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Biological Modification of protracted infusion of 5-fluorouracil with weekly leucovorin*

A dose seeking clinical trial for patients with disseminated gastrointestinal cancers

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Summary. A clinical trial was designed to find the maximally tolerated dose of weekly leucovorin (LV) that could be combined with 4 weeks of protracted infusion (PI) of 5-fluorouracil (5FU) at a fixed dose of 200 mg/m^2. A total of 36 patients with disseminated gastrointestinal malignancies were treated; 9 either progressed or died before receiving 4 weeks of treatment leaving 27 patients evaluable for toxicity and response. 5FU was given as a protracted infusion using an ambulatory infusion pump and indwelling venous access. LV doses included 20, 25, 50, and 75 mg/m^2 given as an i.v. push at the time of weekly pump fill with 5FU. In all, 72% of the patients tolerated LV at 20 mg/m^2 for 4 continuous weeks, whereas the higher doses required treatment rests prior to 4 weeks. The dose-limiting toxicity at all doses was stomatitis. No significant myelosuppression was seen; diarrhea was infrequent. Overall, 40% of the patients with measurable cancer had partial responses. In view of evidence of biologic and therapeutic effects of these weekly doses of 20 mg/m^2 LV with 200 mg/m^2 5FU per day given as a protracted infusion over 4 weeks, phase II trials and multimodality studies for patients with gastrointestinal malignancies are being initiated at our institution using this dose and schedule.

Introduction

Over the last 5 years, the most interesting and important development in the treatment of disseminated gastrointestinal malignancies has been the use of biochemical modulators with the antimetabolite 5-fluorouracil (5FU). In particular, attention has been focused on the modulation of 5FU by leucovorin. Biochemical modulation of 5FU by leucovorin has yielded encouraging results in advanced malignancies in some randomized studies, prompting a new generation of studies.

Leucovorin (LV) exerts its effect by converting the dissociable complex of FdUMP-thymidylate synthase into a tightly bound ternary complex, inhibiting the production of thymidylate and thus of DNA [12]. Response rates in phase II and III studies of this combination, which have ranged from 21 to 58%, are often superior to those obtained with similar regimens of 5FU alone [12]. Increased 5FU toxicity is also found in conjunction with these improved response rates [9, 19]. Although definite enhancement of the therapeutic index remains controversial, enhanced toxicities provide further evidence of biochemical and biologic modulation.

The dose and schedule of both 5FU and LV have varied among the studies reported. In clinical trials containing 5FU with LV the combination demonstrated improved response and survival compared to 5FU alone [8, 23]. While most investigators are optimistic that LV will be an important addition to therapy with 5FU containing regimens, no schedule has emerged as a standard. Moreover, the type of toxicity encountered has varied with both dose and schedule.

The issue of treatment efficacy is further complicated by alteration of the schedule of 5FU. Infusion schedules have been suggested as a means of enhancing response rates and changing clinical toxicities. Prospectively randomized trials conducted by Seifert et al. [21] and Kish et al. [11] have shown superior response rates for a 5-day infusion schedule vs bolus 5FU in patients with measurable large bowel and head and neck tumors respectively [11, 21].

In single arm phase II trials using a protracted infusion schedule of 5FU Lokich and others have found higher response rates than those commonly reported in modern trials using standard bolus 5FU therapy [2, 3, 4, 15]. Subsequently, a large, randomized trial of bolus vs protracted infusion 5FU showed a significant response advantage for the infusion arm (30% vs 8%), and a trend toward survival advantage for the infusion treatment [16].

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Table 1. Demographics and response

Patient	Age	Sex	Primary Disease	Evaluable Site	Prior Therapy	Response Tumor/CEA	
1	50	F	Colon	Liver	None	PR	PR
2	60	M	Colon	Liver	5FU/Mito	PR	PR
3	67	M	Pancreas	Pancreas	None	SD	PR
4	64	M	Gastric	Liver	None	SD-E	ND
5	62	F	Pancreas	Liver/perit	None	SD-E	PR
6	49	M	Pancreas	Liver	FAM	PD	PD
7	70	F	Colon	Liver	None	PR	PR
8	50	M	Colon	Retroperit	5FU	PD-E	NC
9	56	M	Colon	Lung	5FU	PR	NA
10	64	M	Colon	Liver	None	PR	PR
11	68	M	Colon	Liver	None	MR	PR
12	58	F	Colon	Liver	5FU/Mito	SD	PR
13	63	F	Colon	Liver	5FU/XRT	PR	PR
14	57	M	Colon	Retroperit	None	SD-E	PR
15	63	M	Rectum	Lung	5FU; CE	SD-E	PR
16	59	F	Duodenum	Liver	5FU	PD	PD
17	73	M	Colon	Lung	None	MR-E	PR
18	54	F	Pancreas	Liver	None	PD	PD
19	71	F	Rectum	Pelvis	None	PD-E	PD
20	63	M	Pancreas	Pancreas	None	SD	NA
21	53	M	Pancreas	Pancreas	FAM	PR	NA
22	64	M	Colon	Perit	None	SD-E	NC
23	60	M	Colon	Liver	None	PR	PR
24	68	M	Colon	Liver	None	SD	PR
25	66	M	Pancreas	Liver	5FU	PD	PD
26	56	F	Pancreas	Liver	None	PD	PR
27	73	F	Pancreas	Liver	None	PD	PD

Abbreviations: Perit = peritoneum; Retroperit = retroperitoneum; Mito = Mitomycin C; FAM = 5FU, Adriamycin, mitomycin C; XRT = radiation therapy; CE = chemoembolization; CEA = carcinoembryonic antigen; PR = partial response (for CEA this means less than 50% of on study value); MR = minor response; SD = stable disease; PD = progressive disease; E = evaluable, non-measurable disease; ND = not done; NC = no change; NA = not applicable, initial CEA not elevated

The trials with protracted infusion 5FU have shown that patients tolerate greater total doses of 5FU (greater area under the concentration × time curve) than those receiving conventional bolus treatment given either weekly or daily times five every 5 weeks [20]. Both laboratory and clinical studies have suggested that such dose intensity and prolonged exposure time may be important in the achievement of tumor cytotoxicity [6, 10]. As technology for drug administration has advanced with the development of indwelling venous access devices and ambulatory infusion pumps, this method of therapy has allowed patients to continue treatments while at home or at work.

We present a study designed to combine protracted infusion 5FU with weekly i.v. LV. We have previously reported a tolerable and effective protracted infusion schedule for the effector drug, 5FU [13]. The purpose of the current trial was to determine a safe dose of the modulator, LV, to be used in conjunction with this schedule, and to define the toxicity of this new regimen. The choice of weekly LV was strictly empirical, although influenced by practical considerations (i.e., administration at the time of weekly pump fill). The weekly schedule also enabled the close observation of modulation of toxicity as well as the documentation of antitumor effects.

Materials and methods

Between October 1987 and June 1988, 36 patients at the University of Southern California Comprehensive Cancer Center were entered on study. All patients had biopsy proven locally unresectable or disseminated adenocarcinoma arising from the gastrointestinal tract, with measurable or evaluable disease. All patients on the trial were required to be over 18 years of age and to sign a statement of written informed consent. The study required each patient to have a Karnofsky Performance Status of >50% and a life expectancy of at least 12 weeks. Required prestudy laboratory parameters included WBC of >4,000/mm^3, platelets of >100,000/mm^3, and bilirubin and creatinine values of <2.0 mg%. Patients who had received prior bolus 5FU as well as other chemotherapeutic agents were eligible for this trial. Patients who had received therapy with infusion 5FU or leucovorin were not allowed on study.

All patients had an indwelling venous access device placed at the initiation of therapy. Treatment consisted of 200 mg/m^2 5FU per day delivered continuously by ambulatory infusion devices (Pharmacia-Deltec CADD pumps). LV was given as an i.v. bolus on day 1 of treatment and then weekly as a bolus when patients came for pump refills.

The planned LV dose levels were: level I, 0 (5FU infusion only); level II, 25 mg/m^2 per week; level III, 50 mg/m^2 per week; level IV, 75 mg/m^2 per week; level V, 100 mg/m^2 per week; level VI, 150 mg/m^2 per week; level VII 200 mg/m^2 per week; level VIII, 500 mg/m^2 per week. Because of the toxicity patterns described below, an additional ten patients were added at a dose of 20 mg/m^2

Initially, three patients were entered at each LV dose level, with two patients in the 5FU only group. Three additional patients were to be added at the level determined to be the maximum tolerated dose. A dose

Table 2. Toxicity encountered by leucovorin dose level

	Control: No LV (2 patients)	Level I: 20 mg/m² 10 patients	Level II: 25 mg/m² 5 patients	Level III: 50 mg/m² 5 patients	Level IV: 75 mg/m² 5 patients
Leukopenia:					
Grade I (AGC <1,500)	0	0	0	1	1
Grade II (AGC <1,000)	0	0	0	0	0
Nausea/vomiting:					
Grade I	0	0	0	0	0
Grade II	0	1	0	0	1
Stomatitis:					
Grade I	0	2	0	0	0
Grade II	0	7	4	5	4
Grade III	0	0	0	0	1
Diarrhea:					
Grade I	0	1	0	1	0
Grade II	0	1	1	1	0
Grade III	0	0	1[a]	0	0
Dermatitis (Hand-foot):					
Grade I	0	1	1	0	0
Grade II	0	2	1	2	3
Able to tolerate treatment for at least 4 weeks continuously	2/2	7/10	4/5	2/5[b]	0/5[c]

LV, leucovorin; AGC, absolute granulocyte count

[a] progressive pelvic disease on therapy

[b] 2 additional patients tolerated at least 4 weeks of treatment with an LV dose reduced to 25 mg/m²

[c] 3 additional patients tolerated at least 4 weeks of treatment with an LV dose reduced to 25 mg/m²

Total number of patients receiving 20 or 25 mg/m² LV who could continue therapy for at least 4 weeks: 18/25 = 72%

was to be considered to be tolerable if treatment with 5FU could be continued uninterrupted for a minimum of 4 weeks.

No treatment break was scheduled. Patients were monitored weekly for clinical and hematologic toxicity. Treatment was to be interrupted if the patient developed granulocyte or platelet counts of <1000/mm³ or <75,000/mm³, respectively. Treatment was also to be interrupted if the following clinical parameters were found: grade II stomatitis or diarrhea, grade II nausea and vomiting (SWOG criteria), clinically symptomatic hand foot syndrome (defined as redness and burning of the hands or feet to the point of functional disability), anginal chest pain or cerebellar ataxia.

Hematologic abnormalities were to return to baseline and clinical symptoms were to entirely remit before reinstitution of treatment. Initial dose adjustments were not made for 5FU but were provided for the modulator, LV.

Chemistry panels and carcinoembryonic antigen (CEA) levels were drawn every 4 weeks, and tumor measurements were recorded for palpable tumors. Computerised tomographic (CT) scans and chest radiographs for measurement or evaluation purposes were performed at the initiation of therapy and every 8 weeks on study thereafter. Patients were maintained on study until disease progression was documented.

Demographics. Of the 36 patients entered, 9 were inevaluable, as they died or were removed from study due to disease progression prior to completion of 4 continuous weeks of therapy. In retrospect, most of these patients failed to meet the protocol criteria for performance status and/or life expectancy. All nine patients received one or two courses of their prescribed therapy. Grade I stomatitis was seen in four. Reasons for removal from study included institution of radiation for cord compression or control of bleeding (4), bowel obstruction (2), repeated biliary stent sepsis without myelosuppression (1) and death due to hepatic failure within 4 weeks of study entry (2). None of these patients died as a result of treatment.

Table 1 delineates the study population. The median age was 63 years (range 49–73 years). In all, 16 patients had colorectal cancer, 9 had pancreas cancer, 1 had gastric and 1 duodenal cancer. The site of evaluable disease was the liver in 17, the pancreas in 4, the peritoneum/retroperitoneum/pelvis in 4, and the lung in 2. Of the evaluable 27 patients, 10 (37%) had received prior therapy. All of the prior regimens had included bolus 5FU either alone, with other chemotherapeutic agents, or with radiation.

Treatment results

Both patients treated at level I (5FU only) tolerated a minimum of 5 months of uninterrupted therapy (20 and 23 weeks). Four of the five patients at level II (25 mg/m² LV) could complete at least 4 weeks of uninterrupted 5FU infusion without adjustment of the LV dose.

The first three patients treated at level III (50 mg/m² LV) tolerated 5, 4, and 3 weeks of therapy at their starting dose. At level IV (75 mg/m² LV), no patient managed to tolerate 4 weeks of 5FU with the LV. At this point, three additional patients were treated at level III. As each of

these patients developed grade II toxicity before 4 weeks of protracted 5FU and LV could be administered, a lower LV dose was instituted. Ten patients were entered at an LV dose of 20 mg/m^2; seven (70%) could continue therapy with 5FU and LV for at least 4 weeks without interruption.

Five of the ten patients entered at levels III and IV were subsequently capable of tolerating 4 weeks of therapy when the dose of LV was reduced. Thus, 18 of the 25 patients on study who received LV (72%) could tolerate at least 4 weeks of therapy with a minimum LV dose of 20 mg/m^2. With an appropriate rest period for resolution of stomatitis, LV was reintroduced at a reduced dose and therapy was again maintained.

Toxicity

Table 2 summarizes the laboratory and clinical toxicity. The median nadir granulocyte count was 3,200/mm^3 (range, 1,500–6,400/mm^3), and the median platelet nadir was 270,000/mm^3 (range, 87,000–376,000/mm^3). Only 2 of 27 patients developed a granulocyte count of <2,000/mm^3, and only 1 patient had a platelet count of <100,000/mm^3.

All but two patients experienced stomatitis as their limiting toxicity. The pattern that emerged from this study was that higher doses of LV produced higher grades of stomatitis at a shorter duration of 5FU infusion. Generally, the stomatitis was limited to the lower lip, with less frequent gingival involvement. Although uncomfortable, it rarely interfered with daily activity, and in no case producing weight loss, bleeding or infection and typically resolved within 1 week. Mucositis did not predict for diarrhea, abdominal pain, or nausea and vomiting.

One patient developed grade III diarrhea; she had a pelvic recurrence of her rectal cancer, which progressed on therapy. It could not be clearly determined whether her diarrhea was related to treatment or to her disease process.

Hand-foot syndrome occurred in 10 of the 27 patients and occurred earlier in the course of therapy than commonly seen with prolonged infusion of 5FU alone. Progression to disability was averted by planned interruption of treatment. Other toxicities included a nonpainful, nonpruritic erythematous papular rash of the forearms or malar-temple areas (3), conjunctivities (3), and epistaxis (2). Most patients experienced only mild fatigue, and continued with work or other normal daily activities throughout treatment.

Disease response

In all, 19 patients had measurable disease; eight had only evaluable disease. Of 19 patients with measurable disease 8 (42%) had partial responses (PRs, defined as a decrease of at least 50% in the perpendicular diameters of the measurable lesions without progression of disease elsewhere). All of these patients also exhibited at least a 50% decrease in CEA from pretreatment levels, when these values were available. Of the eight patients exhibiting PRs, four had previously been treated with bolus 5FU. Partial responses were seen in the liver (6 patients), pancreas (1) and lung [1 patient who had a complete response by chest radiograph, but small tumors remained on the CT scan of the thorax]. Their median duration was 23 weeks.

Two patients had tumor regressions of >50% of the perpendicular diameters of the measurable lesions and were coded as minor responses (MR). Eight patients, six of whom had evaluable disease, had "stable disease" (SD) while on treatment, that is no change in evaluable parameters. The median duration of MR and SD was 24 weeks. Of these 11 patients, 8 (73%) had CEA levels that decreased by 50% of their on-study value. For the 27 evaluable patients, the overall median time on study was 19 weeks. Table 1 outlines the characteristics of the responding patients.

Discussion

The purpose of this clinical study was to determine a tolerable dose of LV for modulating 5FU given as a prolonged infusion and determining patterns of toxicity. The dose of 5-FU was based upon our previous experience as well as that reported by others [13, 18, 22]. The starting dose of LV chosen was that reported by Bruckner et al. [5]. Incremental LV doses of were chosen to discriminate for toxicity with the PI schedule up to the level of 200 mg/m^2/week, the most commonly reported dose in published series [9]. Had we reached this level, we planned to examine the high dose of LV (500 mg/m^2) recommended by Madajewitz et al. [17]. We showed however, that when the PI 5FU schedule is used, dose limiting toxicity occurs at a much lower LV dose.

Higher weekly doses of LV with PI 5FU could have been attained by reducing the 5FU dose or decreasing the infusion duration. Both Ardalan et al. [1] and Leyland-Jones and O'Dwyer [14] have stated that the goal of "modulator-effector trials" is to give the maximal dose of the effector drug [1, 14]. We have previously reported a PR rate of >30% in patients with measurable colon cancer who received p.i. 5FU at 200 mg/m^2, the dose used in the present study [13]. Therefore, we chose to adjust the dose of LV for toxicity. A 4-week course was selected as being comparable with Phase I studies of PI 5FU alone, as well as with individual courses of other single agent 5FU or 5FU-LV schedules for evaluation of both toxicity and response rates.

The increased dose intensity of 5FU per unit time (4 weeks) may account for the apparent response advantages found in the PI 5FU studies. Over a 4-week period, PI 5FU delivers 5,600 mg/m^2 vs 2,400, 2,500, and 4,000 mg/m^2, respectively, for weekly bolus, daily times five and monthly infusion schedules. Alternatively, the efficacy of the PI regimen of 5FU may be due to maintenance of a constant level of drug to "capture" infrequently dividing cells. If lowering the dose or decreasing the infusion time of 5FU results in toxicity equal to that achieved by decreasing the LV dose, it seemed logical to us to keep the 5FU dose constant and lower the dose of LV.

Our results indicate that PI of 5FU at 200 mg/m^2 daily × 4 weeks with LV 20 mg/m^2 given as a weekly bolus

produces safe modulation of 5FU with predictable and acceptable toxicity. The development of such toxicity has been a hallmark of previous infusion treatments and has indicated that enough 5FU has been given to achieve a biologic (and antitumor) effect.

That this relatively modest dose of weekly LV can mqdulate PI 5FU toxicity is evident from an examination of the differences among the escalating (and finally de-escalating) doses of LV and from their comparison with the control values in this study. Although there were only two patients in this trial who received 5FU alone, their duration of treatment and toxicity pattern were expected, based on our previous experience. Patients treated with PI 5FU at 200 mg/m^2 without LV will usually tolerate several months of uninterrupted therapy before developing toxicity [13]. With weekly LV, toxicity occurred much earlier (4 vs 20 weeks). Hand-foot syndrome, the usual dose limiting toxicity of long term PI 5FU, was replaced by acute stomatitis as the treatment-limiting toxicity of this regimen.

The stomatitis tended to predominate on the lower lip and to be less diffuse and debilitating than that encountered with short-term, high-dose 5FU infusions. Dose limiting or life-threatening diarrhea, which has occurred in trials of weekly bolus 5FU with high dose LV, was not observed in this trial.

Critical questions remain to be answered. Does this treatment yield a response advantage over other 5FU-LV regimens or over the PI 5FU alone? Is the anti-tumor acion of the PI 5FU different from the bolus therapy? Does the addition of leucovorin overcome absolute or innate tumor resistance or simply improve efficacy by overcoming relative tumor resistance through increased effective FdUMP binding? Is the improved response observed with the inclusion of LV in 5FU regimens solely related to greater 5FU toxicity?

The current experience clearly documents biological effects of the addition of weekly LV at 20 mg/m^2 to PI 5FU. This consistent evidence of modulation by a low dose of LV, coupled with the identification of a safe, reversible endpoint makes this dose and schedule ideal for further phase III studies. The latter are being planned by the Southwest Oncology Group, whereas additional phase II experience is being obtained in gastrointestinal, renal and breast cancers at our institution.

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