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Phase I and pharmacokinetic evaluation of floxuridine/leucovorin given on the Roswell Park weekly regimen

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Abstract. A phase I and pharmacokinetics study was carried out of floxuridine (FdUrd) modulated by leucovorin (LV) given on the Roswell Park regimen (LV given at 500 mg/m^2 by 2-h infusion and FdUrd given by i. v. push at 1 h after the start of LV infusion, treatment being given weekly × 6). The dose-limiting toxicity was diarrhea; the MTD and recommended dose for phase II studies was 1,650 mg/m^2 per week of FdUrd. The dose-response curve was steep, with 3/3 patients treated at a dose of 1,750 mg/m^2 developing grade IV diarrhea. With this schedule there was no significant mucositis. Pharmacokinetic parameters showed very wide interpatient variability. Plasma decay was biphasic with a $t^1/_2\beta$ of approximately 2 h. Plasma clearance was high (>200 l h^{-1}). No correlation between pharmacokinetic parameters and toxicity could be identified.

Introduction

The modulation of 5-fluorouracil (FUra) by leucovorin (LV), introduced into the clinic by Machover et al. [7], has become a standard therapy for advanced colorectal carcinoma. Most of the randomized studies comparing FUra/LV with equitoxic doses of FUra have shown a greater response rate for FUra/LV than for FUra alone [1, 3]. FUra/LV has been evaluated on two main schedules: the regimen introduced by Machover (FUra/LV given daily for 5 days once a month) and the Roswell Park weekly regimen [8]. In the Roswell Park regimen, LV is given at a dose of 500 mg/m^2 by a 2-h infusion and FUra is given at a dose of 600 mg/m^2 as a rapid i. v. injection midway through the 2-h infusion of LV. This regimen gives a response rate in colorectal carcinoma of 30%–50% [9, 10].

LV acts as a precursor of 5,10-methylenetetrahydrofolate, which forms a ternary complex with the target enzyme thymidylate synthase (TS) and flurodeoxyuridine monophosphate (FdUMP), one of the active metabolites of FUra. Excess LV leads to stabilization of this complex and increases inhibition of TS [5]. Floxuridine (FdUrd) is a more proximate precursor of FdUMP than is FUra. In vivo it is both converted into FdUMP and broken down to FUra, which is partly converted to fluorouridine triphosphate (FUTP) and incorporated into RNA. The action of FdUrd is a complex result of the comparative rates of the reactions involved in its metabolism. Laboratory data indicate that LV modulates the action of FdUrd more than that of FUra [13].

FdUrd is normally given by low-dose continuous infusion (CI), often intra-arterially into the hepatic artery for hepatic metastases of colorectal carcinoma. The maximum tolerated dose (MTD) of FdUrd given i. v. by CI for 14 days is 1.5 mg/kg per day (~55 mg/m^2 per day). The dose-limiting toxicities are stomatitits and diarrhea [6]. There have been few studies of FdUrd modulated by LV. In our phase I study of FdUrd given by CI for 5 days with LV (500 mg/m^2 per day for 5 days), the MTD of FdUrd was 0.125 mg/kg per day; the dose-limiting toxicity was stomatitis [4]. Laboratory data indicate that giving FdUrd by rapid injection accentuates its conversion to FdUMP, whereas low-dose CI promotes its conversion to FUTP and its incorporation into RNA [14]. Since LV modulates fluoropyrimidine action via the FdUMP pathway, we evaluated LV modulation of FdUrd given by rapid injection in previously treated patients with advanced cancer. We report the results of a phase I/pharmacokinetics study of this modulation using the Roswell Park weekly regimen.

Patients and methods

Drug administration. FdUrd was kindly supplied by Roche Laboratories in 500-mg vials. Each vial was reconstituted in 5 ml of sterile

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water and the whole dose was given by rapid i.v. injection over 5 min at 1 h after the start of the infusion of LV. LV obtained commerically was given by 2-h infusion in 250 ml of Ringer's lactate at a dose of 500 mg/m^2. The treatment was given weekly for 6 weeks (one course) in the absence of toxicity. Drug was withheld for toxicity of $\geq$ grade II until it had diminished to $\leq$ grade I. If toxicity had not resolved within 1 week, the course was terminated ("incomplete course"). Patients with tumor response or stable disease could receive a second course starting on day 50. If toxicity on the first course was $\leq$ grade I, the second and subsequent courses were given at the dose being explored at the time of retreatment. However, the toxicity is reported for the course on which the patient was initially entered to avoid bias introduced by prior therapy. Pharmacokinetic data are reported for all patients studied at a given dose.

Patients. All patients were required to have histologically verified recurrent or metastatic malignant disease not amenable to standard therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; a WBC of $\geq 4 \times 10^9$/l; a platelet count of $\geq 10^{11}$/l; a serum bilirubin level of <2.0 mg/dl; and a serum creatinine value of <2.0 mg/dl. Patients were excluded from the study if they had an active, uncontrolled infection or a severe intercurrent nonmalignant systemic disease or were pregnant or lactating. All patients were required to give written informed consent after an explanation of the investigational nature of the study, the risks involved, and their right to withdraw from the study at any time. The study protocol and abstract of informed consent were approved by the Institutional Review Board of Roswell Park Cancer Institute.

The study design called for 3 patients to be entered at nontoxic doses; up to 5 patients, at doses giving mild to moderate (grade I–II) toxicity in any of the first 3 patients treated; and 6 patients, at the MTD. If 1 of the first 3 patients treated had grade III or IV toxicity, 3 more patients were added unless the toxicity encountered in the first 3 patients indicated that the dose was above the MTD, in which case no further patient was added. The MTD was defined as the dose giving grade III myeloid or gastrointestinal (GI) toxicity excluding controllable nausea and vomiting in at least 2 but not more than 3 of 6 patients and grade IV myeloid or GI toxicity in $\leq$2 of 6 patients. For organ (e.g., hepatic, renal) toxicity, the occurrence of grade III toxicity in 2 of 6 patients or of grade IV toxicity in 1 of 6 patients defined the MTD.

Pre- and posttreatment evaluation. Each patient received a complete history, physical examination, and tumor measurement before entering the study. A complete blood count [hemoglobin (Hb), hematocrit (Hct), WBC, platelet count, and differential count] and a blood-chemistry profile [sodium, potassium, chloride, CO_2, glucose, urea nitrogen, creatinine, calcium, phosphorus, uric acid, total protein, albumin, total bilirubin, aspartate aminotransferase (AST) lactic dehydrogenase (LDH), alkaline phosphatase] were obtained. A complete blood count, blood-chemistry profile, history of symptoms, and physical examination for side effects were obtained weekly before each dose. Tumor evaluation was performed 1 week after the completion of each course. Toxicity was rated using the National Cancer Institute (NCI) Common Toxicity criteria.

Response. A complete response was defined as the complete disappearance of all clinical and radiological evidence of tumor for a 6-week period. A partial response was defined as a decrease of 50% in the sum of the products of two diameters measured at right angles (one of these being the longest diameter) of all measurable lesions along with no appearance of new lesions and no progression in any lesion for a period of 6 weeks. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in the sum of the products of all measurable lesions, measured as noted above, without the appearance of any new lesion for a period of 6 weeks.

Pharmacokinetics. Blood (5–7 ml) for the assay of FdUrd and FUra was collected into heparinized tubes at 1, 3, 5, 15, 30, 45, 60, 90, and 120 min after the administration of FdUrd and placed on ice and the plasma was separated by centrifugation. Plasma was extracted twice in siliconized tubes with 5 vols. of ethyl acetate after the addition of bromouracil as an internal standard. The organic layer was evaporated to dryness, resuspended in methanol, evaporated again, and resuspended in mobile phase for analysis.

High-performance liquid chromatography (HPLC) was carried out on a Sphereisorb ODSII reverse-phase column (4.6 mm $\times$ 150 mm) using two UV detectors (Waters) set at 265 and 254 nm, respectively. Elution was isocratic at room temperature with 1.5% methanol in ammonium acetate buffer (2.5 m*M*, pH 5). The limit of sensitivity of the assay was 0.2 μM for both FdUrd and FUra.

For assay of total LV, 6S-LV (the biologically active stereoisomer), and the metabolite 5-methyltetrahydrofolate (5-CH_3FH_4), 5 ml of blood was collected in heparinized tubes containing 1 m*M* (final concentration) of sodium ascorbate at the end of the LV infusion and again 1 h later and then centrifuged, and the plasma was extracted using methanol protein precipitation after the addition of methotrexate as an internal standard (1 vol. plasma: 4 vols. methanol). The extraction efficiency was $>90\%$. Samples were centrifuged and the supernatant was evaporated and reconstituted in the HPLC buffer. The extract was applied by a Waters WISP Autosampler (Waters Chromatography Division of Millipore Corp., Milford, Mass.) successively to a Waters 3.9- $\times$ 150-mm μ-Bondapak phenyl column (particle size, 10 μm) and a 15-cm $\times$ 4-mm (inside diameter) BSA column (Resolvosil-BSA-7, Macherey-Nagel Duren, Germany) connected by an automated switching valve (Waters 60057). A Perkin-Elmer binary pump 250 (Perkin Elmer Corp., Norwalk, Conn.) and a Waters 400 UV detector (wavelength, 280 nm) were used with the first column and a Waters 6000A pump and a Waters 481 variable-wavelength detector (set at a wavelength of 287 nm) were used with the second column. Elution was carried out with a gradient ranging from 0.05 *M* potassium phosphate buffer (pH 7) to a 50:50 (v/v) mixture of methanol: potassium phosphate buffer from the first column and isocratically with 0.25 *M* potassium phosphate buffer (pH 5) from the second column. The flow rate was 1 ml/min. Data were collected by a Perkin-Elmer Omega Analytical Workstation.

A standard curve was run with each patient's samples and was linear from 0.8 to 100 μg/ml. The lower limit of detection of the assay was 1–1.5 μM for total LV and for 6S-LV.

Data analysis. A noncompartmental analysis of plasma levels (C_p) of FdUrd after the end of infusion was used to derive the pharmacokinetic parameters. The LAGRAN program on a Sperry personal computer (PC) was used to calculate the parameters [12]. This program uses the Langrange function to calculate the total area under the plasma concentration $\times$ time curve (AUC), from which is derived the plasma clearance (Cl_p, dose. AUC^{-1}). For FUra the maximal plasma concentration (C_{max}) and AUC were calculated.

Results

A total of 22 patients developed toxicity or received at least 1 full course (6 weeks) of treatment without developing toxicity and were evaluable for toxicity (Table 1). Of the 8 patients who did not complete a full course, 5 were taken off study because of deterioration in their condition, 2 were excluded because of progressive disease, and 1 patient chose to withdraw. Patients who completed a course of treatment without developing toxicity could be treated at a higher dose level. In all, 7 patients received 2 courses and 1 patient was given 3 courses of treatment. The toxicity is reported for the initial dose at which they were treated; 25 patients had pharmacokinetic studies performed on 30 courses of treatment. In all, 8 patients had pharmacokinetic studies performed but had early disease progression and could not be evaluated for toxicity.

The planned escalation of FdUrd was 500, 1,000, 1,500, and 2,000 mg/m^2 per week $\times$ 6. Toxicity was generally minor at the lowest three doses explored. However, one

Table 1. Patients' characteristics

	Total	Evaluable for toxicity
	30	22
Sex:		
M	16	10
F	14	12
Age:		
Median	64 years	
Ranage	30–79 years	
ECOG performance status:		
0	6	5
1	14	13
2	10	4
Diagnosis:		
Carcinoma:		
Lung:	9	6
Small-cell	3	2
Large-cell	1	1
Adeno-	3	1
Squamous	2	2
Colon	7	6
Stomach	4	2
Soft-tissue sarcoma	2	2
Miscellaneous	8	6
Prior therapy:		
Surgery	29	22
Chemo-	29	22
RT	12	9

Table 2. Gastrointestinal toxicity

		Diarrhea					Stomatitis		
		Grade					Grade		
Dose (mg/m²)	*n*	I	II	III	IV	Total	I	II	Total
500	4	1	–	–	–	1	–	–	0
1,000	5	2	–	–	–	2	–	1	1
1,500	4	1	1	–	–	2	1	–	1
1,650	6	1	–	2	–	3	1	1	2
1,750	3	–	–	–	3	3	1	–	1

Table 3. Other toxicities

Toxicity	Dose (mg/m²)			
	500–1,500 (*n* = 13)	1,650 (*n* = 6)	1,750 (*n* = 3)	Total (*n* = 22)
Nausea & vomiting	1	2	3	6
Anorexia	1	3	1	5
Fatigue	3	1[a]	1	5
Leukopenia	–	1	2[a]	3
Hand/foot syndrome	1	1	–	2
Lacrimation	–	1	–	1
Thrombocytopenia	1	–	–	1

[a] Grade III; all other toxicities are of grade I/II

case of grade II toxicity was seen at 1,500 mg/m². For this reason, escalation to 1,750 mg/m² instead of 2,000 mg/m² was carried out. As this dose was poorly tolerated, a dose of 1,650 mg/m² was studied. Diarrhea was the dose-limiting toxicity (Table 2); grade III leukopenia was seen in 2/3 patients treated at 1,750 mg/m² but was not encountered at lower doses; other toxicities observed are noted in Table 3. All of these were mild to moderate except for one instance of severe fatigue observed at a dose of 1,650 mg/m².

At a dose of 1,750 mg/m² the 3 patients entered developed grade IV diarrhea after receiving 3, 4, and 5 doses, respectively. At 1,650 mg/m², 4/6 patients tolerated 6 doses, with the remaining 2 patients tolerating 5 and 3 doses, respectively; 2 patients treated at this dose developed severe diarrhea. The dose of 1,650 mg/m² per week × 6 was therefore considered to be the MTD and is the recommended starting dose for phase II studies.

A total of 8 patients received a second course, which was complete in 5 cases and incomplete in 3. In 6 patients the dose was escalated because of the occurrence of only minimal toxicity, if any, at their initial dose. The initial dose was 500 mg/m² per week in 3 patients and 1,000 mg/m² per week in 3. The escalated dose was 1,000 mg/m² per week in 2 patients (1 course was incomplete) and 1,500 mg/m² per week in 4 patients (all courses were complete). In addition, 1 patient received a complete course at 1,500 mg/m² per week after an incomplete course at 1,650 mg/m² per week. The toxicity did not differ from that seen in patients entered at the same doses de novo.

Measurement of the AUC, Cl_p and terminal-phase plasma half-life ($t^1/_2\beta$) of FdUrd and of the AUC and C_{max} of FUra showed that the pharmacokinetic parameters were characterized by extensive variability among patients treated at the same dose as well as in individual patients treated at different doses. The parameters for the doses for which data on 6 or more patients were obtained are shown in Table 4. The plasma decay of FdUrd was biphasic. However, only at the dose of 1,650 mg/m² was it possible to generate sufficient data at the later time points for an accurate assessment of $t^1/_2\beta$. Thus, no half-life is given for the lower doses in Table 4. No correlation could be found between the pharmacokinetic parameters of FdUrd or FUra and toxicity. Plasma levels of LV, 6S-LV, and 5-CH_3FH_4 also showed considerable variability. The mean values (± SD) obtained for the three compounds were 61.7 ± 13.2, 18.1 ± 6.4, and 6.6 ± 3.8 μ*M*, respectively, at the end of the LV infusion and 42.3 ± 12.4, 9.8 ± 4.8, and 6.9 ± 4.0 μ*M*, respectively, at 1 h after the end of the infusion.

One patient with carcinoma of the colon who had previously been treated with FUra/LV had a partial response in the liver that lasted for 4 months. Seven patients had stable disease.

Discussion

In this study we examined the toxicity and pharmacokinetics of FdUrd modulated by LV given on the Roswell

Table 4. Pharmacokinetic parameters[a]

		FdUrd			FUra	
Dose (mg/m^2)	n	AUC ($\mu M \cdot$ h)	Cl_p (l $\cdot$ h^{-1})	$t^1/_2\beta$ (h)	C_{max} (μM)	AUC ($\mu M \cdot$ h)
1,000	7	16 (6–35)	240 (216–1,380)	–	148 (52–482)	58 (23–76)
1,500	9	35 (14–93)	282 120–840)	–	160 (128–463)	76 (19–139)
1,650	6	64 (44–98)	210 (132–317)	1.75 (0.7–4.2)	212 (140–342)	125 (71–142)

[a] Data represent median values (range)

Park weekly regimen. The rationale for exploring FdUrd modulation by LV and for using this unusual schedule of FdUrd administration was as follows:

1. The 50% growth-inhibitory concentration (IC_{50}) for HCT8 cells of FUra and FdUrd (5-h exposure) is decreased by LV (20 μM for 24 h); however, the extent of the decrease for FUra is a factor of less than 2, whereas for FdUrd it is a factor of approximately 7 [13].
2. When HCT-8 cells are exposed to FdUrd, the ratio of intracellular FdUMP:FUTP is dependent on the exposure time; for a 24-h exposure the ratio is 2.7:1, whereas for a 3-h exposure it is 10:1 [14]. Since LV acts by stabilizing the complex formed by FdUMP with the target enzyme TS [5], an increase in the formation of this metabolite should favor modulation by LV. Moreover, clinical studies of the modulation of FUra action by LV [9, 10] and by thymidine [2] in patients with colorectal carcinoma strongly suggest that FdUMP inhibition of TS contributes to antitumor response, whereas FUTP incorporation into RNA contributes preferentially to host toxicity.
3. With FdUrd administration, tissues are exposed to relatively high levels of both FdUrd and the metabolite FUra.

The finding in this phase I study that the dose-limiting toxicity is diarrhea and that at and below the MTD other toxicities are relatively minor, parallels our experience with the Roswell Park regimen for FUra/LV, in which toxicities other than diarrhea, notably stomatitis, are markedly less than with other schedules. The dose required to produce dose-limiting toxicity is high, in line with the well-known marked schedule dependency of FdUrd. In a previous study in which we evaluated FdUrd given by 3-h infusion with a 2-h infusion of LV daily × 5 every 4 weeks, we found 2,000 mg/m^2 per day (10,000 mg/m^2 per course; 2,500 mg/m^2 per week) to be the MTD [11]. However, on this schedule, myelosuppression and stomatitis were marked. In the present study a total dose of 9,900 mg/m^2 per course was the MTD. Courses were given every 7 weeks, yielding a weekly planned total dose of 1,400 mg/m^2 and a mean delivered dose of 1,244 mg/m^2 per week. In our study of 5-day continuous infusion of FdUrd with LV (500 mg/m^2 per day) given every 4 weeks, the MTD of FdUrd was 0.125 mg/kg per day (approximately 23 mg/m^2 per course or 5.75 mg/m^2 per week), with stomatitis being the dose-limiting toxicity [4].

Since FdUrd is not normally given by bolus i.v. injection, there is a paucity of data on the pharmacokinetics of the drug given in this way. Our data indicate a very wide interpatient variability, a terminal-phase $t^1/_2$ of about 2 h, and a large plasma clearance. The AUC values suggest the possibility of nonlinear kinetics. However, the interpatient variability is very large. A comparison of the AUC for 1,500 mg/m^2 with that for 1,650 mg/m^2 shows that the difference for FdUrd is not statistically significant ($P = 0.1$ by the Mann-Whitney two-sample rank test, two-tailed test). The difference in the AUC for FUra reaches significance at the $P = 0.05$ level. Moreover, there is no change in the plasma clearance of FdUrd with dose. Therefore, the data do not conclusively demonstrate nonlinear pharmacokinetics. The apparent nonlinearity of the toxicity may be related to events at the cellular level.

The observation that the AUC of FUra is greater than that of FdUrd at all dose levels indicates that FdUrd is acting partially as a precursor of FUra. However, the rapid breakdown of FUra in the liver and the observation that FdUrd is a more proximate precursor of FdUMP, the active metabolite, would suggest that it is not merely a prodrug on this schedule.

The pharmacokinetics of LV were not extensively studied in this trial because the same dose of LV was given to all patients. However, the data indicate that 10 μM 6S-LV, the target level in plasma [5], is achieved during drug administration and for approximately 1 h after the end of the infusion.

The clinical utility of FdUrd/LV given on this schedule will require phase II evaluation in previously untreated patients with colorectal carcinoma. However, a significant increase in activity over that obtained with the present treatment will be needed to justify the additional expense of this approach. The recommended starting dose for phase II studies is 1,650 mg/m^2 per week × 6.

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