Abstract. Background: Stomatitis in cancer chemotherapy manifests with pronounced subjective symptoms, lowers the patient's quality of life (QOL) and may necessitate the discontinuation of chemotherapy. There have been few effective therapies established to date for chemotherapy-induced stomatitis. Patients and Methods: We used frozen allopurinol solution (allopurinol ice balls) in the prevention of stomatitis associated with leucovorin (LV)/5-fluorouracil (5-FU) therapy for colon cancer. Results: Among 32 patients undergoing LV/5-FU therapy, without the use of the allopurinol ice balls, 15 patients developed stomatitis. On the other hand, only 3 patients developed stomatitis among 20 patients receiving the chemotherapy in conjunction with allopurinol ice balls (p=0.0187). Seven patients who developed stomatitis during a course of chemotherapy without allopurinol ice balls were administered the ice balls in the subsequent course; 6 of these patients responded with lessened severity of stomatitis. In 2 of these responders, stomatitis of comparable severity recurred on discontinuation of the medication. Conclusion: Concomitant use of allopurinol ice balls is effective in preventing stomatitis in patients undergoing LV/5-FU therapy.

In recent years, the concept of biochemical modulation in anticancer chemotherapy has become established and increasing attention has been focused on its usefulness. In the treatment of colon cancer, the efficacy of low dose leucovorin (LV)/5-fluorouracil (5-FU) therapy was reported by O’Connell et al. (1) and it is now widely accepted as a standard therapy for advanced colorectal cancer. First-line chemotherapy with the 5-FU plus LV regimen has been performed in our department, with proven efficacy, in the treatment of advanced or recurrent colon carcinoma (2).

Stomatitis is a relatively frequent adverse drug reaction (ADR) encountered in anticancer chemotherapy using 5-FU (3). This complication not only produces pain but also takes time to recover from, often causing a decrease in dietary intake and reduction of the patient’s desire to continue undergoing chemotherapy. Therefore, prevention and alleviation of stomatitis leads to relief of pain and consequent improvement in the patient’s quality of life (QOL). Efforts should be made to circumvent serious stomatitis which constitutes a dose-limiting factor in cancer chemotherapy and to improve the therapeutic outcome.

Strategies to prevent and treat stomatitis associated with 5-FU have been reported. They include pharmacological modulators (4-9) and non-pharmacological methods including oral cryotherapy (10) and helium-neon laser (11). As a pharmacological modulator, the efficacy of allopurinol mouth wash was reported (6-9). In view of these reports, we conceived the idea of having the patient hold a piece of frozen allopurinol gargle in his/her mouth, as a method of combining and realizing the advantages of allopurinol mouth wash and cryotherapy. This paper reports on our experience with frozen allopurinol solution (allopurinol ice balls) in the prevention of stomatitis associated with anticancer chemotherapy consisting of LV/5-FU for colon cancer.

Patients and Methods

Patients. Fifty-two patients with advanced or recurrent colon cancer undergoing systemic LV/5-FU therapy were studied, of whom 20 received prophylactic allopurinol ice ball regimens and 32 patients did not. These 32 patients without treatment were considered as the historical control.

The anticancer chemotherapy was performed as follows: each course of therapy comprised a bolus i.v. dose of 30 mg LV and a
subsequent bolus i.v. dose of 500 mg 5-FU, these combined regimens being administered daily for 5 consecutive days, followed by a 4-week withdrawal period. The course was repeated for as long as was practicable.

Allopurinol ice ball. Allopurinol ice balls were prepared using the following procedure: 5 g of carboxymethylcellulose was mixed with 500 mg of allopurinol and dissolved in sterile purified water in a mortar. The dissolved mixture was filtered through a 50-mesh sieve and the filtrate made up to a volume of 500 ml with sterile purified water to obtain an aqueous allopurinol solution (7). This solution was frozen in aliquots of approximately 10 ml at -4°C to prepare allopurinol ice balls.

Prior to each dose of the anticancer drug regimen and at 2, 4 and 6 hours after dosing, the patient was administered an allopurinol ice ball orally, which was to be held in the mouth until it had melted.

Relationship between allopurinol ice ball medication and anticancer effect. To ascertain the potential of allopurinol ice ball medication to reduce the antitumor effect of the anticancer regimen, data from patients with overt stomatitic lesions were analyzed with respect to the relationship between the use or non-use of allopurinol ice balls and the degree of clinical response to the anticancer chemotherapy.

Statistical analysis. The Chi-squared test was used for statistical evaluation of the data. Patients were assessed for ADRs according to the National Cancer Institute common toxicity criteria (12).

Results

Preventive efficacy of allopurinol ice balls for stomatitis. Out of 32 patients undergoing LV/5-FU therapy without the use of the allopurinol ice balls, the degree of severity of stomatitis was Grade 0 in 17 patients, Grade 1 in 11 patients, Grade 2 in 2 patients, Grade 3 in 2 patients and Grade 4 in none; hence 15 patients developed stomatitis. Stomatitis developed in only 3 of the 20 patients receiving the chemotherapy in conjunction with allopurinol ice balls, the severity being of Grade 0 in 17 patients, Grade 1 in 2, Grade 2 in 1, but Grade 3 or 4 in none. Thus, the occurrence of stomatitis was less frequent among the cases given allopurinol ice balls (Table I).

Seven patients who had developed stomatitis while on the anticancer chemotherapeutic regimen without the concomitant allopurinol ice ball medication were administered allopurinol ice balls from the next course of chemotherapy. The medication was effective in 6 of these patients; stomatitis did not develop in 4 patients and a reduction in severity of the complication was identified in the remaining 2. Two of these responders, however, expressed reluctance to continue on the allopurinol ice ball medication due to its unpleasant taste and they developed stomatitis of a comparable severity to that experienced in the preceding course after its discontinuation (Figure 1).

Anticancer effect of LV/5-FU with or without allopurinol ice ball medication. No significant differences in antitumor therapeutic response were identified between the two groups, indicating that the ice ball medication did not reduce the antitumor effect (Table II).

Discussion

Mechanisms implicated in the pathogenesis of stomatitis associated with anticancer drug medications have been classified into two categories (13,14). One, termed primary stomatitis, comprises the direct destruction of the oral mucous membrane upon exposure to anticancer drugs, leading to interference with the physiological turnover of mucosal tissue, possibly due to free radicals. The other, secondary stomatitis, stems from a local infection occurring in the presence of leukocytopenia. So, prophylactic strategies include administration of direct cytoprotectants, attempts to prevent infection by reducing the quantity of oropharyngeal flora or preventing neutropenia (15).

Measures to treat stomatitis associated with anticancer drug medications have included allopurinol gargle (6-9) and oral cryotherapy (10), which are reported to have been effective. The mechanism of action involved in the allopurinol gargle therapy, though yet to be clarified, has been postulated to be an inhibition of xanthine oxidase and consequent reduction of the production of active oxygen in the oral cavity (16). It has been described that the efficacy of cryotherapy may be attributable to vascular constriction of the oral cavity induced by cooling with an ice cube held in the mouth, thereby reducing the anticancer drug distribution into the oral mucosa (10). In view of these factors, we conceived the idea of having the patient hold a piece of frozen allopurinol gargle in his/her mouth, as a method of combining and realizing the advantages of the two therapies. The preventive efficacy of allopurinol ice balls for stomatitis observed in the present series is believed to comprise the same mechanisms as those just mentioned. Another factor in the efficacy of allopurinol ice balls is the

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*p=0.0187

Table I. Preventive effect of allopurinol ice balls for stomatitis.
relative ease with which prolonged drug contact with the oral mucosa can be accomplished, unlike with the allopurinol gargle.

In the treatment of stomatitis it is also important that the concurrent treatment of stomatitis does not reduce the antitumor effect of the chemotherapy, nor augment the side-effects of the anticancer drugs. Studies have suggested that allopurinol can reduce the toxicity of 5-FU (17, 18), because allopurinol metabolites reduce the formation of 5-fluorodeoxyuridine monophosphate and 5-fluorouridine triphosphate (19). However, enhanced selectivity may be expected under conditions where either normal tissues depend primarily on the orotate phosphoribosyl transferase pathway and malignant tissues on the uridine phosphorylase-uridine kinase pathway for activation of 5-FU, or where the activity of orotate phosphoribosyl transferase 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 (20). We therefore assessed the antitumor therapeutic responses among cancer patients receiving concurrent allopurinol ice ball medication versus a group of patients undergoing chemotherapy alone. The results of the assessment revealed no differences in the antitumor effect between the two groups. No ADRs attributable to allopurinol ice ball medication were observed, though the medication was discontinued in 2 patients due to its unpalatability.

The use of allopurinol ice balls is considered to be an excellent means of preventing stomatitis caused by anticancer drugs, although the present data are preliminary and randomized trials employing conventional procedures are needed to verify the efficacy of this medication. If its taste can be improved, allopurinol ice ball medication will be acceptable for practically all patients undergoing anticancer chemotherapy and may eliminate stomatitis as a dose-limiting factor in chemotherapy.

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**References**


