

# Reevaluation of the Maximum Tolerated Dose of Continuous Venous Infusion of 5-Fluorouracil with Pharmacokinetics

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## ABSTRACT

5-Fluorouracil (5-FU) was administered as a continuous ambulatory venous infusion to 25 patients in a Phase I trial. The principal dose limiting toxic effect observed was mucositis. Skin rash and diarrhea occurred less frequently. Hematological toxicity was modest, and no hepatic toxicity was seen. One partial remission of 138 days duration was seen in a patient with metastatic breast carcinoma who was previously refractory to a 5-FU combination regimen. Patient tolerance of 5-FU delivered in this manner appeared highly variable. On the basis of this trial, we recommend that future studies evaluating the efficacy of long-term venous infusion of 5-FU should utilize a dosage of 450 mg/m<sup>2</sup>/day.

## INTRODUCTION

The fluorinated pyrimidine, 5-FU,<sup>2</sup> is an antimetabolite which is used frequently in the treatment of gastrointestinal, breast, and genitourinary malignancies. A number of schedules of drug administration have been evaluated. Infusion therapy shifts the usual limiting toxicity from myelosuppression to mucositis. We have undertaken a formal Phase I evaluation of infusion 5-FU as the initial stage of a project to determine whether infusion therapy is an advantage to the patient either for reduced serious toxicity, increased efficacy, or flexibility in combination treatment.

Sullivan *et al.* (1) reported in 1960 the use of 24-h infusions at dosages of 15 to 40 mg/kg/day. In his series 4 patients received 5-FU at dosages of 14 to 15 mg/kg/day for 27, 36, 37, and 38 days. None of these patients developed mucositis and one patient developed mild leukopenia (WBC 3500/mm<sup>3</sup>). In 1981 Lokich *et al.* (2) reported the results of a Phase I trial of continuously administered 5-FU over a 30-day period and found the dose limiting toxicity to be oral mucositis. All patients treated at dosages above 300 mg/m<sup>2</sup>/day developed mucositis within 20 days.

While definitive randomized trials comparing the efficacy of protracted ambulatory infusion of 5-FU with more conventional routes of administration are not available, the objective response rate initially reported by Lokich (3) is promising. The discrepancy between Sullivan's data suggesting 500 mg/m<sup>2</sup>/day as the MTD and Lokich's MTD of 300 mg/m<sup>2</sup>/day and the lack of pharmacokinetic data led us to conduct a Phase I trial at increments between these two levels in preparation for formal efficacy trials.

## MATERIALS AND METHODS

**Patient Selection and Evaluation.** Twenty-five patients treated at the University of Southern California Comprehensive Cancer Center were entered into a Phase I trial to evaluate the MTD of continuously infused

Received 7/21/87; revised 10/13/87; accepted 10/16/87.

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<sup>2</sup> The abbreviations used are: 5-FU, 5-fluorouracil; MTD, maximal tolerated dose.

5-FU. Patients were considered eligible who had histologically confirmed solid tumors for which they had previously received or for which there was no available alternative treatment of established greater efficacy. All patients had evaluable or measurable disease, a Karnofsky performance status  $\geq 60\%$ , and an estimated life expectancy of at least 12 weeks (4). All had signed informed consent and had received no chemotherapy or radiotherapy within the preceding 4 weeks. In addition all patients had adequate hepatic function (bilirubin  $< 3.0$  mg/100 ml and aspartate aminotransferase  $< 2$  times normal), and bone marrow function (WBC  $\geq 3,000/\text{mm}^3$  and platelets  $\geq 100,000/\text{mm}^3$ ). Complete history, physical examination, chemistry panel, urinalysis, complete blood count, and platelet count and evaluation of the extent of tumor (using appropriate investigations) were required prior to study entry. Toxicity documentation, complete blood count, and platelet count and liver function studies were evaluated weekly while patients were receiving therapy.

**Treatment Method.** At the time of study entry all patients underwent insertion of a central venous catheter for drug administration. The calculated dose of 5-FU was administered utilizing an ambulatory infusion pump mixed with a daily heparin dose of 5000 units.

Mucositis was scored as Grade II if it was patchy but the patient was able to eat. Grade I and II diarrhea were defined as less than 3 stools/day, and watery as 4-7 stools/day, respectively.

In the event of Grade II or greater toxicity, treatment with 5-FU was discontinued and the line was maintained by twice weekly heparin flush. Following resolution of side effects treatment was resumed at a dose of 67% of the dose that produced toxicity.

At least three patients were entered at each dosage level (300, 350, 400, 450, and 500 mg/m<sup>2</sup>/day) and the toxicity during and following the proposed 28-day infusion was observed before proceeding with the next level evaluation. When Grade II toxicity was encountered 5 or 6 patients were entered at that dosage level to determine the frequency of moderate toxicity.

**Pharmacokinetic Analysis.** A 10-ml heparinized blood sample was obtained prior to administration of 5-FU and was obtained thereafter on a weekly basis. The plasma was immediately separated and frozen at  $-20^\circ\text{C}$  until analysis. Separation of 5-FU was achieved on a Model 6000A solvent delivery system, a Model U6K universal injector (Waters Associate, Milford, MA, USA), and a Model 5F-720 spectroflow monitor (Schoeffel Instruments, Westwood, NJ). Peak areas, retention time, and concentrations based on standards were calculated with a Model 720 system controller and a Model 730 data module (Waters Associates, Milford, MA). Procedures for the extraction of 5-FU from plasma and its subsequent separation on high-pressure liquid chromatography were as described by Buckpitt *et al.* (5).

## RESULTS

Twenty-five patients were entered into this protocol of whom 24 were fully evaluable for toxicity. One patient was removed from study after 5 days for unrelated medical problems. There were 15 females and 10 males whose mean age was 53 years. The mean Karnofsky performance status was 70%. Patients' primary tumor diagnoses are summarized in Table 1. One partial response consisting of a  $> 50\%$  reduction in the products of the perpendicular measurements of chest wall and lymph nodes was seen at the 450-mg/m<sup>2</sup>/day level in a patient with metastatic breast cancer who had previously received 5-FU.

Toxicity. Oral mucositis was the most frequent toxicity noted

Table 1 Primary tumor diagnosis

	No.
Adenocarcinoma of unknown origin	2
Bladder carcinoma	2
Breast carcinoma	6
Colorectal carcinoma	7
Renal carcinoma	1
Adenocarcinoma of lung	1
Prostatic carcinoma	3
Osteogenic sarcoma	1
Gastric carcinoma	2
Total	25

Table 2 Mucositis and diarrhea as toxic events

Level	No. evaluable	Toxicity type	Toxicity grade	Mean onset (days)	Mean cumulative dose (g/m <sup>2</sup> )
350	6	Diarrhea	II	12	4.2
		Mucositis	II	29	10.2
		Mucositis	II	46	16.8
400	5	Diarrhea	I	15	6.0
500	7	Mucositis	II	7	3.4
		Mucositis	III	7	3.5
		Mucositis	II	14	7.0
		Diarrhea	I	14	6.6
		Mucositis	II	19	9.5
		Diarrhea	II	31	15.5

and occurred in 6 patients, including 2 patients at the 350-mg/m<sup>2</sup>/day level and 4 patients at the 500-mg/m<sup>2</sup>/day level (Table 2). The mean time to onset of mucositis was 37 days at the 350-mg/m<sup>2</sup>/day level with a mean cumulative dosage of 13.1 g/m<sup>2</sup>, while for the 500-mg/m<sup>2</sup>/day patients the mean time to onset was 12 days with a mean cumulative dosage of only 6 g/m<sup>2</sup>. For all patients experiencing mucositis there was complete resolution within 7 to 14 days of discontinuing therapy with 5-FU.

Grade I diarrhea occurred in 2 patients. In one it occurred on Day 15 at the 400-mg/m<sup>2</sup>/day level and resolved despite continued therapy at the same dose. Two patients developed Grade II diarrhea, one each at the 350- and 500-mg/m<sup>2</sup>/day levels, on Treatment Days 12 and 31, respectively. In both patients the diarrhea resolved within 7 days off treatment and did not recur with retreatment at a dose of 67% of the initial.

Leukopenia was noted in 4 patients. A WBC of 2800/mm<sup>3</sup> occurred in one patient at both the 350- and 400-mg/m<sup>2</sup>/day levels at Days 49 and 33, respectively. A Level 1 patient's WBC ranged from 2200 to 3000/mm<sup>3</sup> despite continued therapy. A WBC of 1300/mm<sup>3</sup> occurred at Day 25 in one patient at the 500-mg/m<sup>2</sup>/day level, which returned to normal within 14 days off therapy.

**5-Fluorouracil in Plasma.** Patients were treated with 300 to 500 mg/m<sup>2</sup>/day of 5-FU daily as a continuous protracted infusion. At the above dosages of 5-FU, plasma concentration of 0.7–1.4 ng/ml or 5.3–11.2 nM was achieved. At the steady state, *i.e.*, 24 h after the initiation of therapy, there was a linear correlation between the dose of 5-FU administered and the plasma concentration attained (Fig. 1).

## DISCUSSION

The use of fluorinated pyrimidines via an infusion schedule should be explored for the potential for augmenting antitumor activity and reducing toxicity. From a theoretical standpoint, the antineoplastic activity of an antimetabolite with a short half-life could be increased by protracted infusion, inasmuch as

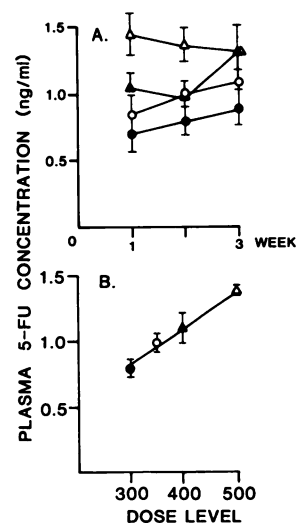


Fig. 1. Plasma 5-FU concentration at 300 mg/m<sup>2</sup>/day (●), 350 mg/m<sup>2</sup>/day (○), 400 mg/m<sup>2</sup>/day (△), and 500 mg/m<sup>2</sup>/day (Δ). A, during first 3 weeks of therapy, a steady state is achieved; B, a linear relationship exists between 5-FU dose and plasma concentration.

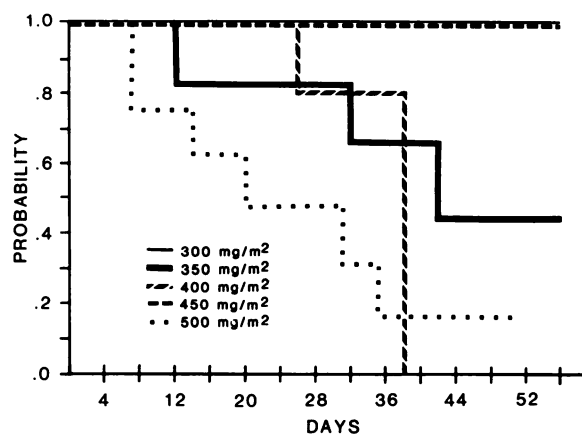


Fig. 2. Probability of remaining on treatment with continuously administered 5-FU.

only a small proportion of tumor cells are in the sensitive phase of the growth cycle at any time. Alterations in the pattern and severity of toxicity with infusions have been previously well described (6–8). In the earliest report of extended 5-FU administration Sullivan found that 15 mg/kg/day could be administered for periods of up to 38 days without significant toxicity (1). At dosages above that he found stomatitis or diarrhea to be dose limiting. In a recent reevaluation of this method of administration Lokich (2) found a substantially lower MTD. In the present trial all 3 patients at 300 mg/m<sup>2</sup>/day, 5 of 6 patients at 350 mg/m<sup>2</sup>/day, 4 of 5 patients at 400 mg/m<sup>2</sup>/day, 3 of 3 patients at 450 mg/m<sup>2</sup>/day, and 3 of 7 patients at 500 mg/m<sup>2</sup>/day were able to tolerate 28 days of continuous treatment. While the number of patients treated at each level is small, a probability curve was developed for each treatment level (Fig. 2). Estimating from these data, 80% of patients who received dosages of less than 500 mg/m<sup>2</sup>/day could be expected to complete 28 days of therapy without experiencing dose limiting toxicity.

While mucositis appears to be the usual dose limiting toxicity associated with continuously administered 5-FU, it is important to note the wide variability in patient sensitivity. For instance 3 patients at the 500-mg/m<sup>2</sup> level received doses of 15.5, 17.5, and 23.7 g/m<sup>2</sup> over 31, 35, and 49 days, respectively, without



Fig. 3. Facial skin rash in patient receiving continuous-infusion 5-FU.

developing mucositis. Thus even at the 500-mg/m<sup>2</sup> level mucositis was dose limiting in only 4 of 7 patients. Analysis of variables including age, performance status, pretreatment alkaline phosphatase, albumin, total bilirubin, aspartate aminotransferase, and serum 5-FU levels were not related to development of mucositis (*t* test, Wilcoxon signed rank test).

Hematological toxicity was not dose limiting; however, four patients developed mild leukopenia. The absence of significant leukopenia has also been noted in patients receiving 5-FU in 5-day infusion schedules. It has been suggested that this is related to low levels of the agent in the bone marrow of infusion treated patients (9), or to a drug-induced resistance in the bone marrow cells (10).

Diarrhea is a frequent side effect of 5-FU when administered as a bolus; however, it is observed less frequently when 5-FU is given on a 5-day infusion schedule. Lokich reported no diarrhea in his Phase I trial; however, in Sullivan's work diarrhea occurred frequently as a dose limiting toxicity at dosages above 15 mg/kg/day. In the present series diarrhea occurred in two patients.

A peculiar cutaneous toxicity has been reported previously in patients receiving protracted ambulatory infusions of 5-FU and consists of paresthesias, swelling, and erythema of the distal fingers and toes (11). One patient in the present series developed an erythematous papular tender rash involving the soles of the feet and face on Day 56 at the 350-mg/m<sup>2</sup>/day level (Fig. 3). Two additional patients experienced similar rashes involving the hands, one on Day 25 at the 400-mg/m<sup>2</sup>/day level and a second on the 450-mg/m<sup>2</sup>/day, level at Day 90. These lesions

resolved over a 2-week interval off treatment but recurred on subsequent courses of therapy.

Recently the importance of 5-FU dose and duration of drug exposure were explored in established cell lines of human colon carcinomas by Drewinsko *et al.* (12). Exposure of LOVO cells to 5-FU at 1 µg/ml for 1 h did not inhibit cell growth or the colony formation. By extending the duration of drug exposure to 72 h, the cell count and colony formation were >50% inhibited. In LOVO cell line, 1 h exposure was effective only when >100 µM concentrations of 5-FU were used, such high concentrations of the agent are obviously not feasible in the clinical setting. Moreover, it is important to note that in our study the steady-state concentration of 5-FU is in the range of 5–11 nM; this is well below the concentrations of 5-FU which have been tested previously *in vitro*. We have recently exposed LOVO cell line *in vitro* to 10 nM 5-FU from 1 to 72 h and noted the absence of any cytotoxicity at this dose in this system. Lokich *et al.* in a phase II study using lower dosage of 5-FU *i.e.*, 300 mg/m<sup>2</sup>/day, have shown an approximately 30% response rate in patients with colorectal cancers. The probable plasma concentration of 5-FU achieved at 300 mg/m<sup>2</sup>/day is approximately 0.7 ng/ml which corresponds to the initial level of our current study. While Lokich *et al.* have reported a promising response rate in patients with advanced gastrointestinal malignancies, definitive evaluation of the efficacy of this approach is lacking. On the basis of the current trial, future studies evaluating the efficacy of long-term venous infusion of 5-FU should utilize an initial dosage of 450 mg/m<sup>2</sup>/day.

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*Cancer Res* 1988;48:459-461.

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