisplatin-based therapy. Six patients had been treated with three or more prior regimens, and two patients had received prior radiation therapy. Half of the patients had bulky disease, defined as tumor masses measuring >2 cm at the time of study entry.

A total of 28 courses of chemotherapy were started, and 9 courses were completed for the planned period of 3 weeks. However, during 19 courses the infusion had to be stopped before the completion of 3 weeks, and during 9 of these it had to be stopped within the 1st week. In all, 14 courses were stopped due to the development of a specific toxicity (Table 2). The incidence of discontinuation due to

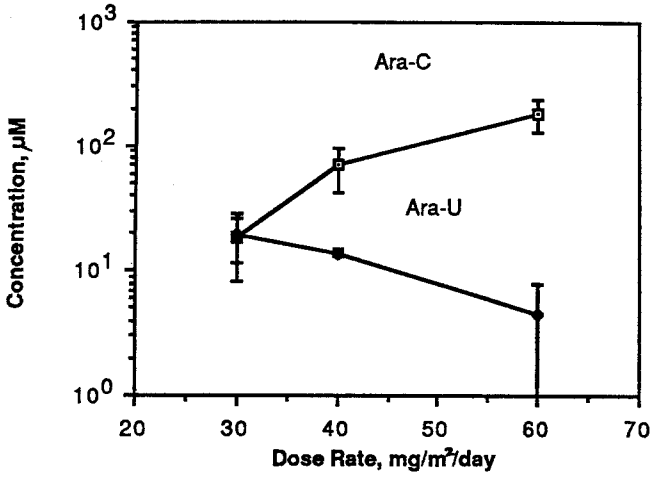

Fig. 1. Steady-state peritoneal concentration of ara-C and ara-U as a function of i. p. ara-C infusion rate. *Vertical bars* represent the SEM

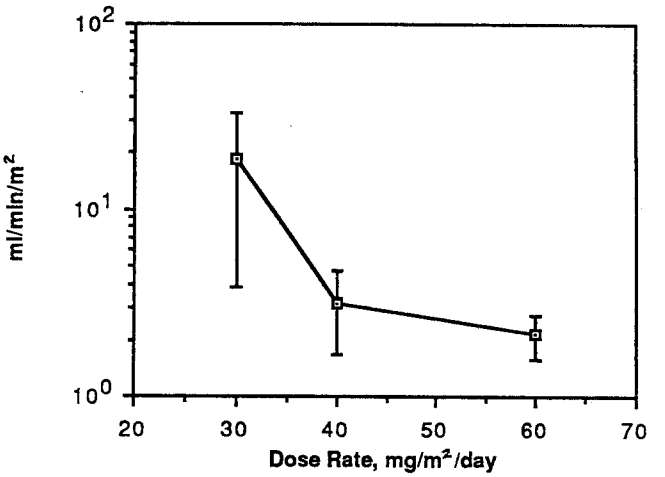

Fig. 2. Peritoneal clearance of ara-C as a function of ara-C i. p. infusion rate. *Vertical bars* represent the SEM

drug-related toxicity was dose-dependent. At the 30 mg/m^2 dose level, 2/5 courses were discontinued prematurely; at the 40 mg/m^2 dose level, 1/7 courses were aborted; and at the 60 mg/m^2 level, 11/16 had to be stopped early. Other reasons for discontinuing therapy included small-bowel obstruction due to tumor growth during two courses, one Hickman catheter infection, tape-induced contact dermatitis around the Port-A-Cath, and gastrointestinal bleeding associated with metastases in the colon wall during three other courses.

The first two dose levels were well tolerated, with minimal toxicity. At a dose of 60 mg/m^2 per day, the frequency of side effects increased. A low-grade fever, mild abdominal discomfort, and mild nausea were the most frequent side effects (Table 2). One patient had a drug fever requiring the discontinuation of therapy during both of her courses. Another patient had moderate abdominal pain secondary to loculation of fluid and was the only patient in whom treatment was stopped because of this toxicity. Most patients had mild nausea and minimal vomiting, but one individual developed severe vomiting and pre-renal azotemia that required i. v. hydration. However, the dose-limiting toxicity of ara-C was chemical peritonitis, which appeared to be dose-dependent; it was observed during 7/16 courses at 60 mg/m^2 per day, and treatment had to be stopped because of this toxicity during 25% of the courses at this dose level.

Table 3. Hematologic toxicity

Dose (mg/m^2 per day)	Courses (*n*)	WBC: Grade[a]					Granulocytes: Grade					Platelets: Grade				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
30	5	3[b]	1	1	0	0	4	1	1	0	0	4	1	0	0	0
40	7	3	3	1	0	0	5	1	1	0	0	4	1	0	2	0
60	16	5	5	3	2	1	6	3	3	2	2	7	4	0	3	2

[a] Common toxicity criteria
[b] Number of courses during which the indicated grade of toxicity occurred

The hematologic toxicity as a function of dose is presented in Table 3. Grade 3 myelosuppression was not seen until the highest dose was reached except in two patients whose platelet count fell to $<50{,}000/mm^3$ at a dose of 40 mg/m^2 per day. One of these patients had chronic renal failure with a creatinine value in the 4–5 range and had been deescalated from a higher dose because of a similar toxicity. The second patient's treatment was discontinued after 5 days because of small-bowel obstruction secondary to a tumor, which required surgery. At the highest dose, five courses in four patients were associated with a platelet count of $<50{,}000/mm^3$. Periportal extravasation occurred on two occasions due to dislodgement of the Huber needle from the Port-A-Cath in a very obese patient. One patient with extensive peritoneal adhesions and fluid loculation had persistence of peritoneal fluid long after the infusion was stopped. The fourth patient developed grade 4 thrombocytopenia after 10 days and her chemotherapy was discontinued. Significant neutropenia developed only in one very obese patient who had extravasation of ara-C around the Port-A-Cath and in another patient with preexisting chronic renal failure.

Other toxicities were minimal. Three patients developed transient liver abnormalities (elevation of alkaline phosphatase levels to twice the upper limit of normal in three cases and elevated serum glutamic-oxalic transferase to twice the upper limit of normal in one patient). In all cases the abnormalities improved while the infusion was continued. There was no instance of bacterial peritonitis in any patient on this study.

There was a great deal of variation in the ara-C and ara-U steady-state peritoneal concentrations both within and between patients. The mean coefficient of variation for ara-C within patients when samples were obtained every 24 h was 85%, whereas it was 37% for ara-U. Figure 1 shows that the mean steady-state ara-C concentration increased nonlinearly with the ara-C infusion rate, whereas the mean ara-U concentration decreased nonlinearly as the ara-C dose rate was increased. Because of the large within- and between-patient variance in ara-C concentrations, the increase in mean steady-state ara-C concentration did not reach statistical significance. However, the fall in mean ara-U concentration was statistically significant at

both the 40 and 60 mg/m^2 per day dose when compared with the value at 30 mg/m^2.

The peritoneal clearance of ara-C at steady state was calculated as the quotient of the infusion rate and the mean peritoneal ara-C concentration. The mean peritoneal ara-C clearance fell from a value of 18.3 to 2.2 ml/m^2 per minute as the ara-C dose rate was increased from 30 to 60 mg/m^2 per day (Fig. 2). This change was statistically significant ($P < 0.05$, t-test).

Patients were not required to have measurable disease to enter this trial. However, 5 of the 14 patients did have measurable disease and were evaluable for response: 2 had stable disease and 3 had disease progression.

Discussion

This study was undertaken to test the hypothesis that because of the extraordinarily high peritoneal-to-plasma concentration ratio attainable with ara-C, it would be possible to maintain cytotoxic concentrations of ara-C in the peritoneal cavity for very long periods of time with little or no systemic toxicity. The results indicate that the hypothesis was correct. Even at the highest dose rate of 60 mg/m^2 per day, the incidence of grade 3 or greater myelotoxicity was only 25% (4 of 16 courses, with 2 courses associated with subcutaneous extravasation). However, even at the lowest dose rate of 30 mg/m^2 per day, the mean ara-C peritoneal concentration of 20 μM was high enough to be cytotoxic to almost all types of dividing malignant cells in vitro with a 7-day exposure, much less a 21-day exposure. The peritoneal ara-C concentration produced by 30 mg/m^2 per day was >11,700 times higher than that required to kill 67% of the cells of the most ara-C-resistant human ovarian carcinoma cell line we have studied in culture [8]. At a dose rate of 60 mg/m^2 per day, the peritoneal concentration was >88,000 times higher.

Substantial evidence is now available to indicate that when maintained at high concentrations in the environment of the tumor for long periods, ara-C is a very active drug against human ovarian carcinoma. First, the human ovarian cell lines that have been studied are quite sensitive to ara-C, with D_o values of 0.017 and 0.0038 μM in clonogenic assays [8]. Second, when fresh tumor samples from drug-resistant patients were tested in vitro, 5/9 tumors demonstrated a cell kill of >50% at an initial ara-C concentration of 4.0 μM (note that ara-C is inactivated in such cultures, with a half-life of 10 h such that these results do not reflect the effect of a truly long-term exposure) [10]. Finally, from our previous trial of i.p. ara-C given by q 6 h peritoneal dialysis [10], two of ten far-advanced, drug-resistant patients are alive and free of disease at 6+ years after treatment. One of the uncertainties regarding this approach is the question of how long an infusion is really necessary to obtain the maximum benefit from ara-C. This clearly depends on the cytokinetics of ovarian carcinoma, and, because of the difficulty in obtaining serial cytokinetic studies in such patients, will be most efficiently addressed through clinical trials using infusions of differing duration.

This study also established that it is technically feasible and safe to carry out a 21-day, large-volume, constant i.p. infusion on an outpatient basis with the patient being responsible for changing to a new 1-l bag of premixed drug every 24 h. Such long-term instillations were not particularly popular with patients, who rapidly grew tired of constantly carrying the pump and 1-l bag with them, but the incidence of technical complications involving the delivery system was very low. There were no episodes of bacterial peritonitis, and the only mechanical problem involved subcutaneous extravasation of the ara-C when the Huber needle became dislodged from the Port-a-Cath in a very obese patient. Subcutaneous administration of ara-C is generally well tolerated, and on neither occasion did this extravasation cause local tissue inflammation or necrosis.

The dose-limiting toxicity of long-duration, i.p. ara-C was chemical peritonitis, which occurred during 44% of the courses at the 60 mg/m^2 per day dose level. The etiology of this chemical peritonitis is not well understood, but a similar pattern of peritoneal toxicity is produced by 5-fluorouracil and methotrexate when they are maintained in the cavity for long periods of time [7, 9]. When chemical peritonitis did occur, it was generally mild, requiring only nonnarcotic analgesics for control of pain and resolving over a period of 2–4 days. Complaints of abdominal pain in the absence of signs of peritoneal inflammation were common but were severe enough to require discontinuation of the infusion during only two courses in a patient with significant adhesions. The only other toxicities were idiosyncractic, consisting of drug-induced fever in one case and transient elevation of liver enzymes in two patients.

The peritoneal clearance of ara-C at 30 mg/m^2 per day, calculated as the quotient of the rate of infusion and the mean steady-state peritoneal concentration, was 19 ml/min per square meter. This is a little higher than would be predicted based solely on the molecular weight of ara-C [13]. At this lowest dose, the concentration of ara-U in the peritoneal cavity was equal to that of ara-C. As the ara-C dose rate was increased, the mean steady-state peritoneal ara-C concentration increased out of proportion to the dose rate and the mean steady-state ara-U concentration decreased. Reflecting the increase in ara-C concentration, the calculated ara-C peritoneal clearance decreased. One interpretation of these results is that deamination of ara-C to ara-U locally within the peritoneal cavity, which contributes to the ara-C clearance, was inhibited at the higher dose rate. At high concentrations, ara-U has been reported to inhibit deamination of ara-C, altering its pharmacokinetics [3]. However, one might still have expected the ara-U concentration to increase rather than decrease with dose rate.

Another possibility is that most of the ara-U found in the peritoneal cavity resulted from inward diffusion of ara-U from the blood generated by deamination of the ara-C in the liver following absorption from the cavity, and that either less ara-C was absorbed or less was deaminated at the high ara-C infusion rate. Our previous observation [10] that ara-U concentrations are very close to the same in the peritoneal cavity and plasma following i.p. ara-C instillation argue for the latter interpretation. In an earlier study, we did not find any evidence of nonlinear kinetics (saturation of clearance) up to a peritoneal ara-C concentration of 1,000 μM when kinetics were determined immediately after drug instillation. However, in the current study, steady-state peritoneal levels were measured after several days of exposure to high concentrations of ara-C and ara-U, which may have produced changes in the capacity of cytidine deaminase to metabolize ara-C. The

variance in ara-C levels both within and between patients in the current study was high enough that we feel that no firm conclusions can be drawn from the data available.

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