

Prevention of Oral Mucositis Due to 5-Fluorouracil Treatment with Oral Cryotherapy

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Introduction: One of the most common and important side effects of 5-fluorouracil (5-FU) is mucositis with ulcerations in the oral cavity. We investigated the effects of local cryotherapy on mucositis incidence administered during 5-FU treatment.

Methods: In a total of 99 courses, 5-FU and folinic acid combination chemotherapy was given to 40 patients. In our study, we considered every course as a single case, and cryotherapy was given to the same patient in one course but not given in the next.

Results: While mucositis developed in 6.7% of the courses given with cryotherapy, this ratio was 38.9% in courses given without cryotherapy. In the logistic regression analysis, development of mucositis had been found to correlate only with cryotherapy. Odds ratio (OR)=11.5; in the 95% confidence interval (CI)=3.2–41.9; (p=0.001).

Discussion: Results of initial studies evaluating the effects of cryotherapy in preventing mucositis due to 5-FU based chemotherapy regimens were promising. We concluded that oral cooling prevents 5-FU induced mucositis. This effective prophylactic treatment should be used in patients who are at increased risk for developing 5-FU induced mucositis.

Key words: 5-fluorouracil ■ oral mucositis ■ cryotherapy ■ prevention

INTRODUCTION

5-fluorouracil (5-FU) is used in the treatment of solid tumors, including stomach, colon, rectum, breast and pancreas carcinomas. One of the most common and important side effects of 5-FU is mucositis with ulcerations in the oral cavity. The addition of folinic acid to 5-FU increases the efficacy of the drug in the treatment; however, the frequency of mucositis also increases. The prevalence of mucositis in patients undergoing standard-dose chemotherapy is approximately 40%, and this ratio exceeds 50% in high-dose chemotherapy protocols.¹ Mucositis-associated pain is one of the main sources of cancer treatment-related pain.² Mucositis prevents oral feeding of the patients and deteriorates their performance. In some of the patients with mucositis, pain and oral dysfunction are of such severity that they require narcotic analgesia and supplemental nutrition. Also, worsening mucositis correlates with longer hospital stays and thereby increases the cost of cancer therapy. There are several studies concerning the prevention of mucositis in patients treated with 5-FU. It was hypothesized that cryotherapy would cause local vasoconstriction and therefore reduce the uptake of chemotherapeutic agents into mucosal cells during the short half-life of 5-FU. Mahood et al. initially tested the efficacy of cooling the oral mucosa with ice chips during bolus application of 5-FU in a randomized crossover trial and observed a 50% reduction in the severity and duration of 5-FU-induced mucositis.³ Subsequently, Cascinu et al. conducted a randomized controlled trial in a sample of 84 patients receiving bolus 5-FU and demonstrated that incidence and severity of mucositis is significantly low in cryotherapy group compared with control patients.⁴

The oral administration of allopurinol, granulocyte macrophage-colony stimulating factor (GM-CSF), sucralfate, chamomile, prostaglandins and chlorhexidine rinses were also used in the prevention of mucositis.^{5-8,10,11}

We investigated the effects of local cryotherapy on

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mucositis incidence during 5-FU treatment. Several factors play a role in the development of chemotherapy induced mucositis: an interaction between epithelial and connective tissue cytokines may account for much of the mucosal injury but other factors, such as alterations in salivary immunoglobulins, proteins and electrolytes, nonspecific host defense in saliva, type and dosage of chemotherapy regimens, oral hygiene level and nutritional status of the patient, are probable causes in the development of mucositis. We aimed to investigate whether there is a preventing effect of cryotherapy on mucositis during 5-FU and folic acid combination chemotherapy by giving oral ice chips during a course and skipping at the next course for the same patient.

MATERIAL AND METHODS

In a total of 99 courses, 5-FU and folic acid combination chemotherapy was given to 40 patients. The mean age of these patients was 54.17 ± 14.19 years (ranged 20–77 years). The cases were carcinomas of the colon, rectum, stomach, head of pancreas, cecum, sigmoid, neuroendocrine tumors, and metastatic tumors of unknown origin of the liver. Every chemotherapy course was considered a single case, and mucositis was judged by a physician on the fifth, 10th, 15th and 21st days of the course according to the World Health Organization's (WHO) toxicity criteria.¹² The manifestations of mucositis rank from 0 to IV. Grade 0: no symptoms; Grade I: painless ulcers, erythema or mild soreness; Grade II: painful erythema, edema or ulcers, but the patient can eat solid meal; Grade III: painful erythema, edema or ulcers, and the patient cannot eat solid meal; Grade IV: requires parenteral or enteral support.

Cryotherapy was administered in a random pattern of 99 courses of chemotherapy. If cryotherapy was instituted in the first course, it was not instituted in the latter and vice versa. Therefore, treatment was completed by consecutive courses with or without cryotherapy. 5-FU

was given at a dose of 450 mg/m² in 10 minutes. Folic acid was also given in 10 minutes at a dose of 20 mg/m² and 30 minutes prior to 5-FU administration.

Patients kept ice pieces in their mouth from the beginning of intravenous 5-FU until 10 minutes after the treatment. This time, interval is consistent with the half-life of 5-FU. Although patients' mouth temperatures were not measured to assure that cryotherapy was evenly maintained, the procedure was conducted under supervision of a chemotherapy nurse who guided the patients. Patients were also evaluated for complications other than mucositis, like fever, diarrhea, nausea and vomiting.

Complete blood counts were obtained prior to every course of chemotherapy. Chemotherapy was administered when the white blood cell and platelet count were above 4.000/mm³ and 100.000/mm³, respectively. Patients were questioned for the presence of dentures, history of drug usage and accompanying diseases. Patients having dentures took them off during the chemotherapy sessions. Three patients were found to have type-2 diabetes mellitus. Two of them were using insulin and the third one was on oral antidiabetic drug treatment.

STATISTICAL ANALYSIS

Chi-square, McNemar and logistic regression tests were used in the analysis of the results.

RESULTS

Seventy-eight (71.7%) of the courses were given to male and 21 (28.3%) were given to female subjects. Cryotherapy was administered in 45.5% of the courses. After the chemotherapy treatment, mucositis was observed in 24.2% of courses (Table 1).

Mucositis was observed in 19.7% of the courses given to the male subjects, and this ratio was 35.7% in females (p=0.094). Mucositis was developed in 22.2% of courses given to subjects who were using

Table 1. Distribution of the chemotherapy courses according to sex, cryotherapy administration and development of mucositis

	(n=99)	%
Sex		
Male	71	71.7
Female	28	28.3
Cryotherapy		
Administered	45	45.5
Not administered	54	54.5
Development of Mucositis		
Yes	24	24.2
No	75	75.8

Table 2. Distribution of courses with and without mucositis according to sex and presence of dentures

	Mucositis				χ^2	P
	Observed		Not Observed			
	n	%*	n	%*		
Sex						
Male	14	19.7	57	80.3	2.798	0.094
Female	10	35.7	18	64.3		
Dentures						
Yes	6	22.2	21	77.8	0.083	0.774
No	18	25.0	54	75.0		

* percent of lines n=99

dentures ($p=0.774$) (Table 2). These two variables have no statistically significant correlation with the development of mucositis.

While mucositis developed in 6.7% of the courses given with cryotherapy, this ratio was 38.9% in courses given without cryotherapy. In the logistic regression analysis, development of mucositis had been found to correlate only with cryotherapy. Odds ratio (OR)=11.5; in the 95% confidence interval (CI)=3.2–41.9; ($p=0.001$) (Table 3). In view of this result, it can be assumed that cryotherapy has a protective effect against development of mucositis.

In the total of 24 courses in which mucositis developed, the percentages of grade I, II and III mucositis were 66.7%, 20.8% and 12.5%, respectively. Grade-IV mucositis was observed in none of the cases. However, only grade-I mucositis was observed in courses given with cryotherapy (Table 4).

Cryotherapy was well tolerated. No local or systemic side effects were observed due to cryotherapy. Common side effects developed secondary to chemotherapy included diarrhea (24.2%), nausea (6.1%), vomiting (3.0%) and fever (2.0%). None of these side effects showed correlation with cryotherapy.

DISCUSSION

5-FU is a synthetic analogous of pyrimidine. In the body it turns to fluorouridilate first and then to fluorodeoxyuridilate. 5-FU gains affectivity after this transformation. Its active metabolite prevents DNA synthesis by inhibiting thymidilate synthetase. Also, fluorouridilate formed in the body participates in the structure of RNA and disturbs this structure and protein synthesis. 5-FU has a stronger cytotoxic affect on proliferating cells than resting ones. After intravenous administration, 5-FU quickly delivers to all tissues. It has a plasma half-life ranging 5–20 minutes.

Although side effects due to chemotherapy, such as nausea and vomiting, play a role in the disturbed oral feeding, mucositis developed during chemotherapy is one of the main factors that prevents oral feeding. It is possible to prevent these side effects by med-

ical treatment. Mucositis leads to poor performance and decreases the quality of life due to insufficient feeding in patients. Preventing mucositis facilitates compliance and maintenance to cancer treatment. Mucositis does not allow giving higher doses of chemotherapy because it may affect the patient's life span. Development of mucositis increases the risk of infection and disturbs the structure of oral mucosa epithelium, which is a natural barrier.

As the local administration of ice pieces will cause vasoconstriction in the mucosal vessels and therefore slow down the circulation, we aimed to prevent mucositis by decreasing the exposure of oral mucosa to chemotherapeutic agents.

Allopurinol and GM-CSF were used in the treatment in order to prevent mucositis.^{5,6} In a study performed with GM-CSF, it has been shown that GM-CSF decreased duration and severity of the mucositis. However, allopurinol mouthwash was not found to be useful in preventing mucositis, and GM-CSF is a very expensive treatment regimen with its obscure long-term side effects. Patients treated with 5-FU-based chemotherapy showed no differences in mucositis between the sucral-fate and placebo treatment.⁷ The results of a randomized controlled trial did not show any benefit of chamomile to ameliorate 5-FU induced mucositis.⁸ Prostaglandin E2 (PGE2) is suggested to possess cytoprotective properties.⁹ In a randomized, double-blind controlled trial in 60 bone marrow transplantation patients, however, there was no significant difference in the severity and duration of mucositis as well as duration of fever between the PGE2 and control groups.¹⁰

Results of initial studies evaluating the effects of cryotherapy in preventing mucositis due to 5-FU based chemotherapy regimens were promising.³ In our study, we considered every patient a single case, and cryotherapy was given to the same patient in one course but not given in the next. Although it is reported in the previous studies that mucositis is more frequent in younger patients, our findings are not consistent with this observation. We concluded that oral cooling prevents 5-FU-induced mucositis. When compared with other measures, this technique has some advan-

Table 3. Incidence of mucositis development in the chemotherapy courses given with and without cryotherapy

Cryotherapy	Mucositis			
	Observed		Not Observed	
	n	%*	n	%*
Administrated	3	6.7	42	93.3
Not administrated	21	38.9	33	61.1
Total	24	24.2	75	75.8

* percent of lines; $p=0.000$; $\chi^2=13.876$

Table 4. Grading of mucositis in the chemotherapy courses given with and without cryotherapy

Mucositis Grade	Cryotherapy			
	No		Yes	
	n	%	n	%
1	13	81.3	3	18.7
2	5	20.8	0	0
3	3	12.5	0	0
4	0	0	0	0
Total	21	87.5	3	12.5

tages: it is easy to perform, cheap and has no side effects. Prevention of oral mucositis increases tolerability of chemotherapy. This effective prophylactic treatment should be used in patients who are at increased risk for developing 5-FU induced mucositis.

The small sample size is the major limitation of this study, and the results must be confirmed by large-scale randomized, controlled trials. On the other hand, the combination of cryotherapy with local vasoconstrictor rinses may increase the effectiveness of the procedure, which can be a subject of future studies. Cryotherapy may also be considered a prophylactic technique in prevention of mucositis induced by other chemotherapeutic agents that have short half-lives, like 5-FU. Despite the benefits of oral cryotherapy, stomatitis is still a dose-limiting toxicity for 5-FU-based chemotherapy regimens, so efforts must be maintained to find other preventive measures or antidotes.

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