

## Allopurinol mouthwash for prevention or alleviation radiotherapy induced oral mucositis: a randomized, placebo-controlled trial

\*<sup>1</sup>Abbasi Nazari M., <sup>2</sup>Sadrolhefazi B., <sup>3</sup>Nikoofar A., <sup>4</sup>Erfan M., <sup>5</sup>Azizian H., <sup>1</sup>Alamy M.

<sup>1</sup>Department of Clinical Pharmacy, Faculty of Pharmacy, <sup>2</sup>Department of Radiotherapy, Faculty of Medicine, Shaheed Beheshti Medical University, <sup>3</sup>Department of Radiotherapy, Faculty of Medicine, Iran University of Medical Sciences, <sup>4</sup>Department of Pharmaceutics, Faculty of Pharmacy, Shaheed Beheshti Medical University, <sup>5</sup>Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

Received: 20 May 2007; Revised: 2 Sep 2007; Accepted: 2 Sep 2007

### ABSTRACT

**Background and the purpose of the study:** A randomized, double-blind, placebo-controlled trial was conducted to evaluate the effectiveness of an allopurinol mouthwash in prevention and alleviation of the oral radiotherapy induced mucositis.

**Methods:** An allopurinol suspension mouthwash having proper physical stability at least for 6 weeks was prepared. A total of 24 patients with oral, nasopharynx or hypopharynx cancer were enrolled in the study. They were randomly allocated to receive either an allopurinol suspension or normal saline as placebo that were identical in appearance. Patients were instructed to use the suspension as a mouthwash 3 times a day for 3 minutes after beginning of each radiotherapy cycle. Patients were graded on the basis of severity of their own symptoms on a weekly basis by using WHO scale.

**Results:** There were no differences in the severity of mucositis between the allopurinol and placebo-treated groups in first and second weeks of treatment ( $p = 0.227$ ,  $p = 0.121$  respectively). In the third, fourth, fifth and sixth weeks, there were significant differences between two groups ( $p < 0.05$  in each weeks separately).

**Major conclusion:** Result of this study support the hypothesis that an allopurinol mouthwash may prevents or alleviate oral mucositis induced by radiotherapy.

**Keyword:** Oral mucositis- Allopurinol – Radiotherapy - Mouthwash

### INTRODUCTION

Oral mucositis occurs as a nonspecific effect of chemotherapy and radiation therapy on the basal epithelium of the mouth. Signs and symptoms of mucositis generally occur about 5 to 7 days after chemotherapy or almost at any time during radiation therapy. While patients present with various symptoms, they often complain of pain, decrease in the ability to eat and speak and local or systemic infections (1). The disruption or loose of rapidly dividing epithelial progenitor cells is a trigger for the onset of the disorder. Complexity of pathophysiology has hampered development of effective or preventative measures. Increase in production of free radicals and induction of inflammation are early events in the onset of mucositis. Prophylactic administration of free radical scavengers or anti-inflammatories can partially counteract or limit some of these therapy mediated effects (2).

Specific measures to reduce the incidence or

severity of oral mucositis have received some attention in the past few years. Treatment by chemotherapy and radiation induced mucositis have been aimed to reduce symptoms and to avoid further trauma to the oral mucosa (1). A standardized approach for prevention and treatment of radiotherapy and chemotherapy induced mucositis is essential, since the efficacy and safety of most of agents have not been established. The prophylactic measures which are usually used for prevention of mucositis include chlorhexidine gluconate, normal saline, acyclovir, amphotericin B and ice (3).

Free radical scavenger effects of allopurinol have well documented in literatures (4-8). However prophylactic effect of allopurinol mouthwash against oral mucositis in radiotherapy has not been reported. Therefore this investigation was designed to evaluate effectiveness of allopurinol versus placebo in prevention or alleviation of radiotherapy- induced oral mucositis.

## MATERIALS AND METHOD

### Preparation of mouthwash

Allopurinol powder, Tween, Avicel, Xanthan, Methyl paraben, Propyl paraben, Disodium hydrogen phosphate, Dihydrogen sodium phosphate were kindly donated by Hakim pharmaceutical Co(Tehran, Iran).

The mouthwash suspension was prepared by combining allopurinol powder (3 gm), Tween 80 (500 mg), Avicel (5 gm) and Xanthan (2 gm), Methyl paraben (1.8 gm), Propyl paraben (200 mg), Disodium hydrogen phosphate (2 gm), Dihydrogen sodium phosphate (3 gm) and Distilled water. All ingredients except allopurinol were used to prepare placebo mouthwash. Allopurinol and placebo suspensions were identical in appearance. Mouthwashes were kept in 250 ml dark bottles and checked for physical stability within two months. During this period there was not any change in color, odor and flavor of suspension and any cake formation.

### Study design and questionnaire

A double-blind, placebo-controlled study design was employed and the proposal of the study was approved by the ethical committee of the Shaheed Beheshti Medical University.

A questionnaire was designed in which the first part contained demographic data of patients including name, sex, age, diagnosis, location of tumor, history of smoking, and plan of treatment (radiotherapy alone or radiotherapy plus cisplatin) and the second part had a table for registration of grade of oral mucositis before and during the six weeks of radiotherapy. Also, guideline for correct use of mouthwash and other necessary recommendations was provided to patients who participated in this study.

### Selection of patients

Patients with cancer in oral cavity, nasopharynx or hypopharynx who had undergone radiotherapy were selected for this study. In all patients daily dose and total dose of X-ray were 180-200 cG and 6000-6500 cG respectively and duration of radiotherapy was six weeks. Patients received radiotherapy alone or radiotherapy plus Cisplatin. (The reason for use of cisplatin was sensitization of malignant cells to X-ray).

Patients aged less than 18 years and those with previous sensitivity to allopurinol, renal, hepatic or hematological disorders were excluded from the study.

All patients signed their informed written consent. A dynamic randomization procedure was utilized to divide patients to receive allopurinol mouthwash (treatment group) or placebo mouthwashes (Control group).

### Examination and follow up of patients

Patients in each 2 groups were instructed during six weeks radiotherapy to take 10 mL of either allopurinol or placebo mouthwash 3 times a day for 3 minutes and then discards them without swallowing. Patients, who experienced hysensitivity reaction or serious side effects, were excluded from the study. Also patients who complained about pain or other signs attributed to severe mucositis, were excluded from the study and received the more aggressive therapy for mucositis. WHO grading system was used for scoring and classification of mucositis (3) (table 1). This physician- Judged score was usually assessed and recorded in the questionnaire by the physician weekly when the patient returned for evaluation.

### Data analysis

Data were analyzed using SPSS-13 software. For comparing two groups' chi-square test or fisher exact test was used and p value less than 0.05 were considered significant.

## RESULTS

24 patients from 4 different hospitals were participated in this clinical trial, of which 14 patients were treatment group and others were in control group. Table 2 shows patient's demographic data and pretreatment mucositis score.

**Table 1.** Severity scoring of radiotherapy –induced mucositis

grade	Definition
0	No problem
1	Erythema of mucosa
2	Patchy pseudomembranous reaction (<1.5 cm in diameter and non contiguous)
3	Confluent pseudomembranous reaction (>1.5 cm in diameter and contiguous)
4	Necrosis or deep ulceration, may include bleeding not induced by minor trauma or abrasion

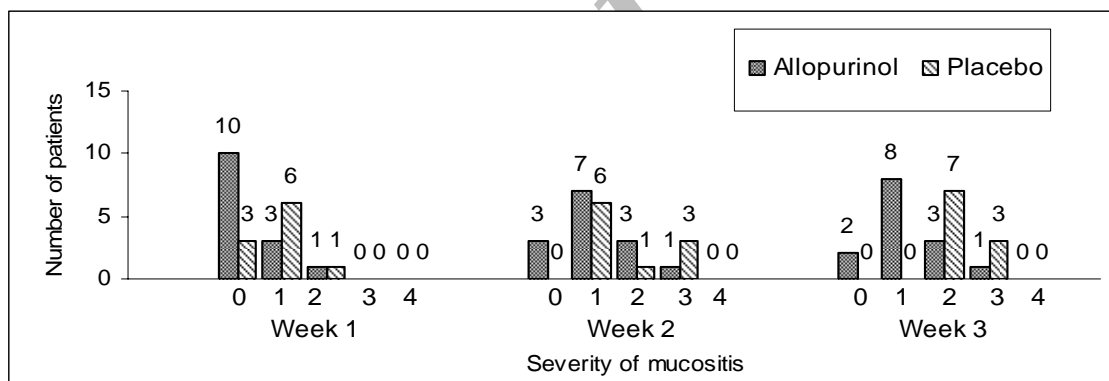
There was no difference in the mean age, smoking habit, tumor location, plan of treatment (radiotherapy alone or radiotherapy plus cisplatin) and pretreatment mucositis score between allopurinol and placebo- treated groups. With regards to sex, there was a difference between two groups (p = 0.028).

Severities of mucositis were determined separately in the first, second, third, fourth, fifth and sixth weeks of radiotherapy and are shown in figures 1 and 2.

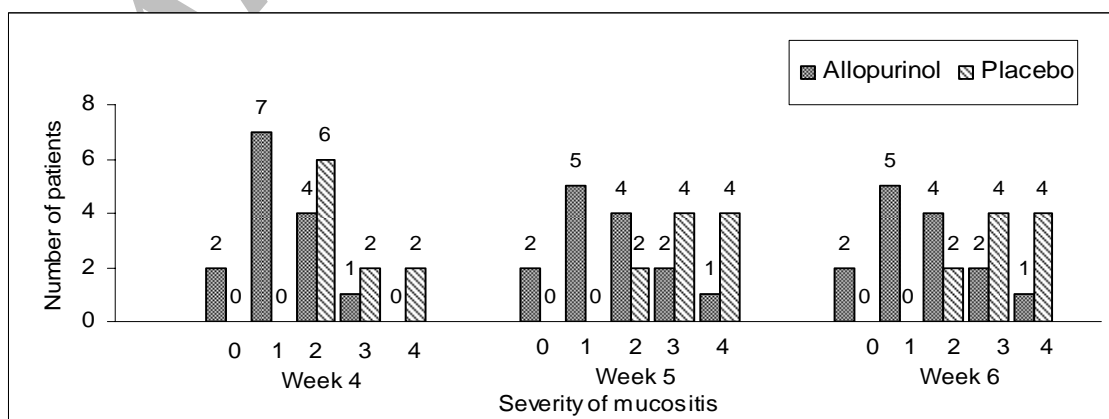
Data analysis showed there were not significant differences between groups in severity of mucositis in the first and second week (p =0.227,

**Table 2.** Demographic data and pretreatment mucositis score of patients

Characteristics		Treatment group	Placebo group	P value
Mean age		50.70 ± 16.60	49.90 ± 22.40	0.983
Sex	Male	14	7	0.028
	Female	0	3	
Smoking habit	Yes	2	1	0.754
	No	12	9	
Tumor location	Oral	2	4	0.291
	Nasopharynx	6	2	
	Hypopharynx	6	4	
Treatment plan	Radiotherapy alone	3	4	0.223
	Radiotherapy+ Cisplatin	11	6	
Pretreatment mucositis score	0	14	9	0.417
	1	0	1	
	2	0	0	
	3	0	0	
	4	0	0	



**Figure 1.** Severity of mucositis in first, second and third weeks of treatment. (0,1, 2, 3, 4 represent degree of mucositis on the basis of WHO classification)



**Figure 2.** Severity of mucositis in fourth, fifth and sixth weeks of treatment. (0,1, 2, 3, 4 represent degree of mucositis on the basis of WHO classification)

$p=0.121$  respectively). However there was a significant difference between two groups in severity of mucositis in the third, fourth, fifth and sixth week of treatment ( $p < 0.05$  in each week separately).

### DISCUSSION

In 1985 Clarke and Slevin reported favorable results of the use of allopurinol mouthwash in six patients who experienced mucositis when treated initially with 5-FU (6). Montecucco et al evaluated a mouthwash containing 5 mg/mL of allopurinol for prevention of methotrexate-induced mucositis in patients with rheumatoid arthritis. Mouthwash was administered 2-4 times every day for 3 consecutive days every week, starting from the day of methotrexate administration. A very good response was found after the first 2 courses of treatment which was maintained in subsequent courses (7). Another reported pilot study concluded that an allopurinol mouthwash alleviated 5-FU induced mucositis in 16 of 16 patients. Mouthwash was prepared by dissolving 3 tablets of allopurinol (900 mg) in 150 mL of water (6mg/mL). In this study patients were asked to use mouthwash 4-6 times every day for at least 6 days. All patients responded to allopurinol by decrease in the grade of mucositis and they did not observe any toxicity, allergic reactions or other side effects on using this mouthwash (8).

Because of short duration of patient observation in previous studies, in this study a mouthwash suspension with proper physical stability to insure content uniformity of dosage form at least for 6

weeks were prepared in order to evaluate long term effects of allopurinol in prevention or alleviation of mucositis.

Loprinzi et al performed a randomized, placebo-controlled; double-blind study on 77 patients receiving 5-FU to evaluate preventing effects of allopurinol mouthwash (1 mg/mL) on oral mucositis. They evaluated patients for 1 month but there was not any difference between allopurinol and placebo mouthwash in relieving of mucositis or pain (5). The low concentration of allopurinol in their studies (1 mg/mL) compared with our studies (3 mg/mL) may be the reason for different results. Also they observed patients only 5 days because of probability of side effects for chemotherapy between 5-7 days. However in this study patients were observed for 6 weeks since signs and symptoms of mucositis generally occur at almost any point during radiation therapy (1). Results of this study show that, demographic features of patients such as age, smoking habit, pretreatment mucositis score that contribute to oral mucositis were similar in both groups, with exception of sex. Significant differences were observed between allopurinol and placebo in prevention or alleviation of mucositis in third week and later. These findings support the hypothesis that an allopurinol mouthwash may prevent or alleviate oral mucositis induced by radiotherapy.

### ACKNOWLEDGMENT

We would like to thank to Hakim pharmaceutical company, especially Dr Avadi and Dr Mostafavi for providing gift samples of materials for doing this investigation.

### REFERENCES

1. Celeste L. Adverse effects of chemotherapy. In: Koda-kimble M. Applied therapeutics; the clinical use of drugs. 8<sup>th</sup> ed. New York: Williams & Wilkins. 2005: 8-10
2. Duncan M, Grant G. Oral and intestinal mucositis- causes and possible treatments. *Alim Pharmacol Ther.* 2003; 18: 853-874
3. Bensadoun R, Magne N, Marcy P, Demard F. Chemotherapy and radiotherapy induced mucositis in head and neck cancer patients: new trends in pathophysiology, prevention and treatment. *Eur Arch Otorhinolaryngol.* 2001;258:481-487.
4. Oredsson S, Plate G, Qvarfordt P. Allopurinol- free radical scavenger – reduces reperfusion injury in skeletal muscle. 1991;5:47-52.
5. Loprinzi CL, Cianflone SG, Dose AM, Ezzell PS, Burnham NL et al . A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil induced stomatitis. *Cancer.* 1990;65:1879-1882.
6. Clarke PZ, Slevin ML. Allopurinol mouthwash and 5-fluorouracil induced oral toxicity. *Eur Surg Oncol.* 1985;11:267-8
7. Montecucco C, Caporali R, Rossi S, Porta C. Allopurinol mouthwash in methotrexate- induced stomatitis. *Arthritis Rheum.* 1994;37:777-778
8. Tsavaris N, Caragiouris P, Kosmidis P. Reduction of oral toxicity of 5- fluorouracil by allopurinol mouthwash. *Eur Surg Oncol.* 1988;14: 405-6.