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ORIGINAL ARTICLE

Impact of periodontal status on the oral mucositis in patients receiving high-dose chemotherapy

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Abstract

Objectives Oral mucositis (OM) is a frequent complication of cancer treatments. Oral mucositis and periodontal disease have a common inflammatory pattern. The purpose of this study was to evaluate the OM and its association with periodontal status in patients with hematologic malignancies who undergo high-dose chemotherapy.

Materials and methods Fifty-five patients who received high-dose chemotherapy were included in the study. Full-mouth periodontal clinical measurements including plaque index (PI), gingival index (GI), clinical attachment level (CAL), and probing depth (PD) values were recorded before the condition chemotherapy regime. OM monitoring was initiated 1 day after the chemotherapy and maintained for 20 days.

Results Twenty-two of patients (40%) were observed oral mucositis after high-dose chemotherapy. Patients with mucositis had significantly higher GI scores than those who did not have mucositis ($p < 0.05$). There was a significantly moderate positive correlation between the grade of mucositis and GI scores ($p < 0.05$). In patients with periodontitis, the incidence of grade 1–2 mucositis was significantly higher than in the healthy group ($p < 0.05$). In individuals with periodontitis and gingivitis, the healing duration of mucositis was significantly longer than the healthy group ($p < 0.05$).

Conclusions The results of this study showed that the severity grades of oral mucositis may increase in patients with gingival inflammation**.** The results also suggest that periodontal diseases may have a significant impact on the duration of oral mucositis.

Clinical relevance The current study contributes to our understanding of the importance of oral health status in reducing the occurrence, severity, and duration of OM in hematological cancer patients treated with high-dose chemotherapy.

Keywords High-dose chemotherapy · Oral mucositis · Gingivitis · Periodontitis

Introduction

High-dose chemotherapy (CT) and radiotherapy are used in various malignancies such as hematologic cancers. However, these therapies induce adverse events including oral mucositis [1, 2]. Oral mucositis (OM) is a frequent complication of cancer therapy that is characterized by erythematous, erosive, and ulcerative lesions of the oral mucosa [3]. OM occurs in 40–80% of patients undergoing chemotherapy [4, 5]. The most common locations of the chemotherapy-induced OM is usually nonkeratinized

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areas [6]. OM causes intense pain, patient discomfort, and secondary infections [2].

The stomatotoxicity of the chemotherapeutic agents causes a complex pathophysiological pathway that leads to the development of oral mucositis. OM is characterized by epithelial atrophy and dyskeratosis, followed by epithelial disintegration and ulcerations [7]. The underlying pathophysiological mechanisms of oral mucositis may be described in 5 phases: initiation, upregulation and message generation, signaling and amplification, ulceration, and healing [6, 8]. To better define the criteria for diagnosis of OM the World Health Organization (WHO) mucositis scale, the National Cancer Institute (NCI) scale for oral mucositis and the Common Terminology Criteria for Adverse Events (CTCAE) can be used [9, 10].

OM negatively affects the outcome of cancer treatment by facilitating opportunistic infections and sepsis. Therefore, clinical approaches to reduce the incidence or severity of OM can improve patient survival and quality of life [11, 12].

Periodontal diseases are inflammatory disorders including gingivitis and periodontitis, which are caused by pathogenic microbiota. This means that the presence of pathogenic bacterial species contributes to the pathogenesis of periodontitis [13].

It is known that various systemic conditions affect periodontal tissues. Taking into consideration the existence of a two-way relationship between radiation-induced oral mucositis and periodontitis, a "two-hit" model was defined. It highlights the role of periodontal conditions as a risk factor for OM; the effect of OM on the inflammatory response of developing periodontitis. Therefore, periodontal disease could be a subsidiary risk factor for mucositis [14–17]. According to our knowledge, to date, there is limited data about the periodontal conditions preceding oral mucositis and its association with the OM in patients with hematologic malignancies who are administered high doses of chemotherapy. Since oral mucositis and periodontal disease share common inflammatory characteristics as mentioned above, periodontal diseases are likely to influence the development of OM.

Studies in the literature generally address the relationship between periodontal diseases and development of OM in various cancer patients [15, 21]. Some reports show that patients with gingivitis or periodontitis show a higher prevalence of mucositis *and* treatment of periodontal diseases in addition to competent oral care would reduce the oral complications of haematopoietic stem cell transplantation (HSCT) [5, 16]. The purpose of the present study was to evaluate the relationship between periodontal status and both OM development and the degree and duration of OM in patients with hematological malignancies who are undergoing high-dose chemotherapy.

Materials and methods

Study population

Patients with hematological cancer who were administered high-dose CT in the hematology department of Malatya Turgut Ozal Medical Center from March to December 2021 were included in the study. The participants were informed in writing about the study, and their written consent was obtained. This study was approved by the Malatya Clinical Research Ethics Committee (#2021/111).

Volunteers over 18 years of age who received same-type (autologous) stem cell transplant were included in the study. The CT regimen included high-dose CT without radiation for all participants. Individuals who underwent radiotherapy or different types of transplant procedures (allogeneic) were excluded from the study. Patients with platelet counts below 20,000 per mm^3 before the conditioning CT regimen were also excluded.

The demographic data, underlying diseases, comorbidities, antimicrobial prophylaxes, and conditioning chemotherapy regimens were collected from the medical records of the patients. Supportive care including antifungal, antiviral prophylaxis, and wide-spectrum antibiotics was initiated at the beginning of the conditioning regimen. To prevent mucositis, antifungal mouthwash and chlorhexidine mouthwash were administered prophylactically along with chemotherapy. Before the high-dose CT was administered, every patient was examined with by a periodontist (A.S.) using a periodontal probe. The examination was carried out with the patient on a stretcher and under artificial lighting. Fifty-five patients aged 18 to 72 years with lymphoma and multiple myeloma completed the study.

Periodontal clinical measurements and evaluation

The periodontal examination was performed by a single examiner who is a periodontist (A.S). Before the conditioning CT regime and HSCT, all periodontal parameters, including the plaque index [17], gingival index [17], probing depth (PD), and clinical attachment level (CAL) were recorded with a Williams periodontal probe (Hu-Friedy, Chicago, USA) from 6 points per tooth. Periodontal diseases were classified according to the 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions [18]. Periodontitis was defined as an interdental clinical attachment loss noticeable at ≥ 2 non-adjacent teeth, buccal or oral CAL ≥ 3 mm with a pocket depth of > 3 mm at ≥ 2 teeth. Gingivitis was defined as a PD of 3 mm or less accompanied by signs of

inflammation. A healthy state was defined as a PD of 3 mm or less accompanied by no clinical signs of inflammation.

Evaluation of oral mucositis

OM monitoring started 1 day after CT and continued for 20 days. Mucositis was diagnosed by the clinical aspects of the oral examination and measured using the Oral Toxicity criteria defined by the World Health Organization (WHO) (grade 0: absence of mucositis; grade 1: soreness with erythema; grade 2: erythema, ulcers, can eat solids; grade 3: ulcers, only liquid diet; grade 4: alimentation not possible) [19]. Also, the patients were visited once to 3 times a week and the duration of mucositis (in days) was recorded.

Statistical analysis

A power analysis was done to determine the sample size of the study by using G*Power software version 3.1.7 (Franz Faul, Christian-Albrechts-University, Kiel, Germany). An initial power analysis based on a significance level of $\alpha = 0.05$ and a confidence level of 0.95 resulted in the required sample size of 36 patients [13]. IBM SPSS Statistics 22 program was used for the statistical analysis. The normal distribution was determined by the Kolmogorov–Smirnov test and Shapiro–Wilks test. Kruskal–Wallis test was used to compare the quantitative data. Dunn's test was used to determine the group that caused the difference. Mann–Whitney *U* test was used for intergroup comparisons. Fisher's exact chi-square test was used to compare qualitative data. Spearman's rho correlation analysis was used to analyze the relations among the data. *P* values lower than 0.05 were considered statistically significant.

Results

Descriptive statistics of the participants are presented in Table 1. Fifty-five patients completed the study. While 26 participants were female (47.3%), 29 were male (52.7%). The average age was 47.16 ± 15.27 years.

The prevalence of mucositis was 40% (*n*: 22). Of all participants, 18 (32.7%) had periodontitis and 18 (32.7%) had gingivitis, while 19 (34.5%) participants were periodontally healthy (Table 1). While, mucositis was not present in 60% of the cases, 8 participants (14.5%) had grade 1, 8 participants (14.5%) had grade 2, and 6 participants (10.9%) had grade 3 mucositis. In patients with periodontitis, the incidence of grade 1–2 mucositis was significantly higher than in the healthy group ($p < 0.05$) (Table 2).

GI scores of the individuals with grade 3 or 4 mucositis was found to be significantly higher than the patients who had no indications of mucositis (*p*: 0.003; $p < 0.05$). There was not any statistically significant difference between the grade of mucositis and PD and PI scores ($p > 0.05$). Patients with mucositis had significantly higher GI scores than those who did not have mucositis (*p*: 0.001; $p < 0.05$) (Table 3). There was a significantly moderate positive correlation between the grades of mucositis and GI scores (45.7%) (*p*: 0.001; $p < 0.05$) (Table 4).

In individuals with periodontitis and gingivitis, the healing duration of mucositis was significantly longer compared to the healthy group (*p*1: 0.012; *p*2: 0.026; $p < 0.05$). However, there was no significant difference between the periodontitis and gingivitis groups ($p > 0.05$) (Fig. 1).

Table 1 Descriptive data of the study subjects

		N: 55
Sex (*n*%)	Female	26 (47.3%)
	Male	29 (52.7%)
Age (mean ± SD)		47.16 ± 15.27
Chemotherapy regimen (*n*%)	Mel	27 (49.1%)
	Bu-Eto-Cy	16 (29.1%)
	Bcnu	12 (21.8%)
Presence of mucositis (*n*%)	(−)	33 (60%)
	(+)	22 (40%)
Duration of mucositis (day) (median-range)		6 (3–10)
Periodontal status (*n*%)	Periodontally Healthy	19 (34.5%)
	Gingivitis	18 (32.7%)
	Periodontitis	18 (32.7%)
Number of teeth (mean ± SD)		23.93 ± 3.40

Mean ± SD mean ± standard deviations, *Mel* melphalan, *Bu* busulfan, *Eto* etoposide, *Cy* cyclophosphamide, *Bcnu* based chemotherapy (carmustine)

Discussion

The purpose of this study was to investigate the OM and its association with periodontal diseases in patients with hematologic malignancies who were administered high-dose chemotherapy. The findings of this study show that GI values were significantly higher in patients who had grade 3 or 4 mucositis. There was a significant association between the grades of mucositis and GI scores. Furthermore, for those patients who presented mucositis, statistically higher GI values were found in comparison with the patients who did not show any sign of mucositis. Also, in patients with periodontitis, the incidence of grade 1–2 mucositis was significantly higher than in the healthy group.

OM has a major negative impact on the quality of life. OM lesions are extremely painful and detrimental to diet/nutrition, speech, and oral hygiene, and increase the risk of infection [20]. Prevention of oral mucositis is important to

Table 2 Relationship between periodontal health status and mucositis grade

Mucositis grade	Healthy (*n*%)	Gingivitis (*n*%)	Periodontitis (*n*%)	*p*
Grade 0	16 (84.2%)	11 (61.1)	6 (33.3%)	
Grade 1–2	3 (15.8%)	4 (22.2)	9 (50%)*	0.015*
Grade 3–4	0 (0%)	3 (16.7)	3 (16.7%)	

Fisher's exact test, *$p < 0.05$

*Compared to healthy

Table 3 Comparison of periodontal clinical parameters according to mucositis grade

Overall		Mucositis			
		Mucositis (−)	Mucositis (+)		
		Grade 0	Grade 1–2	Grade 3–4	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± sd	*p*
PI	1.65 ± 0.80	1.57 ± 0.87	1.75 ± 0.69	1.8 ± 0.71	0.513
GI	1.0 ± 0.60	0.8 ± 0.5	1.12 ± 0.49	1.79 ± 0.76*	0.003*
PD	2.39 ± 0.91	2.27 ± 0.91	2.62 ± 0.87	2.4 ± 1.05	0.313

Kruskal–Wallis test, *$p < 0.05$

PI plaque index, *GI* gingival index, *PD* probing depth

*Compared to grade 0

Table 4 Correlation analysis of individuals between mucositis and periodontal parameters

All participants	*r*	*p*
PI	0.134	0.329
GI	0.457	0.001*
PD	0.143	0.297

Spearman's rho correlation analysis, *$p < 0.05$

PI plaque index, *GI* gingival index, *PD* probing depth

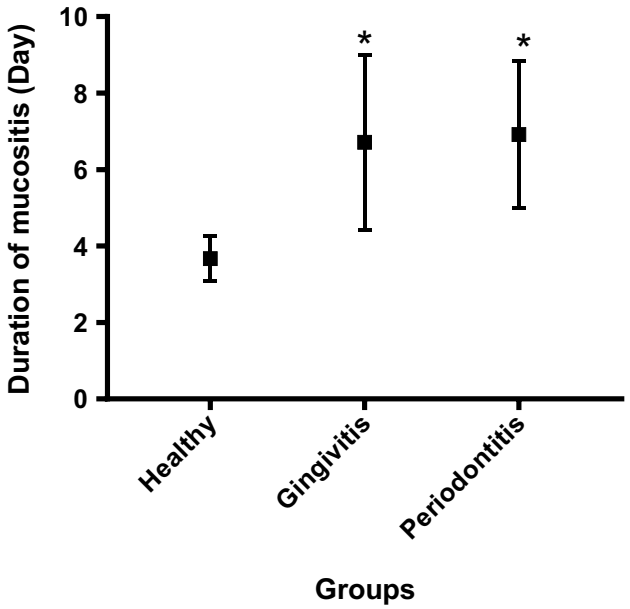

Fig. 1 Relation between duration of mucositis and periodontal health status. *Comparison to healthy group, healing duration of mucositis was significantly longer in the gingivitis group healthy group (*p*: 0.026). Healing duration of mucositis was significantly longer in the periodontitis group than healthy group (*p*: 0.012)

reduce morbidity as well as hospital stay in hematological cancer patients.

As in our study, Bensinger et al. [21] reported that patients with gingivitis are exposed to a higher risk of mucositis. Coracin et al. [22] concluded that the PI and GI values were positively correlated with OM incidence. In line with these studies, Fernandes et al. [16] evaluated the relationship between poor periodontal status and complications after HSCT in patients with hematological malignancy candidates for autologous HSCT and found that the frequency of mucositis was associated with gingivitis in patients undergoing HSCT. They also reported that all patients who had periodontitis prior to the administration of HSCT after chemotherapy developed mucositis. The findings of the studies examining the association between periodontal status and OM revealed that HSCT patients who received a high-dose CT and administered periodontal treatment had fewer OM [23, 24]. Based on our findings, occurrence of advanced mucositis in patients with gingival inflammation may be an indicator of the relationship between mucositis and the periodontal condition.

In the present study, there was no significant difference between the PD values of the groups in terms of the grade of mucositis. However, mucositis scores of 1–2 were found to be higher in patients with periodontitis compared to the healthy subjects. In conclusion, moderate mucositis in patients with periodontitis could indicate a link between the periodontal state and the grade of mucositis in patients wo were administered HSCT.

Corcain et al. [22] analyzed the correlation of this disease with the oral health of at the time of hematopoietic stem cell transplantation for those patients who underwent hematopoietic stem cell transplantation, and suggested that oral inflammation is an indicator of the incidence and healing time of OM. In the present study, we found that the healing time of OM was significantly shorter in the healthy

group than the patients with gingivitis or periodontitis. Periodontal diseases may affect wound healing by altering the biological pathways in the process of healing.

The risk of developing mucositis is directly related to the intensity of the CT regimen and the route of administration. Furthermore, the incidence of mucositis in patients with hematological malignancies may be related to the aggressiveness of the initial induction of chemotherapy and the degree of underlying immunosuppression [25, 26]. To ensure homogeneity of CT regimens and supportive care, only HSCT recipients of the same type (autologous) were included in this study. Further examination of these factors will provide a better understanding of the clinical and pathological properties of mucosal toxicity.

One of the limitations of the present study was that other acute oral diseases were not investigated. Clinical parameters were used to diagnose periodontal diseases. No radiographic examination was performed.

The results of this study showed that patients with periodontitis and gingivitis had mucositis while periodontally healthy patients did not. A positive correlation was observed between the grade of mucositis and GI scores. This study included patients who had the same type of stem cell transplant (autologous). Haematopoietic stem cell transplant type also affects the incidence of oral mucositis. This adds to the validity of the current study's finding that gingivitis is a major risk factor for OM. The results suggest that the combined effect of OM and periodontal diseases has a significant impact on patients. The oral care program should be completed before chemotherapy in this patient group. Additional investigations of other population subgroups are needed to corroborate these findings.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Arife Sabancı, Irfan Kuku, and Halil Sabancı. The first draft of the manuscript was written by Basak Karasu and Omer Alperen Kirmizigul. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval This study was approved by Clinical Research Ethics Committee of Health Sciences, İnönü University, Malatya, Turkey (#2021/111).

Informed consent A written consent form was obtained from each participant prior to the initiation of research protocols.

Conflict of interest The authors declare no competing interests.

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