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Phase I and pharmacologic evaluation of intraperitoneal 5-fluoro-2′-deoxyuridine*

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Summary. Intraperitoneal (i.p.) 5-fluoro-2′-deoxyuridine (Floxuridine, FUdR, FdUrd) was evaluated in a phase I study at a starting level of 500 mg given on 1 day in 2 l 1.5% dialysate. Escalations within patients were allowed every other cycle. A total of 23 patients (age, 32–78 years) received 108 treatment courses. Local tolerance at all dose levels was excellent, with no cases of drug-related peritonitis being observed. Nausea and vomiting increased in severity in relation to dose and was universal at >3,000 mg × 3 days. One patient each developed grade 1 mucositis as well as diarrhea at a dose of 3,000 mg × 3 days and leukopenia and thrombocytopenia at 5,000 mg × 3 days. Peritoneal fluid (PF) and plasma (PL) FdUrd profiles were monitored by an HPLC method in 13 subjects, with 7 being studied serially at 2–4 increment doses for up to 6 h. Profiles that exhibited apparent linear pharmacokinetics gave PF drug levels 2–4 logs higher than the PL counterparts, with the latter essentially declining in parallel to the former, indicating that the disposition of FdUrd from the peritoneal compartment is rate-determining. The mean terminal half-life for PF FdUrd was found to be 115 min and mean peritoneal clearance was 25 ml/min. The vast differences in drug levels and AUC found between the PF and the PL profiles suggests a high systemic clearance of FdUrd, which was confirmed in two patients receiving 2 g FdUrd by short i.v. infusion. A disproportionate increase in the plasma FdUrd levels and the corresponding AUC values was found with increasing dose, suggesting a disproportionate increase in the systemic partitioning of FdUrd when doses were escalated within a patient. Substantial levels of peritoneal 5-fluorouracil (FUra) were also detected in most of the subjects. Thus, FdUrd was found to have several desirable properties for i.p. administration: (1) a 2- to 4-log pharmacologic advantage, (2) the absence of local toxicities, and (3) a favorable antitumor spectrum and some evidence of antitumor effects in this phase I and pharmacology study. A 3,000-mg dose given in 2 l 1.5% dialysate for 3 consecutive days exhibited antitumor activity and produced no systemic toxicity except nausea and vomiting, which was controlled by antiemetics. This dose schedule is therefore recommended for phase II trials directed against small-volume disease in the peritoneal cavity, such as may be found in some stages of ovarian and gastrointestinal cancers. In addition, it is suitable for further exploration as a part of regimens including systemic therapy or drugs that modulate the action of fluoropyrimidines.

Introduction

The i.p. administration of chemotherapeutic drugs has been increasingly evaluated for its possible clinical role in the treatment of ovarian cancer [17]. Presumably, the high local concentrations that are achieved are translated into better tumor control within the serosal surfaces of the peritoneal cavity in patients with small-volume disease. After a decade of i.p. clinical trials, certain guiding principles have evolved that help to identify the drugs that have the most desirable features for this route of administration. Among these principles are: (1) that the drug be effective against the target tumor in question, (2) that a substantial pharmacologic advantage be obtained as a result of slow drug egress from the peritoneal cavity coupled with an appreciable systemic clearance, and (3) that repeated administration be feasible without producing discomfort or complications. Ideally, the i.p. administration of drugs should be limited by systemic rather than by local toxicities. However, this is not an absolute requirement since one can supplement antitumor effects by adding systemic drug treatment. This strategy is less necessary in the presence of

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small-volume disease, a situation that we currently hold to be most advantageous for i.p. therapy.

Fluoropyrimidines fulfill many of the criteria desirable for i.p. administration; in fact, 5-fluorouracil (FUra) was the second drug (after methotrexate) to be clinically studied by the group at the National Cancer Institute that first evolved the pharmacokinetic model of i.p. treatment using high-volume, repeated drug dwells [11, 29]. Fluoropyrimidines are particularly interesting for i.p. therapy because of their activity against gastrointestinal carcinomas [21, 29], the recent interest in enhancing antitumor effects through biochemical modulation [16], and their generally efficient catabolic clearance by the liver and extrahepatic sites [9, 13]. On the other hand, problems encountered with FUra include mild to moderate local intolerance, particularly on repeated administration [30, 31] and erratic systemic dose-limiting toxicities as doses are increased beyond certain levels, a finding that was related to saturation kinetics in hepatic clearance [30]. Interest in the study of 5-fluoro-2′-deoxyuridine (FdUrd, FUdR, floxuridine) arose from the hope that the local intolerance of FUra would be obviated (if FUra's local toxicity could be related to insolubility in an acid pH) and that an even more advantageous pharmacokinetic profile could result. An additional rationale was the enhancement of cytotoxicity and differing opportunities for biochemical modulation using folate cofactors. In preclinical systems, in fact, FdUrd shows significantly more potent cytotoxic effects in both the presence and the absence of leucovorin [18, 19, 24] than does FUra. Therefore, we set out to study the i.p. tolerance and pharmacokinetics of FdUrd.

The study objective was to determine a safe i.p. dose of FdUrd on a daily $\times 3$ schedule repeated every 3 weeks and to characterize the pharmacokinetics of this agent following i.p. administration in selected patients. This schedule was selected as a compromise between the desirability (and feasibility) of repeated dosing to maintain cytotoxic drug levels and span the generation times of most neoplastic cells and its practicality in terms of patient acceptance.

Patients and methods

The present study was begun in November 1985 at NYU Medical Center, and 1 year later it was also opened for patient entry at the USC Cancer Center following the approval of the institutional review board and after all requirements for informed consent had been met. The study was closed for patient entry in November 1988. To be eligible, all subjects had to have been diagnosed as having cancer associated with diffuse intraperitoneal spread of tumor. Patients with gynecologic cancer were required to have failed higher priority protocols or prior treatment consisting of cisplatin-based systemic and/or i.p. chemotherapy.

Ampules of FdUrd (Roche Labs) were added to 2 l 1.5% dialysate (Impersol or Dienal) for i.p. administration. The initial dose was 500 mg for a single 4-h dwell; subsequently dose escalation was carried out by increasing the days of treatment to 3 and then raising the dose to the next level. Escalation within patients took place after two cycles if neither moderate nor severe toxicity (NCI Common Toxicity Criteria) was encountered. At least three patients beginning their treatment at doses of 1,000, 1,500, 2,000, 3,000, and 4,000 mg were entered to determine the maximal tolerated dose and dose-dependent pharmacokinetics of FdUrd. The dose levels were established using a scale of milligrams per 2 l rather than on a per-square-meter basis; it was deemed desirable to set the i.p. concentration of drug because systemic effects, which are usually calculated based on a given dose per square meter, were not expected except at the highest FdUrd doses. Initially, 4-h dwell times were prescribed. However, since the pharmacokinetic data indicated that <15% of the dose was being recovered at 4 h, six additional patients were studied at the final level selected for phase II study, and the protocol was amended such that the i.p. fluid would remain beyond 4 h unless the patients became symptomatic. If outflow was not possible and residual fluid was evident on the 2nd or 3rd day, the volume in which the drug was given was reduced to 1.5 l. Treatment was given for a minimum of six cycles unless disease progression supervened. The outpatient setting was suitable in most instances. If persistent i.p. abnormalities were observed and the clinical outcome appeared to be favorable, treatment could be continued beyond six cycles.

Catheters of the implantable type (Tenckhoff, Port-a-cath) were placed prior to the first treatment except in two patients with ascites in whom temporary "pigtail" catheters were inserted because of concomitant anticoagulant therapy and effusions distributed in two large compartments, respectively. Baseline computerized tomography using i.p. contrast as modified from Dunnick et al. [12] was performed in all but two cases. Serial observations consisted of queries regarding local tolerance during and after each treatment. Blood counts were obtained weekly; chemistry studies and determinations of plasma tumor markers were repeated with each cycle of therapy. Washings for cytology and determinations of i.p. tumor markers were also carried out in ascites (if present) or after 250 ml normal saline had been given i.p. prior to treatment (if returns were inadequate). Reassessment by laparotomy was not required.

Pharmacology studies. Peritoneal fluid and blood samples were obtained at 0, 5, 10, 15, and 30 min and at 1, 2, and 4 h via the i.p. catheter and a heparin-lock system placed in a peripheral vein, respectively. When 4-h dwells were omitted, 24-h samples were also obtained. Samples were collected in heparinized tubes and plasma was separated by centrifugation. The peritoneal fluid and plasma samples were kept frozen at –20° C until analysis.

FdUrd concentrations were analyzed in plasma by the HPLC method of Au et al. [2] and in peritoneal fluid by a modification that includes elimination of the extraction procedure for FdUrd in the peritoneal fluid, since no interference was seen. A C-18, 10-μm reversed-phase column (inside diameter, 4.6 mm; length, 250 mm; Alltech Associates, Deerfield, Ill.) was used with thymidine as the internal standard for the assay of FdUrd both in plasma and in peritoneal fluid. FUra concentrations in peritoneal fluid were measured by an HPLC method modified from that used for FdUrd. In this procedure, the mobile phase was 2.5 mM ammonium acetate (pH 3.8) run alone at a flow rate of 0.8 ml/s and cyclocytidine was used as the internal standard. Under this situation, cyclocytidine and FUra were eluted at retention times of 6 and 12 min, respectively. Peritoneal concentrations of the FdUrd metabolite 5,6-dihydro-5-fluorouracil (FUH_2) and plasma levels of FUra and FUH_2 were analyzed by gas chromatography/mass spectrometry (GC/MS) as described by Aubert et al. [3].

Plasma and peritoneal concentration-time data were analyzed by a compartmental approach using a standard nonlinear least-square statistical package [4] (PLOT4U, courtesy of Dr. M. Bolger, School of Pharmacy, University of Southern California). The peritoneal fluid and total body or systemic clearances, i.e., C_{PF} and C_T, respectively, were computed using the equation:

$$C_{PF} = \text{dose}/AUC_{PF} \text{ and } C_T = \text{dose}/AUC_{PL},$$

where AUC_{PF} represents the area under the concentration-time curve for peritoneal fluid (PF) extrapolated to infinity and AUC_{PL} represents the area under the concentration-time curve for plasma (PL), also extrapolated to infinity. This calculation must assume no dose removal for all patients and was kinetically justifiable. The FdUrd peritoneal to plasma concentration or AUC ratio was related to peritoneal clearance and total clearance, C_T, by the following equation [11, 22]:

$$C_{PF}/C_{PL} \text{ or } AUC_{PF}/AUC_{PL} = [R(C_{PF}) + C_T]/C_{PF},$$

where R is the partition ratio between the peritoneal fluid and the plasma that accounts for protein binding of FdUrd [11]. Since protein binding of FdUrd was found to be negligible, R was determined to be unity.

Results

Treatment tolerance

Table 1 shows the patients' characteristics and Table 2 lists the dose-escalation steps, indicating the expanded number at the level of 3,000 mg FdUrd ×3 days. Table 3 indicates specific toxicities observed in subjects receiving <3,000 mg ×3 days and in those receiving this dose or more. Nine patients received six or more cycles of therapy. Local tolerance was generally excellent, with repeated administration of i.p. FdUrd evoking no complaints. The most severe abdominal discomfort was experienced by two patients recovering from laparotomy; one required parenteral analgesics. In one other subject, catheter malfunction led to pain and discontinuation of treatment (see below).

The most prominent toxicity was nausea and vomiting, which occurred at all levels except the first. This toxicity became more prominent and universal at dose levels of ⩾3,000 mg. Typically at this dose, one or more episodes of vomiting were documented at 2–4 h after the completion of i.p. treatment; except at the last two dose levels, it appeared to be ameliorated by routine antiemetics (prochlorperazine or metoclopramide) and subsided quickly, resulting in similar, if not improved, tolerance on days 2 and 3 of treatment. At the 4,000- and 5,000-mg levels, nausea and vomiting were universal and more severe. In one case, the dose was escalated to 6,000 mg and then to 7,000 mg on two occasions, but this patient subsequently requested to be treated at the next lower dose level due to subjective intolerance.

Diarrhea was erratically observed and led to a two-step de-escalation in one case. Symptoms of mucositis of beyond grade 1 were not observed except in two patients who also experienced hematologic toxicities. Hematologic toxicity was absent except in one subject each at levels of 4,000 mg ×3 days and at 5,000 mg ×3 days. These patients incurred grade 3 leukopenia and grade 4 thrombocytopenia, respectively, and developed grade 3 complicating mucositis. No hematologic or mucosal toxicities of greater than grade 1 were observed in any of the 12 patients treated at 3,000 mg ×3 days. This dose was therefore selected for phase II study based partly on pharmacokinetic considerations (see Discussion).

Catheter-related problems independent of drug effects were identified in several patients. Lack of outflow was common (occurring after the second cycle in most cases) but did not interfere with drug administration. One patient with inflow problems was shown to have a hematoma at the distal end of the catheter; she experienced severe abdominal pain on the administration of chemotherapy, necessitating interruption of the treatment after 1.4 l had been given. She was removed from the study after this incident. Both patients who had "pigtail" catheters incurred complications: one developed a symptomatic small-bowel obstruction, and the other developed *Staphylococcus aureus* peritonitis and subsequently died of pulmonary edema that was possibly attributable to the lymphangitic spread of cancer.

Therapeutic effects

The course of treatment had to be interrupted during the first cycle in five patients. In one case, therapy was discontinued because of technical (catheter-related) problems; another subject died of sepsis prior to his second cycle; and three patients manifested increasing intestinal obstruction soon after receiving the first cycle. In retrospect, the latter subjects had shown obstructive symptoms at the outset and were poor candidates for catheter placement and i.p. therapy.

Table 1. Patients characteristics

Median Age (range	59 (32–78) years
Men/women	8/15
Primary sites:	
Ovary	9
Fallopian tube	1
Colon	4
Stomach	3
Appendix	2
Pancreas	1
Unknown	3
Prior therapy:	
i.v. chemotherapy only	5
i.v. + i.p. chemotherapy	9
i.v. + i.p. chemotherapy + radiation	1
None	6

Table 2. Patients treated and courses given/dose level

Dose (mg)	Patients (*n*)	Courses (*n*)
500 ×1 day	4	5
1,000 ×1 day	4	5
1,000 ×2/3 days	5/3	7/4
1,500 ×2/3 days	2/2	3/3
2,000 ×2/3 days	3/5	5/11
3,000 ×2/3 days	3/12[a]	4/28
4,000 ×2/3 days	1/11[b]	1/21
5,000 ×3 days	4[c]	4
6,000 ×3 days	1[c]	5
7,000 ×3 days	1[c]	2

[a] 8 began at 3,000 mg ×3 days
[b] 4 began at 4,000 mg ×3 days
[c] Doses of all patients were escalated from lower levels

Table 3. Toxicities of i.p. FdUrd

Toxicit/Dose	<3,000 mg	⩾3,000 mg
Nausea + vomiting	6/11	13/13
Abdominal pain	1/11	2/13
Diarrhea	1/11	2/13
Mucositis	–	2/13[a]
Thrombocytopenia	–	2/13[a]
Neutropenia	–	2/13[a]

[a] Toxicity of greater than grade 2 occurred in the same 2 patients

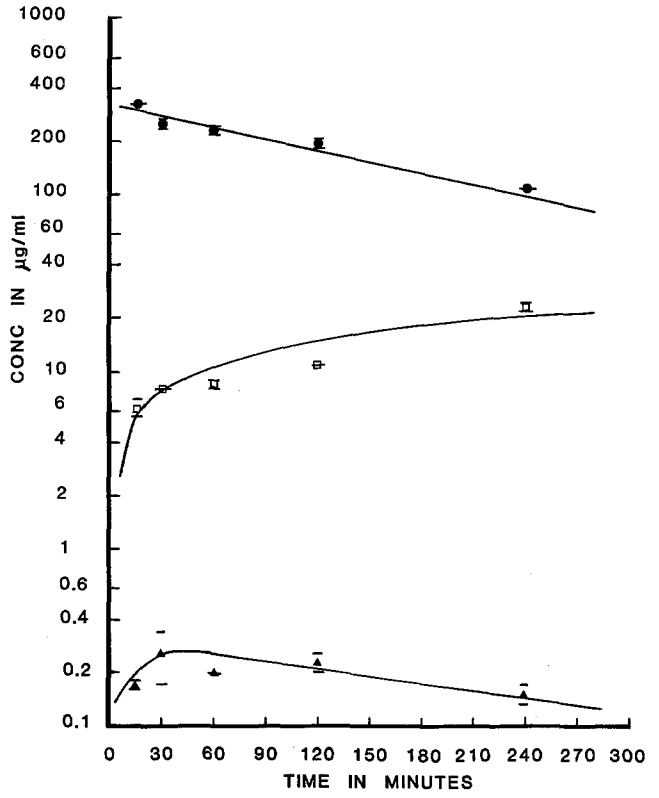

Fig. 1. Concentration-time profiles for FdUrd in peritoneal fluid (●) and plasma (▲) and for FUra in peritoneal fluid (□) obtained from patient LM, who was given 1,500 mg FdUrd i. p. Data points represent averages of two determinations; differences are shown as horizontal bars. Only the curve for peritoneal FdUrd derives from computerized fitting

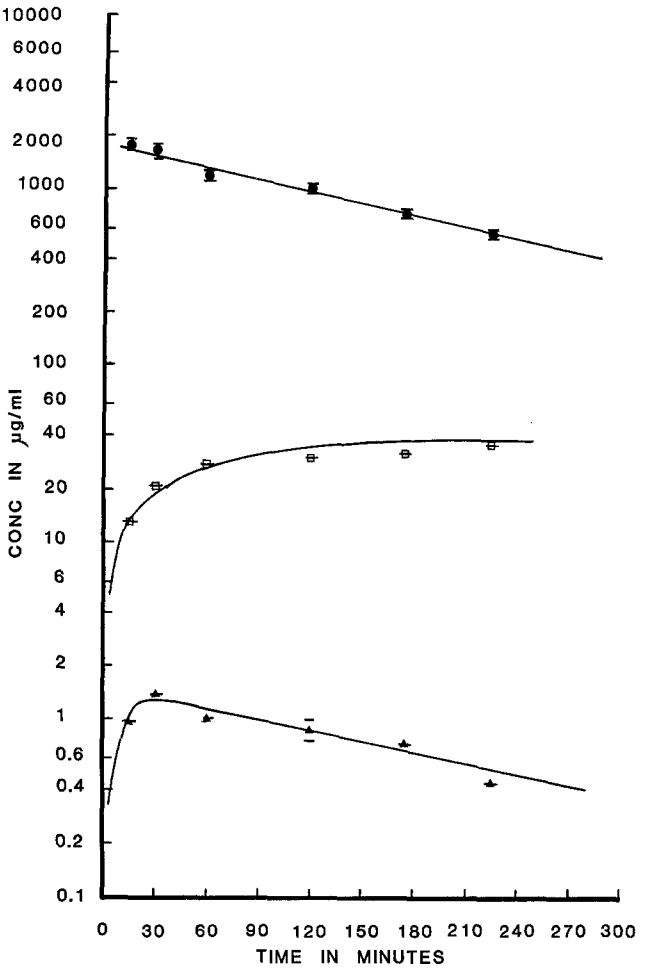

Fig. 2. Concentration-time profiles for FdUrd in peritoneal fluid (●) and plasma (▲) and for FUra in peritoneal fluid (□) obtained from patient WD3, who was given 5,000 mg FdUrd i. p. Data points represent averages of two determinations; differences are shown as horizontal bars. Only the curve for peritoneal FdUrd derives from computerized fitting

The other 18 patients remained on study for a median of 14 weeks (range, 4–36 weeks). Of these, 3 who entered toward the end of the study with stable clinical findings were continued on i.p. therapy on a new protocol consisting of 3,000 mg FdUrd ×3 days supplemented with escalating doses of leucovorin. Analysis of sites of failure for the other patients remaining on the study revealed that 6 exhibited systemic or extraperitoneal progression within 13.5 weeks (range, 6–26 weeks) and 9 displayed i.p. disease manifestations at a median of 12 weeks (range, 6–48 weeks).

Standard criteria of response were not applicable to this group of patients exhibiting small-volume disease in the peritoneal cavity. Of four patients (all with ovarian cancer) who were reevaluated surgically, three underwent laparoscopy and one, a laparotomy with simultaneous removal of the i.p. device. One of these subjects showed no evidence of disease at laparoscopy. Four patients (only one of whom had disease of ovarian origin) exhibited a reduction of $\geq 50\%$ in plasma tumor marker and/or conversion to negative i.p. cytology. Two others (both of whom had ovarian cancer) showed the disappearance of ascites. One subject displayed a reduction of >50% in a mass as determined by computerized tomography. Three patients who showed no sign of any increasing disease and were subsequently treated with i.p. FdUrd plus leucovorin were not included as objective responders, although subsequent laparoscopy revealed objective regression of disease in one case.

Pharmacokinetics

FdUrd concentrations were determined in peritoneal fluid and plasma from 13 patients, with at least 1 subject being studied on day 1 of each dose level. In all, 7 patients were serially studied at 2–4 increment doses, giving a total of 27 profiles. Of 27 peritoneal concentration profiles, 14 exhibited monoexponential decays and 7 showed apparent biexponential declines. Three representative profiles at different doses are illustrated in Fig. 1–3, and the estimated pertinent pharmacokinetic parameters are shown in Table 4. The mean pertinent pharmacokinetic parameters are summarized in Table 5. The remaining 6 peritoneal FdUrd profiles showed apparent saturation kinetics as evidenced by the convex profiles characteristic of Michaelis-Menten kinetics. A representative profile is shown in Fig. 4.

Profiles that exhibited apparent linear pharmacokinetics gave peritoneal drug levels 2–4 logs higher than the plasma counterparts, which essentially declined parallel to those of the peritoneal fluid (Fig. 1–3). This suggests that the clearance of FdUrd from the peritoneal compartment is

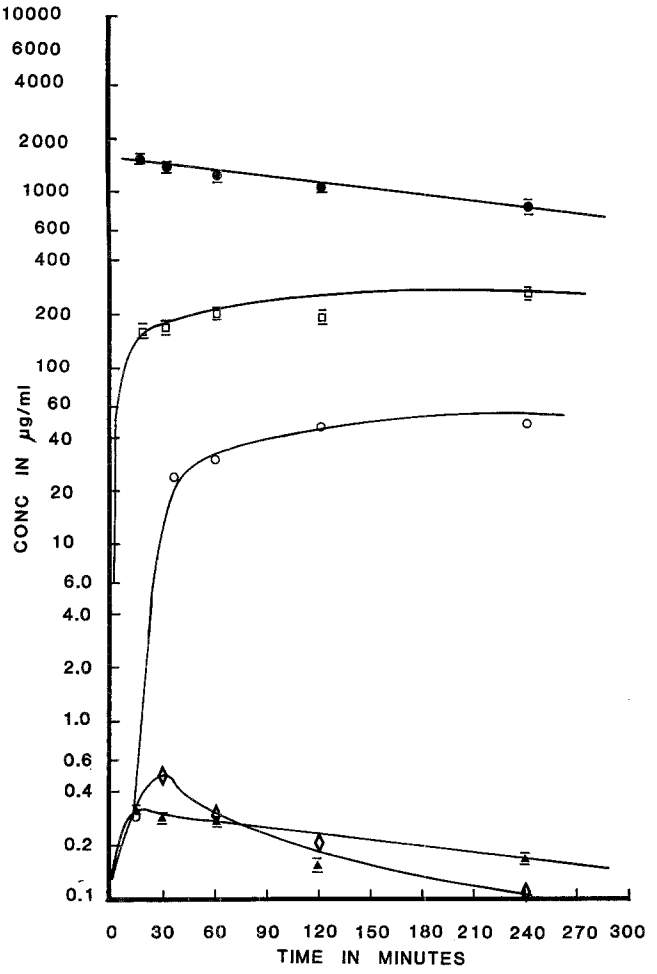

Fig. 3. Concentration-time profiles for FdUrd in peritoneal fluid (●) and plasma (▲), for FUra in peritoneal fluid (□) and plasma (○), and for FUH_2 in plasma (◇) obtained from patient IDe4, who was given 6,000 mg FdUrd i.p. Data points represent averages of two determinations; differences are shown as horizontal bars. Only the curve for peritoneal FdUrd derives from computerized fitting

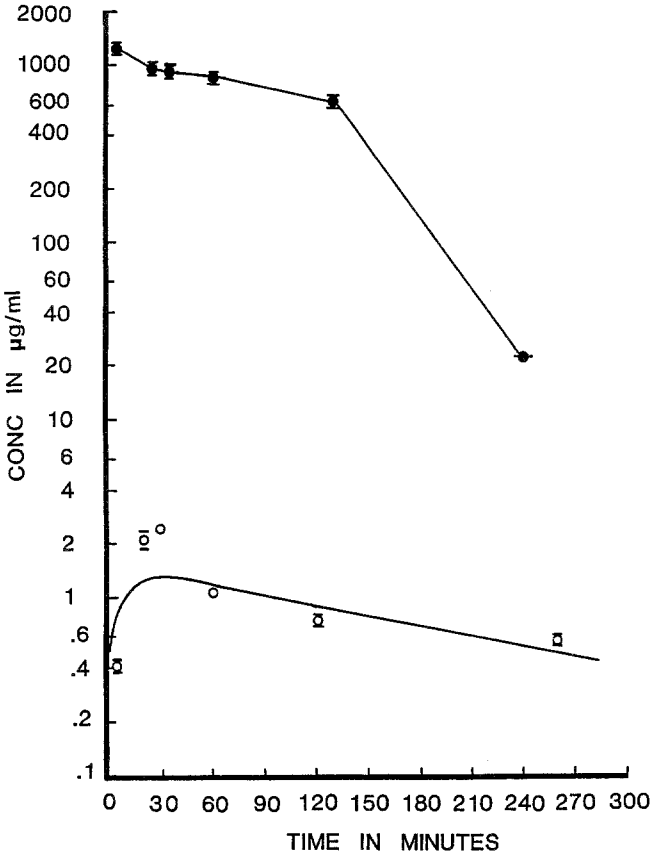

Fig. 4. Concentration-time profiles for FdUrd in peritoneal fluid (●) and plasma (○) obtained from patient VK3, who was given 5,000 mg FdUrd i.p., showing apparent saturation kinetics. Data points represent averages of two determinations; differences are shown as horizontal bars

rate-determining, assuming that the systemic clearance of FdUrd is rapid. That this assumption is correct is shown in Fig. 5, which is a plot of the data on patient HG, who received one dose of 2,000 mg FdUrd i.v. 6 h before undergoing i.p. therapy. In three sets of profiles, plasma FdUrd was not detectable, and two of the PF profiles of these patients exhibited rather high AUC values as compared with those of other patients receiving the same dose (data not shown). The terminal half-lives of i.p. FdUrd for profiles exhibiting linear pharmacokinetics ranged from 50.25 to 210 min (mean, 115.5 min). The peritoneal clearance values ranged from 6.8 to 78 ml/min (average, 25 ml/min). The AUC ratios between peritoneal fluid and plasma ranged from 449 to 8,712 (average, 2,773).

We attempted to measure FUra levels in PF using a modified HPLC method; this was achieved in most of the patients, many of whose values were determined in retrospect, since sufficient samples were available. The PF FUra levels in all patients were found to be quite high and either persisted or continued to rise even at 240 min after FdUrd administration. Thus, the decay half-life was not measurable during the experimental period. Table 5 shows the AUC values and the molar ratios of FUra ot the parent drug FdUrd. In general, the ratios were high but variable, indicating significant and variable conversion of FdUrd to FUra. Plasma FUra levels were measured in only one patient, since the quantity of plasma available for all other patients was insufficient after the completion of FdUrd determinations. The plasma FUra levels were also found to be high and sustained; the continuing rise in levels observed during the period of sampling made the assessment of the apparent decay half-life impossible.

Discussion

Clinical findings

We chose to study FdUrd for i.p. administration primarily to see advantages in tolerance over FUra and, possibly, more favorable pharmacokinetics. The results of this study lend support for both these premises. The tolerance of repeated administration of FdUrd was excellent in 18 of the 23 patients who went on to receive repeated cycles. Specifically, no local drug-related toxicity was observed. The most reproducible toxicity was transient nausea and vomiting, occurring universally in patients receiving $\geqslant$3,000 mg i.p. Other drug-related toxicities were mild

Table 4. Pharmacokinetic parameters of FdUrd in patients following i. p. administration

Parameter	Patients																									Mean (SD)
	JK1	JK2	JK3[a]	SM1[a]	SM2[a]	SM3	SM4	IDe1	IDe2	IDe3	IDe4	WD1	WD2	WD3	VK1	VK2	VK3[a]	LJa1	LJa2	JF1[a]	JF2	LJo[a]	RT	LMu	LM	HG	PH	
AUC_{PF}[c] FdUrd ($\mu g\ ml^{-1}\ min$)	50,860	50,050	107,200	891,400	138,800	239,400	162,900	69,510	108,840	249,600	376,300	155,400	168,800	382,500	91,220	191,800	150,100	89,820	199,900	11,870	66,762	443,300	38,460	108,576	74,650	97,230	100,300	–
AUC_{PL}[b] FdUrd ($\mu g\ ml^{-1}\ min$)	5.838	8.397	93.2	–[d]	19.65	72.5	128.9	26.6	ND	46.24	71.9	100	56.3	199.2	19.65	34.19	226.4	178	262.9	13.43	53.07	–[d]	70.29	46.14	116.4	43.6	21.35	–
AUC_{PF}[c] FUra ($\mu g\ ml^{-1}\ min$)	–[d]	1,110	177.4	–[d]	2,229	3.164	2,645	5,776	–[d]	6,034	48,710	3,808	4,619	6,706	–[d]	1,514	–[d]	10,710	–[d]	970	–[d]	–[d]	11,780	9,336	1,831	8,625	2,712	–
Beta[g] $\times 10^{-3}$ FdUrd (min^{-1})	13.79	7.4	(9.87)	–[e]	(8.22)	5.71	5.88	5.89	9.2	6.2	3.3	3.81	6.72	2.21	10.06	5.99	(4.68)	6.23	4.93	(7.41)	4.51	(2.21)	8.51	7.22	4.2	11.87	4.46	6.56 (2.76)
$t^1/_2$ PF, FdUrd (min)	50.25	93.65	(70.2)	–[e]	(84.3)	121.4	117.8	117.6	75.31	111	210	182	103.2	164.2	68.89	115.7	(148)	111.3	140.5	(93.5)	153.5	–[e]	81.4	96	164.9	58.38	155.3	115.5
R[f]	8,712	5,961	1,151	–[e]	7,030	3,301	1,263	2,613	–[e]	5,399	5,226	1,168	2,266	1,258	3,372	3,752	452	449	556	884	1,258	–[e]	547	2,353	641	2,230	4,698	2,773 (2,267)
CL_{PF}[g] (ml/min)	19.54	27.82	(18.65)	(2.24)	(21.61)	16.71	30.70	26.01	27.56	16.02	15.95	19.31	23.7	13.07	31.06	18.44	(33)	33.40	20.01	(42.14)	14.98	(6.77)	78	27.63	18.61	30.85	29.91	24.58 (13.51)
Dose (mg)	1,000	1,500	2,000	2,000	3,000	4,000	5,000	2,000	3,000	4,000	6,000	3,000	4,000	5,000	3,000	4,000	5,000	3,000	4,000	500	1,000	3,000	3,000	3,000	1,500	3,000	3,000	–

[a] Apparent nonlinear kinetics
[b] All AUC values were extrapolated to time infinity
[c] AUC values were estimated to 240 min
[d] Not measured
[e] Not measurable
[f] FdUrd area ratio to time infinity between peritoneal fluid and plasma
[g] Values in parentheses were estimated by assuming linear kinetics

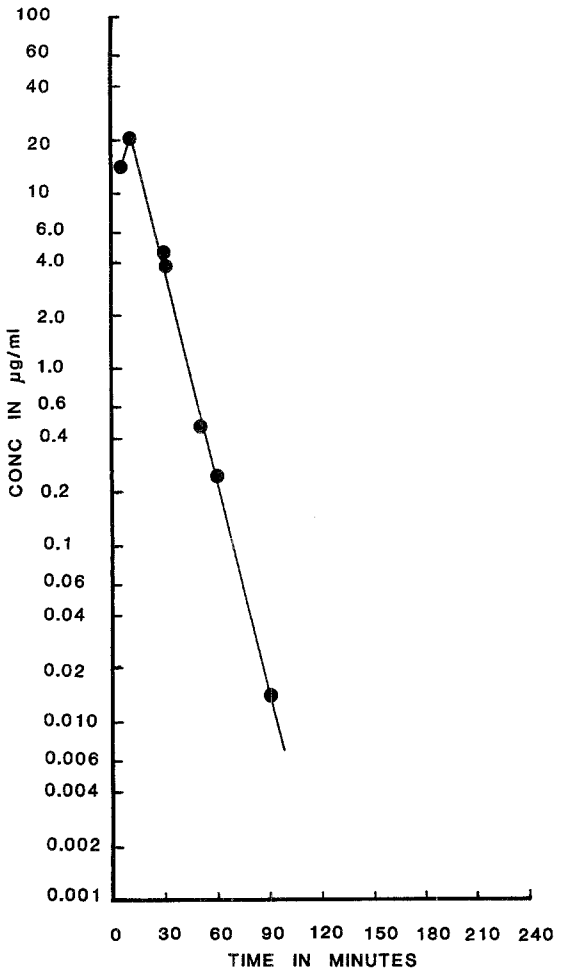

Fig. 5. Concentration-time profiles for FdUrd in plasma obtained from patient HG, who was given 30-min i. v. infusion of 2,000 mg FdUrd

and infrequently observed, except in two patients who developed grades 3 and 4 reversible myelosuppression at the 4,000- and 5,000-mg levels, respectively. One patient complained of diarrhea that required dose reduction, and moderate mucositis occurred in the two patients who manifested leukopenia. These results are not unlike the experience with FUra, which, following initial 4-h dwells $\times 12$ [30] has subsequently been given on daily $\times 5$ rapid administration schedules [7, 31, 33], by continuous infusion for 5 days [15], weekly [6, 23], and in single doses combined with other drugs [5, 8, 25]. However, abdominal pain has frequently been noted in these trials. As in these investigations, we encountered catheter- or disease-related complications that rendered treatment difficult. Five patients in the present study did not proceed beyond the first cycle; with experience in patient selection, this early attrition may be minimized. Except for outflow problems, implantable catheters appear to be advantageous in avoiding septic complications.

Potential therapeutic effects of FdUrd were evaluated in the 18 patients receiving repeat dosing. Since a criterion for entry was small-volume i. p. disease (even including the presence of extraperitoneal disease as long as it was asymptomatic), we did not require laparotomy assessment. Nevertheless, several indicators of antitumor effect could be verified: clearing of a lesion at laparoscopy, improvement of tumor markers and/or conversion of positive to negative cytology in four subjects, clearing of ascites in two, and improvement in a computerized tomographic (CT) scan lesion. Median time to progression was 12 and 13.5 weeks in extraperitoneal and peritoneal sites, respectively.

Because of the individual variation in pharmacokinetic parameters (Table 4), systemic toxicity could be quite unpredictable. For this reason, as in FUra trials, studies on FdUrd will likely use dose levels that produce little or no systemic toxicity. We therefore sought to verify that a dose of 3,000 mg $\times 3$ days was reproducibly tolerable and to recommend it for further study. This choice was made based on both the kinetics and the one instance each of hematologic toxicity observed at levels of 4,000 and 5,000 mg $\times 3$ days, respectively. Experience gained using this regimen in Southwest Oncology Group study 8835 supports this selection, since hematologic toxicities have occasionally been observed when doses were escalated beyond this level (personal communication, F. Muggia and D. Alberts, study coordinators, with permission from the Southwest Oncology Group). Alternatively, day 1 plasma pharmacologic monitoring must be evaluated for its possible usefulness in predicting tolerance. The number of toxic events observed in the present study were insufficient to enable us to arrive at such correlations.

The dose schedule used does require additional comment. The i. p. pharmacologic advantage would predict the drug to be highly cytotoxic to most tumor cells that are exposed to these maximal concentrations. On the other hand, systemic levels would generally be inadequate. When given systemically by i. v. push, FdUrd does not lead to toxicity until a dose of 40 mg/kg $\times 5$ days is reached [20]. This schedule would easily explain the absence of systemic effects in nearly all patients. If one were to provide more sustained systemic levels by repeated dwells or by continuous i.p. infusion, systemic toxicity would undoubtedly be more prevalent, but local cytotoxicity would not necessarily be favored. For these reasons as well as the practical advantage of a daily $\times 3$ administration protocol, we chose to pursue this i. p. schedule further.

Therefore, at the conclusion of this study we initiated a phase II trial of FdUrd at 3,000 mg $\times 3$ days in patients with ovarian cancer who exhibited minimal residual disease at second-look laparotomy within the Southwest Oncology Group. In addition, we opened a phase I and pharmacokinetics study of FdUrd given on the same dose schedule alone with escalating doses of i. p. leucovorin. The purpose was to document whether other systemic or local dose-limiting toxicities would occur with leucovorin enhancement of fluoropyrimidine action. This study is currently continuing. The possibilities for other modulation concurrent with i. p. FdUrd and for concurrent systemic administration of fluoropyrimidines or other drugs are also worthy of consideration, particularly as surgical adjuvants in gastric or other gastrointestinal cancer associated with high risk of peritoneal spread.

Table 5. Mean pertinent pharmacokinetic parameters of FdUrd in patients following i.p. administration

Parameter	Dose					
	500–1,500 mg ($n = 4$)	2,000 mg ($n = 3$)	3,000 mg ($n = 10$)	4,000 mg ($n = 5$)	5,000 mg ($n = 3$)	6,000 mg ($n = 1$)
AUC_{PF} FdUrd ($\mu g\ ml^{-1}\ min$)	50,863±24,188	356,057±464,033	137,196±111,916	209,881±33,776	231,786±13,626	376,280
AUC_{PL} FdUrd ($\mu g\ ml^{-1}\ min$)	19.93±17.22	59.9 (33.3)[b]	70.17±60.13	120.7±119.8	254.9±89.84	71.9
AUC_{PF} FUra ($\mu g\ ml^{-1}\ min$)	1,401 (431)[b]	5,775	7,029±3,706	3,833±1,680	4,676 (2,030)[b]	48,706
Beta FdUrd (min^{-1})	0.007463±0.003853	0.007881±0.002813	0.007180±0.003011	0.005918±0.003011	0.004259±0.001871	0.0033
$t^1/_2$ PF, FdUrd (min)	92.86 [50.25–164.9]	97.93 [70.2–117.6]	96.52 [103.2–140.5]	117.1 [112.8–164.2]	162.7 [117.8–164.2]	210
R1[a]	3,491±3,264	1,883 (730)	2,731±2,109	3,055±1,607	991.1 ±381	5,233
CL_{PF} (ml/min)	24.68±9.68	22.33±3.68	30.58±18.41	18.98±2.74	25.59±8.9	15.95

[a] FdUrd area ratio to infinity between peritoneal fluid and plasma

[b] Average of 2 values (difference)

Values in square brackets represent ranges

Pharmacologic findings

The mean peritoneal clearance value for FdUrd, 25 ml/min (Table 4), fell slightly above the value that would be predicted on the basis of the molecular weight for a wide range of drugs, although substantial variation existed [22]. This higher clearance may possibly suggest a contribution by extrahepatic metabolism, which was found for FdUrd (see degradation in plasma, below). Together with the observed vast AUC ratio between the peritoneal fluid and the plasma, rapid systemic clearance of FdUrd that is even greater than that of FUra can be predicted on the basis of theoretical considerations [11]. Although this contention has previously been substantiated by hepatic extraction ratio estimation following constant i.v. infusions of FdUrd [14], no direct measurement of total clearance was reported. Toward the end of the study, two patients volunteered to receive short 30-min i.v. infusions of FdUrd at a dose of 2 g prior to their i.p. treatment for pharmacologic study: the post-infusion profile declined monoexponentially, showing a half-life of 7.5 min (Fig. 5). These two patients exhibited a mean total clearance of 7,000 ml/min, which is in the range of the values previously reported for intrinsic clearance of FdUrd [14], thus substantiating the above prediction. This rapid systemic clearance, in part probably hepatic [30], results in peritoneal to plasma concentrations that are generally higher than those determined for FUra [7, 9, 30].

With regard to linearity, five profiles from these patients exhibited apparent nonlinear kinetics and precluded accurate determination of the terminal half-lives. Since the pharmacokinetics of seven subjects were studied in two to four increments of FdUrd dose, several pertinent pharmacokinetic parameters were examined for a subtle indication of nonlinear kinetics in these patients using common statistical criteria. However, the values for AUC, peritoneal clearance, and half-life for the parent drug were found to be quite variable, precluding a definitive indication of nonlinearity, although in the majority of patients no strong indication of nonlinear kinetics was evident (data not shown). Thus, peritoneal elimination as a whole appears to be an efficient process that is difficult to saturate until an extremely high dose is reached.

In three patients, plasma FdUrd levels and the corresponding AUC values increased disproportionately with increasing dose. In one subject (JK) whose dose was increased from 1,000 to 2,000 mg, the PF/PL AUC ratio decreased from 8,700 to 1,200; in the other two patients (SM and VK) who underwent a dose increase from 3,000 to 5,000 mg, this ratio decreased from 7,000 to 1,300 and from 3,400 to 450, respectively. This suggests a disproportionate increase in the systemic partitioning of FdUrd when doses in the peritoneal cavity were escalated within a patient. Alternatively, this increase could be due to saturation of the phosphorylase for cleavage of the glycosidic bond, causing an increase in systemic levels of the nucleoside. The disproportionate increase in plasma FdUrd levels may relate to the systemic toxicity seen at doses of >3,000 mg in two patients. Plasma FdUrd concentrations measured in most subjects were <1 μg/ml, with the exception of one patient receiving a 5,000-mg dose, one subject receiving a 4,000-mg dose, and another receiving a 3,000-mg dose. All three of these patients experienced toxicity of at least grade 2.

Sugarbaker et al. [32] reported that the maximal tolerated dose (MTD) for i.v. infusion was 7 mg/24 h and that for i.a. infusion was 21 mg/24 h. Since the amount of drug given under the present i.p. conditions was >500-fold that of the MTD yet produced no significant toxicity, the fate of the drug following administration by this route is of interest. FdUrd has been shown to be cleaved to FUra by phosphorylase, and the pyrimidine base is presumably metabolized by the usual catabolic pathways. Thus, we attempted to measure FUra levels in PF using a modified HPLC method, and this was achievable in most of the patients. To ascertain that no significant degradation of the drug occurred due to storage, thawing, and refreezing, the stability of FdUrd in human plasma and peritoneal fluid was evaluated. No appreciable degradation was detected when plasma and peritoneal fluid samples containing FdUrd were kept frozen for >2 months or when the sample went through one cycle of freeze-thawing. At 8°C and at room temperature (25°C), however, FdUrd in plasma degrades to FUra in a first-order fashion, exhibiting half-lives of 64 and 9.1 h, respectively. In all of our analyses, the samples were thawed in cold water for only a brief period, which caused no significant degradation.

In plasma, FUra and its catabolite FUH_2 cannot be analyzed simultaneously by HPLC; however, they could be measured by gas chromatography-mass spectrometry. In one patient receiving 6 g FdUrd whose plasma FUra concentrations were measured, the levels were extremely high and sustained, reaching about 350 μM (46 μg/ml) at 240 min (Fig. 3). However, concentrations of the catabolite dihydro-5-fluorouracil were quite low and also sustained. The high FUra levels were not attributable to the degradation of FdUrd during the assay procedure, as evidenced by the stability study. Thus, these data suggest that FdUrd is probably cleaved to FUra rather rapidly and efficiently in the surrounding peritoneum and/or in the liver tissue by phosphorylase; the FUra returns to the PF as well as entering into the liver. In turn, FUra is further catabolized to FUH_2 by saturable reduction via dihydropyrimidinase. Because of the massive dose of FUra generated, FUH_2 and the unmetabolized FUra enter the peripheral circulation.

Interest in the biochemical modulation of fluoropyrimidines has stimulated others investigators to combine i.p. FUra with leucovorin [1, 6]; more recently, our dose schedule for FdUrd has been adopted for a similar study in combination with leucovorin [27]. The pharmacokinetics of FdUrd reported in the present study confirmed our previous observations, which were published elsewhere in on abstract [26]. Along with clinical studies, one should also pursue the determinants of resistance to these substantial levels of FdUrd. Possible reasons for resistance that could be examined include deletions in the nucleoside transporter [28] or in thymidine kinase [10]; in either event, sensitivity to FUra should be retained. Further investigations of the i.p. administration of fluoropyrimidines may have considerable impact on extending our knowledge of their disposition, of any therapeutically useful interactions or modulation of activity, and of resistance mechanisms. Such knowledge may improve their therapeutic index against currently refractory intraabdominal disease.

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