A Controlled Evaluation of an Allopurinol Mouthwash as Prophylaxis Against 5-Fluorouracil–Induced Stomatitis

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Pursuant to a promising report suggesting that an allopurinol mouthwash could have a protective effect against 5-fluorouracil (5-FU)–induced stomatitis, the authors performed a randomized, placebo-controlled, double-blind, crossover study. Seventy-seven patients, receiving their first 5-day course of chemotherapy with 5-FU ± leucovorin, were assigned to use a mouthwash containing 20 mg of allopurinol or a placebo. The mouthwash was administered every hour for four doses commencing with each chemotherapy dose. The severity of subsequent mucositis was graded (on a 0–4 scale) by the attending physician and also by a patient-completed questionnaire. There was trend toward less mucositis in the placebo group with mean physician-judged mucositis scores of 1.3 for placebo and 1.8 for allopurinol ($P = 0.07$) and mean patient-judged mucositis scores of 1.5 for placebo and 1.9 for allopurinol ($P = 0.15$). There were no substantial differences in mucositis attributable to the two mouthwashes in the patients who crossed-over on their second cycle of chemotherapy. These data demonstrate that the tested allopurinol mouthwash regimen does not offer any protective effect against 5-FU–induced mucositis. *Cancer* **65:1879–1882, 1990.**

ORAL MUCOSITIS is one of the more frequent toxicities of 5-fluorouracil (5-FU), a commonly utilized drug for patients with a variety of malignancies. Although usually not life threatening, 5-FU–induced oral ulcerations are frequently painful and may interfere with nutrition and quality of life. An effective prophylactic measure for decreasing the incidence of this distressing toxicity would have the potential to significantly enhance patient comfort. It might also allow a greater opportunity for tumor response if higher doses of 5-FU could be safely given.

Clark and Slevin suggested that an allopurinol mouthwash substantially decreased the incidence and severity

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of stomatitis in six patients who experienced stomatitis after their initial exposure to 5-FU.[1] When allopurinol was given in 3% methylcellulose as a mouthwash immediately after, and 1, 2, and 3 hours after, 5-FU administration, stomatitis was not observed in three patients and was significantly lessened in the remaining three patients after a second course of 5-FU at the same dose level. The rationale for the development of this allopurinol mouthwash was based on information suggesting that systemic allopurinol could attenuate 5-FU–induced toxicity by inhibiting the enzyme orotidylate decarboxylase and thereby decreasing the formation of the metabolites fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP).[2–4] However, the precise biochemical mechanism for any effect of allopurinol on 5-FU metabolism has not been clearly defined.

After the above report, the use of an allopurinol mouthwash became incorporated into clinical practice in some institutions.[5,6]

Alternatively, our group decided to determine, by a double-blind study, whether this allopurinol mouthwash therapy could actually alleviate 5-FU–induced mucositis. Before undertaking this study, we demonstrated that there was no significant systemic absorption of this allopurinol mouthwash which might theoretically attenuate the antineoplastic action of 5-FU.[7]

Materials and Methods

This current study utilized patients entered on a clinical trial studying 5-FU ± leucovorin for colorectal cancer. These patients had not received any prior chemotherapy. They were enrolled on this current trial before their first chemotherapy cycle which consisted of 5 consecutive days of either (1) 5-FU, 500 mg/m^2/day; (2) 5-FU, 370 mg/m^2/day plus leucovorin, 200 mg/m^2/day; or (3) 5-FU, 425 mg/m^2/day plus leucovorin, 20 mg/m^2/day. In each regimen both 5-FU and leucovorin were given by rapid intravenous injection. The patients could not be currently taking allopurinol and all patients signed informed consent forms.

The mouthwash solution was prepared by combining allopurinol (450 mg), 150 ml of cologel (450 mg/5 ml methylcellulose with 5% alcohol), and 450 ml of a flavoring agent. The resultant suspension contained 1 mg/ml of allopurinol. The placebo mouthwash utilized the same ingredients minus the allopurinol.

The mouthwash was given on each of the 5 days of 5-FU therapy. Patients were instructed to first coat their lips with the mouthwash, then swish 20 ml of the mouthwash solution in their mouth for 30 seconds and subsequently discard it without swallowing. The mouthwash was administered immediately after receiving 5-FU and at 1, 2, and 3 hours. No oral intake was allowed for at least 15 minutes after each mouthwash.

A double-blind, placebo-controlled study design was employed. Patients were stratified based on their assigned chemotherapy regimen and their age (50 years old and younger *versus* older than 50 years). A dynamic randomization procedure was utilized for assigning patients to initially receive either the allopurinol or the placebo mouthwash. During their second course of 5-FU–based therapy, patients whose chemotherapy had not changed were crossed over, again in a double-blind manner, to receive the alternative mouthwash.

End point evaluations for this study were obtained by two independent mechanisms. The first consisted of routine physician judgment of mucositis severity with ranges from Grade 0 to Grade 4. (NCCTG toxicity guidelines for mucositis during the course of this study were as follows: Grade 0—no toxicity; Grade 1—minimal erythema; Grade 2—diffuse intense erythema [ulceration, if present, is minimal and superficial]; Grade 3—intense erythema with edema or ecchymoses or deep ulceration [able to take soft foods and maintain fluid intake]; Grade 4—intense erythema with edema or ecchymoses or deep ulceration [unable to take food or fluid by mouth].) This physician-judged score was usually assessed by historical means and recorded by the attending physician when the patient returned for evaluation approximately 1 month after treatment initiation, in the manner commonly used in cancer clinical trials. In addition, patients completed questionnaires which allowed them to rate their own degree of mucositis, as none (Grade 0), mild discomfort (Grade 1), definite discomfort but able to eat solid foods (Grade 2), marked discomfort which interfered with eating solid foods (Grade 3), or marked discomfort which prevented taking fluid or food by mouth requiring intravenous feeding (Grade 4). The patients were given a copy of the questionnaire when they entered the trial and were requested to hand it back approximately 1 month later when they returned for evaluation.

Mucositis scores between groups were assessed using a Wilcoxon statistic. Other comparisons, such as the balance of allopurinol treatment across chemotherapy regimens, were assessed with a chi-square test. Early termination considerations were based on a calculation of predictive power.[8]

Results

Seventy-seven patients were entered on this clinical trial; three of whom did not receive all 5 days of chemotherapy (shingles in one patient and allergic reactions attributed to chemotherapy in two patients). All 77 patients were used for our analysis (no substantial differences were seen with the exclusion of the three patients who did not receive full planned 5-FU doses). In addition, 20 patients were studied during their second chemotherapy course according to our crossover design. Patients were

TABLE 1. Stratification Data

	Placebo	Allopurinol
Age		
≤50 yr	6	5
>50 yr	33	33
Chemotherapy regimen		
5-FU	1	3
5-FU + low-dose LV	21	19
5-FU + high-dose LV	17	16
Total	39	38

5-FU: 5-fluorouracil; LV: leucovorin.

well stratified by age and chemotherapy regimens (Table 1).

Physician-judged mucositis grades for the initial cycle of chemotherapy are illustrated in Table 2. The mean physician-judged toxicity grade for the allopurinol mouthwash was 1.8 whereas it was 1.3 for the placebo mouthwash ($P = 0.07$). Results obtained from patient-graded mucositis toxicities were quite similar and are illustrated in Table 3. The mean patient-graded toxicity was 1.9 for the allopurinol mouthwash and 1.5 for the placebo ($P = 0.15$). The mean number of days of mucositis, as judged by patient completed questionnaires, was 7.2 for allopurinol and 6.6 for placebo. Table 4 compares physician and patient toxicity grading in individual patients. Overall, there was a good correlation between these results with a slight tendency for patients to record higher toxicity grades.

Twenty patients on this study received both placebo and allopurinol mouthwashes on separate cycles of chemotherapy (with no change in their chemotherapy doses). Mean mucositis toxicity scores for the two mouthwashes, as judged by both patients and physicians, are illustrated in Table 5. After the second cycle of chemotherapy, patients were asked to judge which cycle of chemotherapy was associated with more mucositis. Eight patients thought the mucositis was worse with placebo, seven thought it was worse with the allopurinol mouthwash, four patients did not believe that there was any significant difference in the amount of mucositis with the two different chemotherapy cycles, and one patient did not answer the question.

TABLE 2. Physician-Judged Mucositis (Initial Cycle Only)

		Placebo	Allopurinol
None	(0)	17	6
Mild	(1)	4	9
Moderate	(2)	8	12
Severe	(3)	10	9
Intravenous feedings	(4)	0	2
Mean score		1.3	1.8

TABLE 3. Patient-Judged Mucositis (Initial Cycle Only)

		Placebo	Allopurinol
None	(0)	10	2
Mild	(1)	9	9
Moderate	(2)	7	11
Severe	(3)	10	9
Intravenous feedings	(4)	1	1
Mean score		1.5	1.9

Questionnaires were not collected on eight patients.

Exploratory analyses did not reveal any relationship between the incidence of mucositis and patient age. In addition, there was no suggestion that the allopurinol mouthwash was preferentially beneficial for any of the three individual chemotherapy regimens.

The original accrual goal for this protocol was 120 patients. Based on a planned interim analysis which showed convincingly negative results, the protocol was closed to patient accrual after 77 patients had been entered. There is less than a 1.5% chance that the allopurinol mouthwash would have shown a significant protective effect against 5-FU–induced mucositis had we continued patient accrual to our original goal of 120 patients.[8]

Discussion

As noted in the introduction, a small pilot study suggested that an allopurinol mouthwash beneficially influenced 5-FU–induced stomatitis in six of six patients.[1] The current protocol was designed to replicate the procedure used by these authors in order to delineate by a randomized, double-blind clinical trial whether this allopurinol mouthwash was helpful. Both studies used virtually identical allopurinol mouthwash concentrations, doses, and schedules. Unfortunately, the results of our controlled study are convincingly negative.

Another recently reported pilot study suggested that an allopurinol mouthwash alleviated 5-FU–induced stomatitis in 16 of 16 patients.[9] This study used a many fold higher allopurinol mouthwash concentration and involved patients who were receiving 5-day intravenous 5-FU infusions (as opposed to daily bolus doses employed in the

TABLE 4. Patient *Versus* Physician Mucositis Grades

	Patient score				
	0	1	2	3	4
Physician score					
0	10	6	3	1	—
1	2	7	3	—	—
2	—	4	11	3	1
3	—	1	1	15	—
4	—	—	—	—	1

TABLE 5. Crossover Data (n = 20)

	Placebo	Allopurinol
Physician-judged mucositis (mean)	1.0	1.3
Patient-judged mucositis (mean)	1.4	1.5
Patient-recorded days of toxicity	5.4	5.7

above two studies) with the mouthwash being administered four to six times per day and retained in the oral cavity for 5 minutes each time. This represents a situation very different from the one we studied. It, too, should be further evaluated by controlled clinical trial before it is incorporated into routine clinical practice. In addition to defining whether this procedure actually decreases mucositis, it also should be determined whether this higher dose of allopurinol results in systemic levels of allopurinol or its metabolite, oxypurinol, as these theoretically may attenuate 5-FU antitumor activity.[2-4]

One difference between the present trial and the two above-mentioned pilot studies is that the majority of patients in the current trial received leucovorin to potentiate 5-FU activity. In addition to improving the response rate and survival in patients with advanced colorectal cancer, leucovorin does increase the incidence of stomatitis.[10] It might be expected that this would have better illustrated any protective effect that allopurinol might have. Although it is conceivable that an allopurinol mouthwash might inhibit mucositis induced by 5-FU alone (as opposed to 5-FU plus leucovorin), there is no convincing evidence for this. In addition, the improved response rates and survivals reported when leucovorin is added to 5-FU[10] has changed the standard of practice so that patients with colorectal carcinoma are now commonly treated with 5-FU plus leucovorin.

At this time, 5-FU–induced stomatitis continues to be a prominent clinical problem with no known, reasonable, adequately documented preventive therapy. Development of an antidote for this toxicity remains a laudable goal. The methodology described in this manuscript can be utilized for the evaluation of other promising preventive treatments for chemotherapy-induced mucositis. Currently, based on some early promising but uncontrolled pilot data, we are involved in a randomized trial to test whether mouth cooling with oral ice chips can decrease 5-FU–induced mucositis in much the same manner that cryotherapy can diminish chemotherapy-induced alopecia.[11]

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