

# Modulation of 5-Fluorouracil Toxicity by Allopurinol in Man

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Oxipurinol, the major metabolite of allopurinol, decreased the toxicity of 5-fluorouracil (5-FU) to human granulocyte colony-forming units *in vitro* by a factor of four. The ability of allopurinol to reduce 5-FU toxicity *in vivo* was studied in 23 advanced cancer patients during 42 courses of treatment. 5-FU was administered by continuous intravenous infusion for five days; allopurinol, 300 mg, po, every 8 hours was started 2 hours before and continued during and for 24 hours after 5-FU infusion. 5-FU was escalated from 1.5 to 2.25 g/m<sup>2</sup>/day on separate courses; the dose-limiting toxicity was mucositis which occurred at a level of 2.0 g/m<sup>2</sup>/day. At a 5-FU dose rate of >2.0 g/m<sup>2</sup>/day 5-FU pharmacokinetics were nonlinear, reflecting saturation of catabolic pathways, and the steady-state 5-FU serum concentration was approximately 4 times that which was tolerable without allopurinol. At these concentrations of 5-FU oxipurinol significantly influenced the clearance of 5-FU. Thus concurrent allopurinol therapy permitted a doubling of the maximum tolerated dose of 5-FU and a four-fold increase in the tolerated concentration  $\times$  time exposure to 5-FU.

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**A**LLOPURINOL IS A POTENT INHIBITOR of xanthine oxidase,<sup>1,2</sup> and is widely used to control hyperuricemia in gouty subjects, and in patients receiving chemotherapy. Less well recognized is the effect of allopurinol therapy on the activity of orotidylate decarboxylase (ODCase),\* the last enzymatic step in the *de novo* pyrimidine synthesis pathway. In addition to inhibiting xanthine oxidase, allopurinol is itself converted by xanthine oxidase to oxipurinol<sup>3</sup> which is subsequently phosphorylated by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to 1-oxipurinol-5'-monophosphate,<sup>4,5</sup> a potent inhibitor of ODCase<sup>4-7</sup> (Fig. 1). Inhibition of ODCase results in increased urinary excretion of orotidine and orotic acid.<sup>6,8</sup> This is thought to reflect enhanced formation of

orotidine from elevated levels of orotidine-5'-monophosphate, which also causes inhibition of orotate phosphoribosyltransferase and increases the intracellular concentration of orotic acid.<sup>3,6</sup>

In order to produce cytotoxicity, 5-fluorouracil (5-FU) must be converted intracellularly to either fluorodeoxyuridine monophosphate (FdUMP), which is a potent inhibitor of thymidylate synthetase and produces inhibition of DNA synthesis,<sup>9,10</sup> or fluorouridine triphosphate (FUTP) which is incorporated into and interferes with the function of RNA.<sup>11,12</sup> *In vivo*, the first step in the formation of these two nucleotides is the conversion of 5-FU to fluorouridine monophosphate (FUMP) (Fig. 1) which can be mediated by either of two pathways: the sequential action

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\* Abbreviations used in this paper: FdUMP, fluorodeoxyuridine monophosphate; 5-FU, 5-fluorouracil; FUMP, fluorouridine monophosphate; FUTP, fluorouridine triphosphate; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; ODCase, orotidine monophosphate decarboxylase.

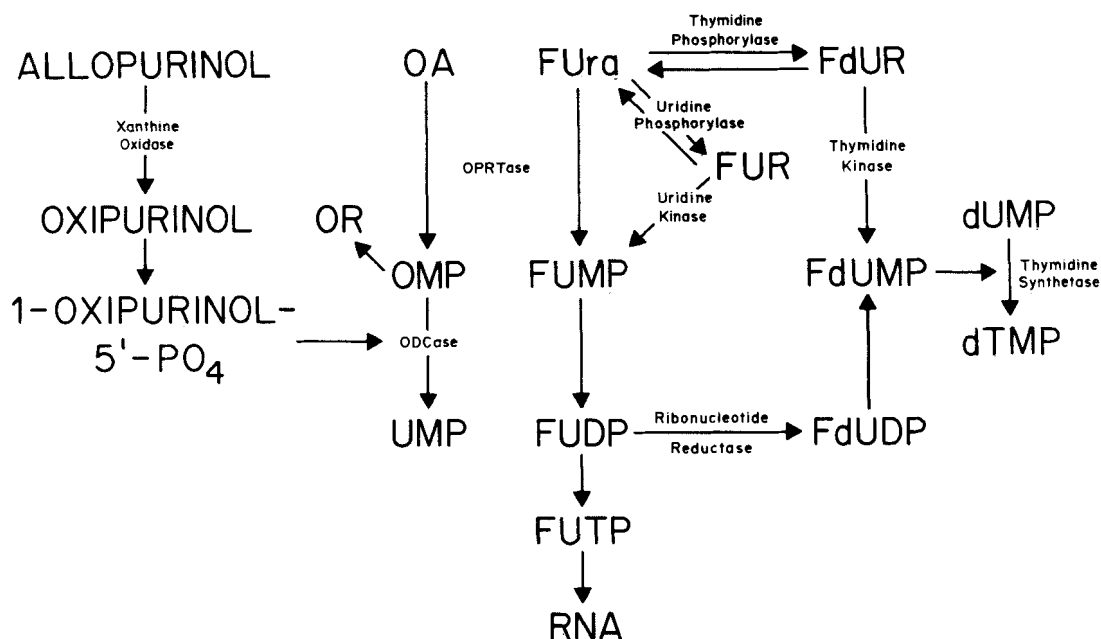


FIG. 1. Pathways of allopurinol, orotic acid, and 5-fluorouracil metabolism. OA, orotic acid; OMP, orotidine monophosphate; OR, orotidine; UMP, uridine monophosphate; FUra, 5-fluorouracil; FUMP, 5-fluorouridine monophosphate; FUDP, 5-fluorouridine diphosphate; FUTP, 5-fluorouridine triphosphate; FdUR, 5-fluorodeoxyuridine; FdUMP, 5-fluorodeoxyuridine monophosphate; FdUDP, 5-fluorouridine diphosphate; dUMP, deoxyuridine monophosphate; dTMP, thymidine monophosphate.

of uridine phosphorylase and uridine kinase, or the direct conversion of 5-FU to FUMP by orotate phosphoribosyltransferase, the same enzyme responsible for converting orotic acid to orotidine monophosphate.

Schwartz and Handschumacher<sup>13,14</sup> have reported that oxipurinol can reduce the toxicity of 5-FU to some cell lines in culture, and that allopurinol can reduce the toxicity of 5-FU to mice and rats while simultaneously improving the therapeutic ratio of 5-FU for some types of murine tumors. The putative mechanism of this effect is that the high concentration of intracellular orotic acid that results from inhibition of ODCase by 1-oxipurinol-5'-monophosphate effectively competes with 5-FU for orotate phosphoribosyltransferase<sup>15</sup> thus decreasing the formation of FdUMP and FUTP. Enhanced selectivity may be expected under conditions where either normal tissues depend primarily on the orotate phosphoribosyltransferase pathway and malignant tissues on the uridine phosphorylase-uridine kinase pathway for activation of 5-FU, or where the activity of orotate phosphoribosyltransferase is substantially higher in malignant tissues, so that when just enough oxipurinol nucleotide is present to block the enzyme in normal tissues, some activity remains in the tumor.

We have conducted a trial to determine whether allopurinol can modulate the toxicity of 5-FU in man. The aim of this study was to confirm the preliminary

report by Fox *et al.*<sup>16,17</sup> which indicated that allopurinol could reduce the toxicity of 5-FU given by continuous infusion for five days, and that the 5-FU/allopurinol combination produced responses in five of ten patients with adenocarcinomas of the gastrointestinal tract.

## Materials and Methods

### Patients

Twenty-three patients with histologically proven cancer who had received and failed all therapies of proven merit, and who had recovered from any toxicity associated with prior therapy, gave their informed consent to enter this trial. Eligibility criteria also required that patients have a serum creatinine <1.5 mg/dl and/or a creatinine clearance of >60 ml/min, white blood count >4000/mm<sup>3</sup> and platelet count >150,000/mm<sup>3</sup>, bilirubin <3 mg/dl, alkaline phosphatase <2-fold increased, serum glutamic-oxalacetic transaminase of <3-fold elevated, and that the patient be able to ingest medications.

### Study Design and Treatment Plan

5-FU was administered intravenously using a constant infusion pump for a total of five days. Allopurinol, 300 mg by mouth every 8 hours, was started

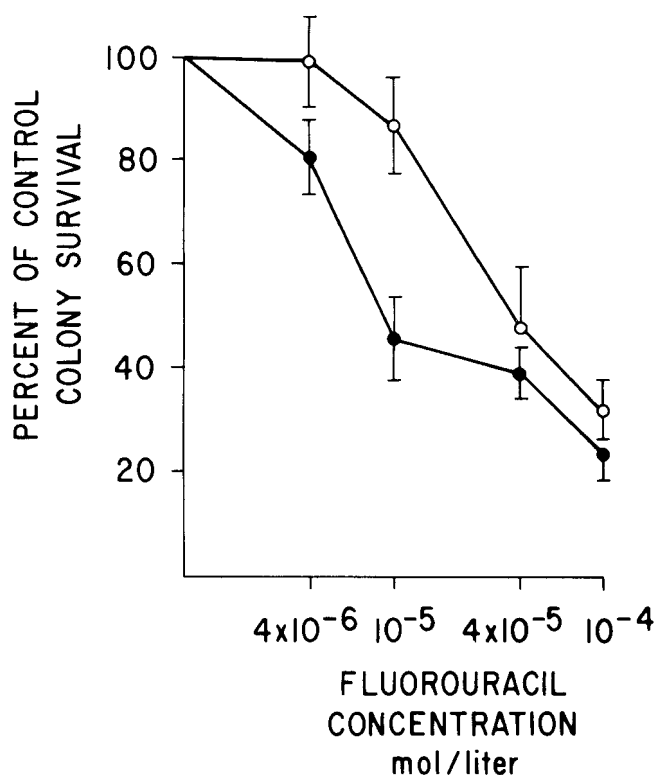


FIG. 2. Toxicity of 5-FU to normal human macrophage/granulocyte colony-forming units in the absence (●—●) and presence (○—○) of  $10^{-4}$ M oxipurinol. Normal human marrow was cultured at  $2 \times 10^5$  cells/ml in methylcellulose with leukocyte conditioned medium for seven days and colonies were counted with an inverted microscope. The 5-FU and oxipurinol were allowed to remain in the culture for the full seven days. Each point represents the mean percent colony survival of triplicate cultures from four experiments ( $\pm$ SEM).

2 hours before the 5-FU infusion and continued for 24 hours after the 5-FU infusion was discontinued. The starting 5-FU dose rate was  $1.5 \text{ g/m}^2/\text{day}$ , and this was escalated both on subsequent courses in the same patient and in new patients to 2.0 and  $2.25 \text{ g/m}^2/\text{day}$ . Treatment was repeated every four weeks; the extent of measurable disease and liver function tests were assessed before each course of therapy. Patients were examined and blood counts were obtained weekly. A partial response was defined as a greater than 50% decrease in the product of perpendicular diameters of measurable lesions. Stable disease was considered to be present when measurable lesions either diminished by less than 50% or increased by less than 25% in the absence of new lesions. Duration of response was considered from the time response was achieved.

#### Bone Marrow Cultures

Human bone marrow was collected in heparin from patients with non-hematologic diseases undergoing routine marrow examination, and the mononuclear cells were separated from other formed elements on a Ficoll-Hypaque gradient (Ficoll/Paque, Pharmacia Fine Chemicals, Piscataway, NJ). After washing three times in alpha medium (Gibco, Grand Island, NY),

cells were cultured at  $2 \times 10^5/\text{ml}$ . Granulocyte/macrophage progenitors (CFU-GM) were grown using a modification of the technique of Iscove.<sup>18</sup> The final culture mixture contained 0.8% methylcellulose, alpha medium with nucleosides, 15% fetal calf serum (Flow Laboratories, Inglewood, CA) and 20% leukocyte conditioned medium, which was prepared according to the method of Iscove.<sup>18</sup> Triplicate 1 ml cultures were incubated at 37 C in 7.5%  $\text{CO}_2$  and aggregates of more than 40 cells were scored as colonies on day 7–10 with an inverted microscope. The composition of colonies was assayed by aspirating individual colonies with fine capillary pipettes, pooling the cells, and preparing cytopspins stained with Wright-Giemsa,  $\alpha$ -naphthyl-esterase, or chloroacetate esterase.

#### Drug Measurements

5-FU, oxipurinol, and allopurinol serum concentrations were measured using a high-pressure liquid chromatographic technique developed in this laboratory and described in detail elsewhere.<sup>19</sup> Serum was deproteinized with 0.1 volume of 4.4 N perchloric acid, and neutralized with 2 volumes of alamine/freon as described by Khym.<sup>20</sup> Twenty  $\mu\text{l}$  aliquots were chromatographed using a Waters Associates high-pressure

TABLE 1. Incidence of Toxicity in Patients Receiving Concurrent 5-FU and Allopurinol

5-FU Dose (g/m <sup>2</sup> )	No. of courses started	No. of patients started	Incidence of toxicity/evaluable courses				
			Mucositis*	Leukopenia†	Thrombocytopenia‡	Rash	Neurotoxicity
1.5	20	16	Grade I—5 Grade II—3 Grade III—2	1/15	0/15	4/15	3/20
2.0	18	13	Grade I—1 Grade II—3 Grade III—8 Grade IV—2	2/14	4/14	10/17	0/18
2.25	4	3	Grade III—4	0/4	0/4	2/4	0/4

\* Grade I = oral pain but no limitation of oral intake; grade II = mild limitation of oral intake; grade III = severe limitation of oral intake; grade IV = no oral intake possible.

† WBC <2000/mm<sup>3</sup>.

‡ Platelets <100,000/mm<sup>3</sup>.

liquid chromatograph and a reverse phase  $\mu$ Bondapak C<sub>18</sub> column (Water Associates, Inc., Milford, MA) under isocratic conditions using a 50 mM phosphate buffer pH 4.60, at a flow rate of 1.5 ml/min for 15 minutes.

## Results

Figure 2 shows the survival of human marrow macrophage/granulocyte colony-forming units (CFU-GM) exposed *in vitro* to 5-FU either in the presence or absence of a clinically achievable concentration of oxipurinol. 5-FU by itself killed 50% of the colonies at a concentration of 9  $\mu$ M. Oxipurinol at a concentration of 100  $\mu$ M increased the concentration of 5-

FU required to achieve 50% colony kill by a factor of approximately 4, indicating that oxipurinol provided some degree of protection, and that in marrow orotate phosphoribosyltransferase accounts for a significant proportion of 5-FU nucleotide formation at clinically relevant 5-FU concentrations.<sup>21</sup>

The toxicity associated with 42 courses of continuous 5-FU infusion for five days given concurrently with allopurinol to 23 patients is outlined in Table 1. The 5-FU dose was escalated from 1.5 to 2.0, and then to 2.25 g/m<sup>2</sup>/day. Mucositis was the dose-limiting toxicity.

Mucositis was graded on a scale of I to IV, with grade I being oral pain but no limitation of oral intake, grade II mild and grade III severe limitation of oral intake, and grade IV no oral intake possible. At a 5-FU dose of 1.5 g/m<sup>2</sup>/day, 20% of the evaluable courses were associated with grade III mucositis. At a 5-FU dose of 2.0 g/m<sup>2</sup>/day, 71% had grade III or greater mucositis, and this increased to 100% at a 5-FU dose of 2.25 g/m<sup>2</sup>/day. When it occurred, mucositis generally appeared on day 6 and lasted an average of six days. In contrast to this mucous membrane toxicity, marrow toxicity was very mild. Leukopenia, defined as a WBC of <2000/mm<sup>3</sup>, occurred on only 9% of the evaluable courses, and thrombocytopenia, defined as a platelet count of <100,000/mm<sup>3</sup>, occurred on only 12% of evaluable courses. Neither leukopenia nor thrombocytopenia were dose-related, and in no case did myelosuppression delay repeated treatment at four weeks. A maculopapular, mildly pruritic skin rash involving mainly the trunk and proximal limbs occurred on 44% of evaluable courses. In all cases this rash responded promptly to discontinuation of allopurinol. In no patient did the rash constitute more than a minor annoyance or prevent retreatment. Nausea was minimal and no vomiting occurred during 5-FU infusion.

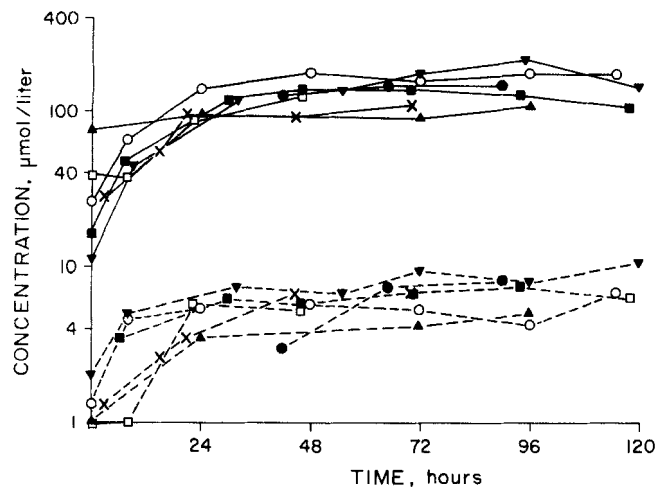


FIG. 3. Serum concentrations of oxipurinol (—) and 5-FU (---) in six patients receiving 5-FU 2.0 g/m<sup>2</sup>/day as a constant intravenous infusion, and allopurinol 300 mg by mouth every 8 hours starting 2 hours before the 5-FU. 5-FU and oxipurinol concentrations were measured by high-pressure liquid chromatography.

There was no cumulative toxicity on repeated courses of therapy. Based on these results the maximum tolerated dose of 5-FU was 2.0 g/m<sup>2</sup>/day.

Three episodes of possible 5-FU-related neurotoxicity occurred during this trial. These occurred only at the lowest 5-FU dose rate, and consisted of a single episode of focal motor seizure activity in one patient, an episode of transient hemiparesis and aphasia lasting less than ten minutes in a second patient, and an acute fluctuating syndrome of brainstem dysfunction followed by recurrent generalized seizures and death in a third patient. Postmortem neuropathologic examination of the latter patient revealed no structural abnormalities in the brain. The only common therapeutic denominator among the three patients, in addition to 5-FU exposure, was that they were all taking phenothiazines. Serial electroencephalograms subsequently performed in three other patients during 5-FU infusion revealed no significant abnormalities.

Figure 3 shows the serum concentrations of 5-FU and oxipurinol as a function of time on six courses of therapy given at a 5-FU dose rate of 2.0 g/m<sup>2</sup>/day. Steady-state was achieved for both 5-FU and oxipurinol by 24 hours, and the geometric mean oxipurinol concentration for the 21 courses on which it was measured was 120 (range 57–180)  $\mu$ M. The allopurinol concentration averaged 4.3 (range 0.6–140)  $\mu$ M (data not shown).

A plot of the steady-state 5-FU serum concentration as a function of dose rate is depicted in Figure 4, and suggests that the relationship was not linear at the higher dose rates. The mean 5-FU concentration during infusion of 1.5 g/m<sup>2</sup>/day was 3.2 (range 0.9–6.5)  $\mu$ M. The 5-FU concentration rose to 5.2 (range 2.9–7.2)  $\mu$ M with infusion of 2.0 g/m<sup>2</sup>/day, and then increased much more rapidly to 12 (range 7.0–28)  $\mu$ M when the 5-FU dose rate was raised to 2.25 g/m<sup>2</sup>/day. Clearance of 5-FU from the blood, shown in Figure 5, was also not linear with dose rate, averaging  $2.2 \pm 0.7$  (SD) L/min/m<sup>2</sup> at an infusion rate of 1.5 g/m<sup>2</sup>/day, and  $2.1 \pm 0.6$  (SD) at 2.0 g/m<sup>2</sup>/day, but dropping by a statistically significant amount to  $1.1 \pm 0.5$  (SD) L/min/m<sup>2</sup> at an infusion rate of 2.25 g/m<sup>2</sup>/day ( $P < 0.05$ ). These observations are consistent with saturation of 5-FU catabolic pathways at 5-FU dose rates above 2.0 g/m<sup>2</sup>/day. The ratio of the renal clearance of drug to that for creatinine in five patients receiving 1.5 g/m<sup>2</sup>/day was 0.99 for 5-FU and 0.28 for oxipurinol, indicating no net secretion or reabsorption for 5-FU, but substantial reabsorption for oxipurinol. At this dose rate renal clearance accounted for only 2.3% of the total 5-FU clearance. In the five patients in whom it

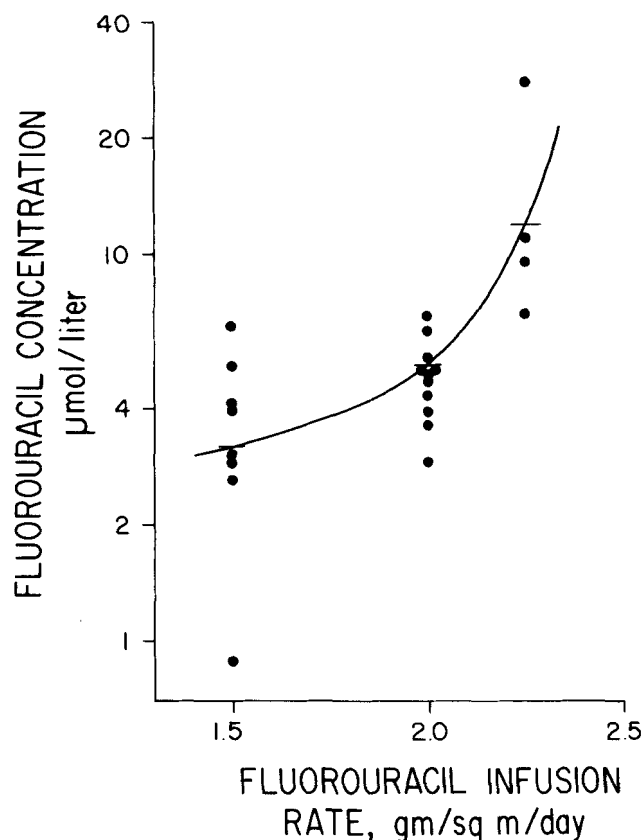


FIG. 4. Steady-state serum 5-FU concentration as a function of 5-FU dose rate. The serum 5-FU was measured by high-pressure liquid chromatograph at 72 hours after the start of a five-day constant infusion of 5-FU at various dose rates. All patients were also receiving allopurinol 300 mg by mouth every 8 hours throughout the period of infusion.

was measured, the dose schedule of allopurinol used in this trial caused a 7.8-fold increase in the urine orotic acid to creatinine ratio, and a 17-fold increase in the orotidine to creatinine ratio by 72 hours after the start of 5-FU infusion.

One might have expected to find that patients who developed mucositis would have either higher steady-state 5-FU or lower oxipurinol serum concentrations. Figure 6 shows a plot of the grade of mucositis versus the steady-state 5-FU and oxipurinol concentrations. Perhaps because the data are limited, there is not a clearly defined relationship between the incidence and severity of mucositis and the serum concentrations of either drug; this may be due to the fact that toxicity reflects differences in events at the cellular level rather than differences in steady-state serum concentrations.

Oxipurinol is not thought to interfere with the catabolism of 5-FU, and at the 1.5 g/m<sup>2</sup>/day infusion rate there was no correlation between steady-state

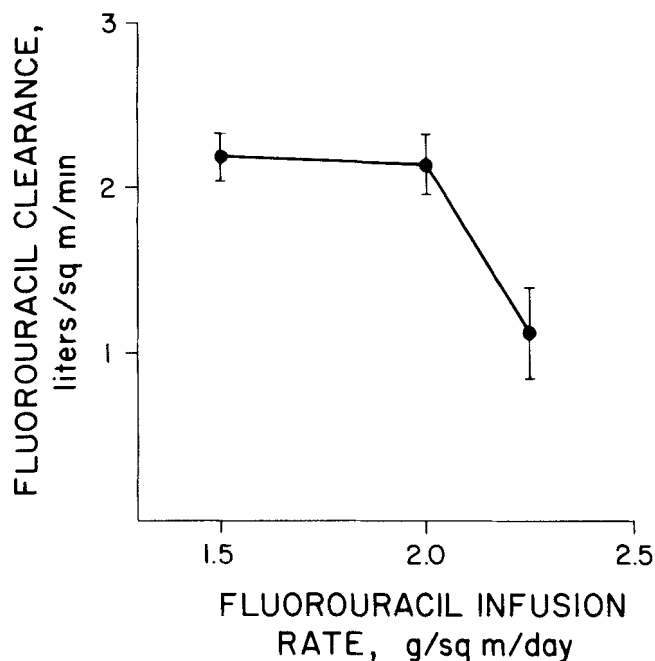


FIG. 5. Mean clearance of 5-FU from the blood ( $\pm$ SD) as a function of 5-FU dose rate in patients receiving a five-day constant infusion of 5-FU at various dose rates, and concurrently receiving allopurinol 300 mg by mouth every 8 hours during the period of infusion. The clearance was calculated as the quotient of the constant infusion dose rate and the steady-state FUra serum concentration measured by high-pressure liquid chromatography.

FUra and oxipurinol concentrations ( $r = 0.07$ ). However, at the higher 5-FU dose rate of 2.0 g/m<sup>2</sup>/day the drug levels were positively correlated with a coefficient of 0.75 ( $P < 0.01$ ). A similar correlation was observed at the 2.25 g/m<sup>2</sup>/day dose rate with a correlation coefficient of 0.51. These results indicate that as 5-FU catabolic pathways become saturated, another pathway sensitive to oxipurinol starts contributing significantly to 5-FU clearance.

Although this was a Phase 1 trial directed mainly at determining the maximum tolerated dose of 5-FU, 21 of the 23 patients were evaluable for response by virtue of receiving at least one course of therapy and having measurable disease. Eleven of the 21 evaluable patients had received prior 5-FU therapy. Table 2 lists the responses by histologic diagnosis: the only significant response in this group of heavily pretreated patients occurred in an individual with chemotherapy-resistant Hodgkin's disease. This, however, was an excellent and very near complete response of bulky disease that was maintained for four months until the patient went off therapy because of generalized Herpes zoster. None of the ten patients with colorectal carcinoma responded.

## Discussion

When administered as a constant five-day infusion without allopurinol, the maximum tolerated dose rate of 5-FU is 30 mg/kg/day<sup>22</sup> or approximately 1.1 g/m<sup>2</sup>/day. The steady-state 5-FU serum concentration associated with this dose rate is 1.2  $\mu$ M,<sup>21</sup> and the limiting toxicity is mucositis with some degree of myelosuppression also manifest in most patients.<sup>22</sup> When 5-FU was administered with allopurinol, the maximum tolerated dose was found to be 2.0 g/m<sup>2</sup>/day, or nearly twice that tolerated in the absence of allopurinol. The average serum concentration of 5.2  $\mu$ M 5-FU that was maintained by this dose rate was, however, approximately four times higher than that tolerated in the absence of allopurinol. Thus the concurrent administration of allopurinol permitted a slightly greater than four-fold increase in the concentration  $\times$  time exposure to 5-FU. The pattern of toxicity associated with 5-FU/allopurinol therapy was the same as that for 5-FU alone given on the same dose schedule, with predominance of mucositis and only mild myelosuppression.<sup>22</sup> Therefore, *in vivo*, allopurinol afforded the same relative degree of protection to both the gastrointestinal epithelium and marrow, indicating that the orotate phosphoribosyltransferase pathway contributes significantly to the activation of 5-FU in both tissues. The success of the combination of 5-FU and allopurinol for the treatment of cancer, however, will depend on differences between normal and malignant tissues in their activity of, or dependence upon, orotate phosphoribosyltransferase for the metabolism of 5-FU to active nucleotides, and such differences remain to be completely identified for human tissues.

Concurrent administration of allopurinol permitted a four-fold increase in 5-FU concentration  $\times$  time *in vivo*, and a concentration of oxipurinol equivalent to that found in the serum of patients receiving allopurinol provided a four-fold degree of protection for human CFU-GM in culture. This correspondence may be purely fortuitous, since in order to grow in culture CFU-GM require unphysiologic concentrations of nucleosides that may potentially alter the cellular pharmacology of 5-FU. However, the sensitivity of CFU-GM in culture correlates well with the *in vivo* sensitivity of marrow for several drugs<sup>23,24</sup> despite the limitations of the assay system.

The results of this trial are in agreement with those of Fox *et al.*,<sup>16,17</sup> who concluded that the maximum tolerated dose of 5-FU was 2.25 g/m<sup>2</sup>/day when given for five days with allopurinol. Their ability to achieve a slightly higher maximum tolerated dose was probably

due to the difference in allopurinol dose schedule. In this study allopurinol was given for 24 hours before the 5-FU infusion was begun. We found that when allopurinol was started 2 hours before 5-FU, steady-state oxipurinol levels were not reached for 24 hours so that suboptimal protection may have been present during the initial portion of the 5-FU infusion. Fox *et al.*<sup>6</sup> found that with conventional doses of allopurinol, urinary excretion of orotic acid and oritidine did not stabilize for 6–8 days after the start of therapy, so that attainment of maximum intracellular levels of orotic acid and inhibition of 5-FU activation by orotate phosphoribosyltransferase may require even longer periods of allopurinol pretreatment.

Three of the 23 patients in this trial, and one of the 20 patients reported by Fox *et al.*<sup>16</sup> had associated neurologic syndromes, which consisted of one or more frank seizures in three of the patients and paresthesias and aphasia possibly due to a seizure in the fourth patient. These symptoms, which were presumed to be due to 5-FU neurotoxicity, are clearly different from the acute cerebellar syndrome which has been reported to occur in a small fraction of patients treated with high dose-rate bolus infusions of 5-FU.<sup>25</sup> The etiologic relationship between treatment with 5-FU and the occurrence of neurotoxic symptoms in the patients in this trial is not clear. None of the three patients had metastatic disease in the central nervous system, and although all three had evidence of pretreatment metabolic abnormalities, neurologic symptoms were inexplicably observed only at the lowest 5-FU dose rate.

The steady-state 5-FU measurements indicate that the clearance of 5-FU from the blood changes with dose rate, and thus that the pharmacokinetics of 5-FU are not linear. Dose-dependent changes in clearance have also been observed for oral,<sup>26</sup> intraperitoneal<sup>27</sup> and bolus intravenous<sup>28</sup> infusion of 5-FU. Variation in clearance with dose rate is consistent with saturation of 5-FU catabolic pathways, and studies in animals have shown that the first step in the degradative metabolism of 5-FU, the reduction of 5-FU to dihydro-5-fluorouracil, is readily saturated.<sup>29,30</sup> The results of this study suggest that the degradative pathway was not saturated at 1.5 g/m<sup>2</sup>/day 5-FU, since only 2.3% of the unchanged drug appeared in the urine at this infusion rate, but that saturation occurred at an infusion rate of about 2.0 g/m<sup>2</sup>/day or serum concentration of about 5 μM.

Previous studies described the pharmacokinetics of 5-FU in terms of one or two compartment models with elimination half-lives varying from 10 to 37 min-

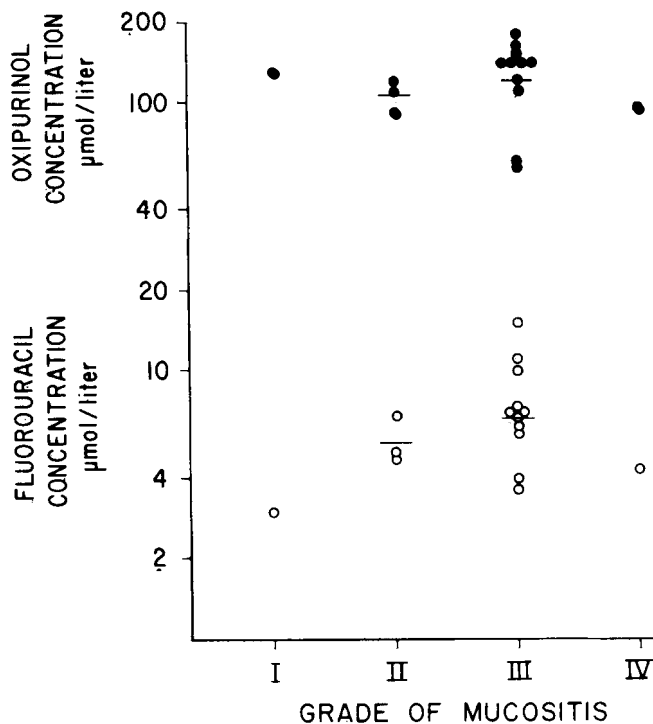


FIG. 6. Relationship between the grade of mucositis and the steady-state oxipurinol (●) and 5-FU (○) serum concentrations in patients receiving a five-day constant infusion of 5-FU at various dose rates and allopurinol 300 mg by mouth every 8 hours during the period of infusion. Mucositis was graded on a scale of I to IV with grade I being oral pain but no limitation of oral intake, grade II mild limitation of oral intake, grade III severe limitation of oral intake, and grade IV being no oral intake possible. 5-FU and oxipurinol serum concentrations were measured by high pressure liquid chromatography. Horizontal bar indicates geometric mean.

utes.<sup>26,28,31–35</sup> Our results provide indirect evidence that there is an additional substantially longer FUra half-life. The time required for a drug to reach steady-state concentration in the serum during constant infusion is a function of its half-life(s), with approach to steady-state being nearly complete after 4–5 half-lives have elapsed.<sup>36</sup> In the six patients in whom they were

TABLE 2. Clinical Responses to 5-Fluorouracil/Allopurinol Therapy

Tumor type	Total patients	Evaluable patients	Response
Colorectal	11	10	2 SD: 3,4 mo
Lung (non-oat cell)	3	2	NR
Melanoma	3	3	NR
Ovarian	2	2	1 SD: 4 mo.
Hodgkin's	1	1	PR: 4 mo.
Astrocytoma	1	1	NR
Breast	1	1	SD: 3 mo.
Adenocarcinoma, unknown primary	1	1	NR

\* PR = partial response; SD = stable disease; NR = no response.

measured, steady-state 5-FU concentrations were not reached for approximately 24 hours after the start of infusion, suggesting an additional half-life in the range of 4–6 hours. Cano *et al.*,<sup>28</sup> using a very sensitive gas chromatographic–mass spectrometric technique for measuring 5-FU, have identified such an additional half-life of approximately two hours in some patients.

The results of this trial also suggest another novel feature of 5-FU pharmacokinetics. Clearance of 5-FU from the blood has been largely attributed to hepatic catabolism.<sup>37,38</sup> The only known site at which oxipurinol affects 5-FU metabolism is at the point of its conversion to the nucleotide level by orotate phosphoribosyltransferase. The observation that at the 5-FU dose rate of 1.5 g/m<sup>2</sup>/day there was no correlation between the serum 5-FU and oxipurinol concentrations is consistent with this single point of action, and indicates that at serum concentrations in the range of 3 μM the conversion of 5-FU to intercellular nucleotides does not contribute significantly to the clearance of 5-FU from blood. However, at 5-FU serum concentrations in the range of 5 μM and greater, the serum 5-FU and oxipurinol concentrations were significantly correlated, suggesting that as the 5-FU catabolic pathway becomes saturated, the movement of 5-FU into cells and its trapping in the form of nucleotides becomes an important component of 5-FU clearance. The finding that allopurinol given at 300 mg every 8 hours can modulate the toxicity of 5-FU raises the question of whether allopurinol given at the more conventional dose rate of 300 mg per day can do the same thing. The peak serum oxipurinol concentration in four patients given a single dose of 300 mg allopurinol was 37 ± 15 μM.† This is only one-third of the 120 μM concentration maintained by the every 8 hour schedule, but whether it is adequate to alter 5-FU activation *in vivo* remains unknown.

Fox *et al.* reported a 50% response for patients with gastrointestinal adenocarcinomas. We were not able to confirm this observation, having achieved no responses in ten patients with colorectal carcinoma. We did, however, obtain an excellent response in a patient with Hodgkin's disease. There is no information on the activity of continuously infused 5-FU alone against lymphomas, and additional patients are required before it can be concluded that this drug combination is either inactive against gastrointestinal adenocarcinomas or uniquely active against lymphomas or other tumor types.

† Howell SB, Wung WE, unpublished observations.

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