INVESTIGATION OF ORAL MUCOSITIS INCIDENCE AND RISK FACTORS IN PATIENTS RECEIVING CHEMOTHERAPY

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ABSTRACT

Purpose: Oral mucositis is a common complication of cancer treatment that may negatively impact the patient's cancer treatment outcome. This study was done to determine the incidence of oral mucositis development and risk factors in patients receiving chemotherapy.
Material and Methods: This cross-sectional study included 150 participants undergoing outpatient cancer chemotherapy. To determine the development of oral mucositis, the participants were evaluated for the first course of chemotherapy (day 0) and the next course of chemotherapy treatment (day 14). 'Patient Information Form' and the World Health Organization' Mucositis Grading Scale' were used to collect data for the study. Descriptive statistics, and logistic regression were used to analyze the results.
Results: According to oral mucosal assessment, incidence of oral mucositis was 27.3%. The mean onset and the mean recovery of oral mucositis were 4.16 ± 2.13 days and 8.72 ± 2.32 days. The most common oral problems were mouth dryness (53.3%), dental caries (44%), and decreased sense of taste (32%). In the oral mucosal assessment performed on the 14th day, 9 patients were found to be grade 1. Patients with a history of mucositis (OR = 5.76, CI = 2.33–14.24, p = 0.00) showed a significantly higher incidence of oral mucositis.
Conclusion: In this study, the incidence of oral mucositis and risk factors that may affect the development of oral mucositis in patients receiving chemotherapy were investigated. Mucositis history was found as a risk factor in oral mucositis development. Early recovery of oral mucositis after chemotherapy was observed. Therefore, patients should be followed up in the early period after chemotherapy.

Keywords: Chemotherapy, oral mucositis, mucositis, risk factors.

INTRODUCTION

One of the common complications of cancer treatment is oral mucositis that negatively impacts the patient's cancer treatment outcome. Oral mucositis affects the entire mucous membrane-covered surface from the mouth to the rectum and usually begins as early as 3 to 4 days after the administration of chemotherapy and generally peaks in severity 7 to 14 days later (1,2). Many drugs used in cancer treatment are known to increase the risk of mucositis. Due to the lack of standardized scoring criteria, tumor location, and different treatment regimens the prevalence and incidence data of oral mucositis vary (1,3).

A study conducted on chemotherapy protocols showed that the incidence of oral mucositis ranged between 6.1% and 90% (4). The results of the study showed the effects of chemotherapy regimens on the

development of mucositis. According to the study, the incidence of ulcerative mucositis is up to 70%. (5). Although the diagnosis and treatment are similar, patients are not equally at risk in oral mucositis development. In addition to the chemotherapy and radiotherapy treatments given, some individual characteristics of the patient facilitates the development of mucositis. Risk factors associated with the patient are more complex and less defined (2,6-8). Although the impact of patient-related factors on the development of oral mucositis in adults is obvious, findings are inconsistent and very few appear to be evidence based (6,9-11).

There is no proven gold standard for the prevention and/or treatment of oral mucositis. Although mucositis is a common complication of cancer treatment, the quality of life of the patient can be improved by providing comfort. Thus, oral diagnosis and effective oral care can improve the quality of life (12,13). As it is very important to assess the associated risk factors of mucositis for its prevention and management; therefore, additional research is needed to identify these risk factors (14,15). This prospective cohort study is carried out to determine the incidence and risk factors for oral mucositis in patients receiving chemotherapy.

Research Questions:

- Do the sociodemographic characteristics and features related to oral hygiene affect the development of oral mucositis?
- Do the disease and treatment-related characteristics affect the development of oral mucositis?

MATERIAL AND METHODS
Study Design and Sample
Outpatients receiving chemotherapy from the daily chemotherapy unit of a training and research hospital in the west of Turkey from April to August 2016 were selected for this a cross-sectional study. All the patients enrolled for the study were over 18 years of age, agreed to participate in the study, and underwent the first course of chemotherapy. Patients who had impaired oral mucous membrane integrity were excluded from the study. Power analysis on the G-Power statistical program based on Type 1 error of 0.05 and Type 2 error of 0.20 (80%) was used to determine the sample size of the study, which was 139. Logistic regression analysis results from the study conducted by Salvador (2005) were used (16). A total of 166 patients were reached, but 16 refused

to participate in the study. A total of 150 patients were included in the study.

Data Collection and Research Tools
The Patient Information Form
This form was prepared by the researchers, which consisted of both personal characteristics (age, gender, diagnosis, education level, income status, presence of chronic illness, body mass index) and illness/oral health characteristics (smoking status, dental caries, dental brushing, oral care frequency, sense of taste, dryness and cracking on the lips, chemotherapeutic agent, number of chemotherapy courses, chemotherapy history and history of oral mucositis development).

The World Health Organization Mucositis Grading Scale
Based on the anatomical variation of the oral mucous membrane and rating at the scale of "0" to "4" according to the mucositis formation, classification was made. Grade "0" indicates no change; Grade "1" shows soreness or erythema; Grade "2" shows erythema, ulcers, patient can swallow solid diet; Grade "3" shows ulcers, extensive erythema, and Grade "4" denotes mucositis to the extent that alimentation is not possible (7,17).

The applicability of the questionnaires was evaluated by conducting a pilot study. Patients in the pilot study were not included in the study data. Data were collected by the first researcher through face-to-face interviews. The patient provided the demographic and oral care information, and the hospital database provided the data regarding the clinical condition (diagnosis, chemotherapeutic agent, number of chemotherapy courses, chemotherapy history). Potential participants who met the inclusion criteria were informed about the study when they came to receive the first chemotherapy course (day 0). On receiving their consent, their mouth was evaluated using the 'World Health Organization Mucositis Grading Scale'. Intraoral examination was conducted using the 'World Health Organization Mucositis Grading Scale' when patients came to receive their next course of chemotherapy (day 14), and 'Patient Information Form' was used to collect all information. Then, the inner parts of the mouth were examined using a light source. Filling out the forms for the first and second follow-up and do the intraoral examination took about 30–40 min. All intraoral assessments were performed by the first researcher to eliminate interobserver variability. As per the

Table 1. Sociodemographic and Treatment Characteristics of the Patients (n: 150).

Characteristic	n	%
Gender		
Female	96	64.0
Male	54	36.0
Income Situation		
Low	79	52.7
Middle	71	47.3
Education Level		
Illiterate/Primary education	129	86.0
High school/University	21	14.0
BMI		
Thin/Normal	47	31.3
Overweight/obese	103	68.7
Chronic Diseases		
Yes	74	49.3
No	76	50.7
Smoking		
Yes	16	10.7
No	134	89.3
Alcohol use		
Yes	2	1.3
No	148	98.7
Diagnosis		
GIT cancer[*]	65	43.4
Gynecologic cancer[**]	41	27.3
Breast cancer	26	17.3
Other diagnoses[***]	18	12.0
Chemotherapeutic agent[****]		
5-FU	57	38.0
Paclitaxel	44	29.3
Carboplatin	34	22.7
Other drugs[*****]	146	97.3
Chemotherapy History		
Yes	124	82.7
No	26	17.3
Mucositis History (n:124)		
Yes	57	46.0
No	67	54.0

*: Stomach, colon, rectum, and pancreas cancer. **: Cervical, ovarian, fallopian tube and endometrial cancer
: Renal, prostate, lung, bladder, head and neck cancer. *: Each drug has been used by more than one patient.
*****: Cisplatin, cyclophosphamide, doxorubicin, oxaliplatin, gemcitabine, and irinotecan

chemotherapy protocols, patients came to the unit for treatment every 14 days. Therefore, intraoral assessments of the patients were carried out twice, during the first (day 0) and the second course of chemotherapy (day 14).

Data analysis
SPSS 22.0 program was used to analyze data. The descriptive characteristics of patients were evaluated using the percentage test. The risk factors affecting oral mucositis development were examined using logistic regression analysis. The variables related to demographic characteristics, treatment, and oral care in the model were chosen by considering univariate analysis and were in line with the literature (9,15,18-20). For all analyses, $p < 0.05$ was accepted as the level of significance.

Ethical Considerations
The non-interventional ethics committee of the university and a training and research hospital in İzmir where the study was conducted approved the study (Dokuz Eylül University Non-Interventional Researches Ethics Committe, Date: 07.04.2016,

J Basic Clin Health Sci 2023; 7: 747-755

Göktuna G et al. Oral Mucositis Risk Factors

Decision no: 2016/09–33). The verbal and written informed consent were provided from patients. Research and publication ethics were complied with in the article.

RESULTS

This study examined a total of 150 patients. The mean age of the participants in the study was 57.05 ± 10.96. Of the patients, 64% were female, 52.7% had less income than their expenses, 64.6% were primary school graduates, 34.7% were overweight, 49.3% had chronic diseases, 89.3% did not smoke, 98.7% did not use alcohol. The patients had gastrointestinal cancer (42.7%), gynecologic cancer (26%), and breast cancer (17.3%). When the most used chemotherapeutic agents by patients were taken into account, 38% of the patients were treated with 5-FU, 29.3% with paclitaxel, 22.7% with carboplatin (Table 1). Of the patients, 44% had dental caries, 32% had a decreased sense of taste, 53.3% had mouth dryness, 25.3% had decreased appetite, and 18.7% had dry and cracked lips. Of the patients, the rate of those who brushed their teeth once a day and those who never did were found to be the same (32%). Of the individuals, 30% did oral care once or twice a day while 22% did not practice oral care at all. It was found that 82.7% of the patients had received chemotherapy previously and among these (n = 124), 46% had a history of mucositis. According to oral mucosal assessment, 94% of the patients were found

Table 2. Oral Care Characteristics of the Patients (n: 150)

Characteristic	n	%
Dental caries		
Yes	66	44.0
No	84	56.0
Decrease in the sense of taste		
Yes	48	32.0
No	102	68.0
Dryness in mouth		
Yes	80	53.3
No	70	46.7
Decrease in appetite		
Yes	40	26.7
No	110	73.3
Dry and cracked lips		
Yes	28	18.7
No	122	81.3
Dental brushing frequency		
Never	48	32.0
Once a day	48	32.0
Twice a day	39	26.0
Three times a day	15	10.0
Frequency of oral care		
Never	33	22.0
Once a day	45	30.0
Twice a day	45	30.0
Three times a day and more	27	18.0
14th day Oral Mucositis Grading Score		
Grade 0	141	94.0
Grade 1	9	6
Development of Oral Mucositis within the 14-day period		
Yes	41	27.3
No	109	72.7
Variable	$\bar{X}$ ±SS	
Start after chemotherapy (days)	4.16 ±2.13	
Ending after chemotherapy (days)	8.72 ±2.32	

to be grade 0 on day 14. However, oral mucositis developed and recovered in some patients within a period of 14 days. Thus, 27.3% of oral mucositis incidence is presented in Table 2.

The development of mucositis within the 14-day period was examined, and the mean starting day and the mean ending day of oral mucositis were found to be 4.16 ± 2.13 days and 8.72 ± 2.32 days. The risk factors affecting the oral mucositis development were determined using logistic regression analysis. According to the logistic regression analysis, age, gender, chronic disease, smoking status, chemotherapy history, dental caries, dental brushing frequency, oral care frequency and body mass index were not found to be risk factors for the development of oral mucositis. However, mucositis history was found to be a risk factor in the development of oral mucositis (OR = 5.766, CI = 2.33–14.24, p = .000) (Table 3).

DISCUSSION

Oral mucositis is a common problem seen in patients receiving chemotherapy. The examination of studies on its incidence show that the related literature has spread over a wide range (4). The study by Wilberg et al., (2014) reported that 12% of patients had grade 1–2 (21). The incidence of oral mucositis was found to be 27.3% in our study, whereas 51.7% was reported in the study by Çakmak and Nural (2019) (22). In another meta-analysis, the incidence of oral mucositis ranged from 20% to 80.4% (23). The results of our study are consistent with the literature and it has been revealed that mucositis is an important problem in patients receiving chemotherapy.

After chemotherapy, oral mucositis begins on days 3–4th and peaks on days 7–14th (1). The study by

Vokurka et al., (2011) showed that the mean onset of oral mucositis was 4 days, and the end was 11 days while the study by Cheng Fong et al., (2011) showed that the onset of oral mucositis as 4.7 ± 2.7days and the duration of mucositis was 6.3 ± 4 days (9,11). This study showed that the onset of oral mucositis was 4.16 ± 2.13 days, and the end was 8.72 ± 2.32 days. The results showed that the day oral mucositis ended was earlier compared to the literature.

Some studies found a significant relationship between age and oral mucositis, while others did not. The risk of oral mucositis was high in patients 60 years of aged, as per the study by Yang et al., (2013) (10). Another study showed that the risk of oral mucositis increases with age (22). However, few studies did not show any relationship between age and oral mucositis (11,16,24,25). Similarly, there was no significant correlation between age and oral mucositis in this study. The fact that our result was not related to age is thought to be due to the characteristics of the study group.

This study showed gender was not a risk factor for oral mucositis development. Similarly, other studies did not show any correlation between gender and oral mucositis (11,16,24,26,27). However, according to the studies the incidence of oral mucositis developed by women is higher (10,19,28,29). Similarly, another study also reported a higher risk of oral mucositis in females than that in males and interpreted that the metabolism of 5-FU might differ according to gender (30).

In this study, no relationship was found between cancer types and the risk of oral mucositis. Similarly, the study by Çakmak and Nural (2019) showed that cancer types did not affect the incidence of oral mucositis (22). The study by Nishimura et al., (2012)

Table 3. Distribution of Risk Factors Affecting Oral Mucositis Development in Patients

Risk Factor	OR	CI		p
Age	1.012	0.98	1.04	.526
Gender	2.104	0.93	4.71	.073
Diagnosis	0.974	0.88	1.06	.562
Mucositis history	5.766	2.33	14.2	**.000**
Chronic disease	0.741	0.36	1.53	.415
Smoking	1.700	0.58	5.01	.338
Chemotherapy history	0.816	0.32	2.05	.666
Dental caries	0.491	0.23	1.04	.065
Dental brushing frequency	1.036	0.71	1.50	.850
Oral care frequency	1.188	0.83	1.70	.347
Body mass index	0.975	0.91	1.03	.418

OR = Odds ratio, CI = confidence interval

J Basic Clin Health Sci 2023; 7: 747-755

Göktuna G et al. Oral Mucositis Risk Factors

showed that the risk of oral mucositis was higher in breast cancer patients (31). Different results may have been obtained due to the diagnosis in different stages, changes in treatment protocols, and individual differences (22).

Shouval et al., (2019) found that low body mass index was a risk for oral mucositis (18) while Robien et al., (2004) reported a body mass index of ≥ 25 as a risk factor for oral mucositis (26). However, some studies did not find body mass index as a risk factor for oral mucositis (11,16). In this study, the regression analysis showed that body mass index was not a risk factor for oral mucositis development.

The risk of mucositis is triggered by factors such as poor oral hygiene, dental problems, high levels of microorganisms in the mouth flora, and a decrease in salivary secretion (15,32). Ramirez-Amador et al., (2010) found no significant relationship between oral hygiene and mucositis (24). As for this study, dental caries, oral care, and tooth brushing were not found to be risk factors for oral mucositis. The results showed that the most common oral problems were mouth dryness (53.3%), dental caries (44%), and decreased sense of taste (32%). Like our study results, the most common oral complications reported in other studies were mouth dryness and changed sense of taste (21,22). It is thought that the risk factors found should be taken into account by nurses in oral care planning.

Individuals with a history of chemotherapy and mucositis are at higher risk of developing oral mucositis as they are more susceptible to oral mucosal cell damage (6). In our study, no correlation was found between the history of chemotherapy and the development of oral mucositis. Similarly, studies by Nishimura et al., (2012) and Çakmak & Nural (2019) did not find any relationship between chemotherapy history and the development of oral mucositis (22,31). However, regression analysis in this study showed that a history of oral mucositis and previous chemotherapies increased the risk of oral mucositis to 5.76-fold. Cheng Fong et al., (2011) and Vokurka et al., (2011) reported that the development of oral mucositis in previous chemotherapies was a risk factor for oral mucositis (9,11). Considering all these results, it is thought that it may be important to know the chemotherapeutic agents that patients are exposed to in oral care planning.

Smoking has an adverse impact on tissue healing as it affects microcirculation (6). The risk of oral mucositis was increased due to smoking (22),

whereas other studies had different conclusions. Vatca et al., (2014) found that the incidence of oral mucositis was lower in smokers since the activity and percentage of keratinized cells in the buccal mucosa of smokers increased (27). Smoking was not found to be a risk factor in this study. In addition, many studies do not correlate smoking with the development of oral mucositis (10,24,26). Findings may be related to characteristics such as the patient's smoking frequency, cigarette content, and oral care after smoking.

Many of chemotherapy agents used for cancer treatment increase the risk of mucositis (6). Studies conducted on this topic also demonstrate differences. A meta-analysis study (n = 2448) showed about 14% of the incidence of severe mucositis (grade 3–4) was related to 5-FU (25). The study by Shouval et al., (2019) found correlation between oral mucositis and methotrexate (18). Cheng Fong et al., (2011) reported that patients who received methotrexate or adriamycin-based therapy developed oral mucositis frequently (9). The study by Vokurka et al., (2009) found that high-dose melphalan-containing regimens increased oral mucositis development (33). This study showed no correlation between the chemotherapy agents and the development of oral mucositis. It is thought that the risk of oral mucositis development depends not only on the chemotherapy agent but also on the duration and the dose of chemotherapy.

CONCLUSION
This study examined the incidence of oral mucositis and risk factors that may influence oral mucositis development in patients receiving chemotherapy. Mucositis history was found as a risk factor in oral mucositis development. The incidence of oral mucositis was 27.3%. Most of the patients were grade 0 on day 14 after chemotherapy, but oral mucositis ended before day 14 in the patients. Therefore, it is important to do early follow-up of patients after chemotherapy and manage oral mucositis. Health professionals should give importance to patient training and follow-up in consistent with clinical guidelines.

Limitations
This study has a few limitations. First, the patients were treated on an outpatient basis, so they visited on day 14 in line with their chemotherapy protocols. Therefore, intraoral assessments could not be

conducted before day 14. Patients were asked regarding the beginning and end of oral mucositis. Second, each patient was in a different stage, different treatment procedures were being applied, and the oral care practices of the patients differed. Finally, the risk of oral mucositis may increase with increasing duration and number of chemotherapy courses. In this study, patients were not followed up after the 14th day. Therefore, longer patient follow-up is recommended in future studies. Our results may not be generalisable and need to be further investigated in a larger cohort.

Implication for Nursing Practice

Mucositis is an important complication that negatively affects the quality of life because it causes many psychological, social and economic problems in the patient. There is no standard treatment or care practice to prevent mucositis. Effective management of oral mucositis can be sustained by continuing nursing care during cancer treatment. It should not be forgotten that patients with a history of mucositis are in the risk group, oral health of these patients should be evaluated regularly during chemotherapy and changes in the mouth should be noticed in the early period. The mouth area should be brought to a full healthy level before chemotherapy. Identification of patients with a high risk of mucositis is very important in order to prevent complications that may occur in the patient. It will also alleviate the clinical, psychosocial and economic burdens that may occur during the chemotherapy process. The important role of mucositis risk estimation in providing individualized cancer care should not be forgotten. It is expected that the importance given to oral care by patients who have knowledge about oral care needs will increase.

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