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A Preliminary Study of Oral Manifestations in Cancer Patients Receiving Chemotherapy at Basrah Tumor Center

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Abstract

Oral complications can be detected during chemotherapy and are the main side effects that may directly affect anti-cancer therapy, even causing septicemia in some cases. Oral cavity health is a great reflection of an individual's systemic condition. This research was done in order to evaluate changes in oral manifestations in patients with cancer treated at the oncology and hematology department of Al Sadir teaching hospital, from November 2021 until May 2022. The study comprised patients above the age of 15 who were willing to participate and cooperate in clinical evaluations. The study design was longitudinal, 36 patients were evaluated and monitored for 6 months after the initiation of chemotherapy. The examinations were done in a hospital bed with artificial lights and a mirror. Any abnormal changes in the oral mucosa were examined. Twenty-four patients were male (67 %) and 12 female (33 %), ranging from 15 to 55 years old, and weight from 46 to 120. Sixty-four percent of patients included in the study were suffering from oral mucositis (OM) after chemotherapy treatment, and around 36 % of patients showed no effects. The results show an increase in the number of ulcerative cases (38 %), followed by candidiasis (17 %), xerostomia (8 %), and 36 % showed no effects. The researchers noticed that age of the patients was highly significantly correlated with the presence of OM, followed by weight and gender. Based on this finding, the results suggest that most male gastric cancer patients aged 36-45 and weight between 66 to 75 kg suffer ulceration in the oral cavity after receiving chemotherapy. Therefore, oral complications can be avoided by maintaining good oral health, and by minimizing outbreaks of infection. It is also possible to obtain an early diagnosis and treatment of this oral complication, preventing it from following a more severe clinical course that may adversely affect an individual's treatment. This finding requires a dental surgeon to be on the multidisciplinary cancer treatment team.

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1. Introduction

Cancer is a disease described by the abnormal proliferation of cells, which can inhibit anti-growth signals and causes invasion and metastasis. Thus, cancer cells affect the normal functioning of the organ and the balance in the body. Several treatment techniques such as chemotherapy, hormonal therapy, radiotherapy, immunotherapy, gene therapy, and targeted therapy have been used to control this disease [1–5]. Chemotherapy (CT) is a modern treatment used, by at least 70 % of patients. This treatment is worked by killing or inhibiting cell growth without any distinction between normal and carcinogenic cells. CT is usually toxic to cells with high turn-over, which will not only cancer cells but also bone marrow and the gastrointestinal tract mucosa, including the oral mucosa [6]. Oral mucositis (OM) is a very serious and challenging complication for both CT and radiotherapy in cancer patients [7]. Combined CT and radiotherapy can cause mucosal atrophy, local or widespread inflammation, and mucosal ulcers by decreasing the average rate of epithelial cell renewal [7, 8]. There are more than 100 different CT drugs that cause different toxic side effects such as bone marrow suppression (leucopenia appears after 10 days of the chemotherapeutic course while thrombocytopenia after 10-14 days), anemia, hair loss, nausea, fatigue, and vomiting (common side effects of CT), defects in spermatogenesis, diarrhea, hand-foot syndrome, cardio-toxicity, that correlated with both older and newer therapies which may lead to left ventricular impairment or congestive heart failure, or they can cause hypertension, thromboembolism, and pericardial thickening or cardiac arrhythmias. In addition to hepatitis B reactivation, neurologic complications such as peripheral and cranial neuropathy, seizures, myelopathy, cerebellar syndrome, aseptic meningitis, encephalitis, and stroke [6]. However, chemotherapeutic agents commonly used in all treatment protocols such as methotrexate, fluorouracil, cyclophosphamide, and daunorubicin, are particularly toxic to the oral mucosa [9].

OM is characterized as aggravation of the mucosa oral cavity and is clinically described by appearing of erythematous regions that in this pattern converge with ulcerations. OM is caused by the destruction of the oral mucosal epithelium and suppression of its growth after antineoplastic treatment in the form of chemotherapeutic drug substances or radiotherapy [10]. CT can cause direct or indirect oral complications. Direct toxic effects of CT on oral structures include mucositis, temporary dysgeusia, neurotoxicity (severe toothache-like pain not associated with local pathology), xerostomia, and salivary gland dysfunction. While indirect side effects include myelosuppression and immunosuppression and bacterial, fungal, and viral infections, oral bleeding can also be caused by thrombocytopenia. There are five stages of the pathobiology of the mucositis process include initiation, signaling, amplification, ulceration, and healing. Further, these oral complications can threaten the patient's life or cause severe side effects leading to delaying the patient's recovery [8].

Many factors can influence the presence and severity of oral complications, such as the patient's age, type, and location of cancer, nutritional status, dental and periodontal health, and oral hygiene status before and after treatment [8], in addition to the dose and types of chemotherapeutics that can increase the oral complications. These factors can induce mucositis, reduced salivary flow (xerostomia), pain (neurotoxicity), infections (e.g. oral candidiasis), and bleeding gums [9].

Due to the limited treatment of mucositis, prevention is emphasized. Emphasis is placed on patient education regarding oral hygiene. Pre-treatment should be aimed at decreasing systemic infection, the nutritional status of the patient should not be compromised, and the patient's life quality should not be affected [7]. Dental pretreatment (particularly periodontal treatment) has been shown to significantly reduce episodes of fever, septicemia, and prevent inflammation of the oral mucosa through an intensive oral care program, such as dental treatment and oral hygiene recommendations (brushing teeth and gums after each meal and before sleep) [11]. It is reported that mucositis affects 40 % to 80 % of patients treated with CT. OM is often observed in patients receiving CT for head and neck cancer (HNC). According to the literature, the ability of several synthetic agents for lesion healing has been examined. However, these agents have not yet been approved [12]. Several studies reporting CT-induced OM in children and many of them focused on one type of cancer especially leukemia or one chemotherapy, have been published. However, little literature reported the prevalence of CT-induced OM in the adult population [13].

With this background, our study aimed to identify and describe the oral side effects arising in cancer patients receiving different types of CT at Basrah tumor center for the first time. We also sought to ascertain whether these complications were related to a state of oral health.

2. Experimental Procedure

A total of 36 patients were enrolled in this descriptive cross-sectional study conducted to evaluate the prevalence of oral manifestations in patients with cancer treated at the oncology and hematology department of Al Sadir

teaching hospital, from November 2021 until May 2022. The study comprised patients above the age of 15 who were willing to participate and cooperate in clinical evaluations.

2.1. Clinical examination

The most probable clinical diagnosis was documented on a form in this study, and diagnostic criteria in the oral mucosa are based on history and clinical findings. According to previous investigations, the authors who had received additional training under the supervision of an experienced oral medicine specialist established the diagnosis based on clinical examination. The examinations were done in a hospital bed with artificial lights and a mirror. Any abnormal changes in the oral mucosa were examined.

2.2. Data collection

The data were collected from each patient's medical records: type of cancer, medication, age, sex, weight, and clinical diagnosis of oral mucosal lesions. According to these data, the variables analyzed in this study were designated for being the most current buccal adverse signs in oncologic patients, such as OM especially ulcerated, candidiasis, and xerostomia.

2.3. Exclusion criteria

The following were excluded:

- Patients with diseases in the oral cavity showing manifestations before chemotherapy.
- Patients with systemic diseases and oral manifestations such as acquired immunodeficiency syndrome or diabetes mellitus, chemical trauma, self-inflicted trauma, anemia, neutropenia, and nutritional deficiencies (e.g., vitamin B12, folate, iron).
- Patients earlier exposed to head and neck radiotherapy (<3 months).

2.4. Statistical analyses

The data obtained were exported to an excel database and evaluated with a statistical package for social science (SPSS); the Chi-square test was applied with a significance level of 5 % ($p \leq 0.05$).

3. Results

3.1 Demographic characteristics of patients

A total of 36 patients with cancer who received CT were enrolled in this study. The results showed that the number of males (67 %) patients was higher than females (33 %) (Table 1), this is supported by other studies [10]. For patients' ages, we noticed that most patients were aged 36 to 45 years (39 %), 46 to 55 years, (36 %), and 26-35 years (17 %). Similar results were observed in other studies, where aging was a risk factor for the development of OM [9], [11]. For patients' weight, 36 % of patients with weight ranging from 66 to 75. Sixty-four percent of patients included in the study were suffering from OM after receiving CT treatment as shown in Table 1, and around 36 % of patients showed no effects on OM after receiving CT. As shown in Figure 1, ulcerative was shown the highest percentage (38 %) of patients suffering from OM, followed by candidiasis (17 %), and xerostomia (8 %). Our results agreed with Atoof et al. [10] while contrasting with another study [9], which showed higher xerostomia. Table 2 shows that the most common type of cancer was mandible and gastric (17 %), followed by stomach (14 %), and ovary and CTX=3 (9 %). However, other studies highlighted a range of other cancers as the most common, namely breast, lung, prostate, and endometrial cancer [9] [12]. All CT protocols are presented in Table 3. Regarding CT treatment protocols, the most common was cisplatin (19.4 %), which is in agreement with the findings of Tonkaboni and Batebi [13], Jena et al. [9], followed by oxaliplatin with 5-FU at 16.7 %, and carboplatin with 5-FU at 11.1 %.

Table 1. Distribution of patients according to the gender, age, weight and the presence or absence of OM

	No.	(%)
Gender		
Male	24	66.7
Female	12	33.3
Age		
15-25	3	8.3
26-35	6	16.7
36-45	14	38.9
46-55	13	36.1
Weight		
46-55	4	11.1
56-65	10	27.8
66-75	13	36.1
76-85	8	22.2
100-120	1	2.8
Presence or absence OM		
Positive	23	63.9
Negative	13	36.1
Total	36	100

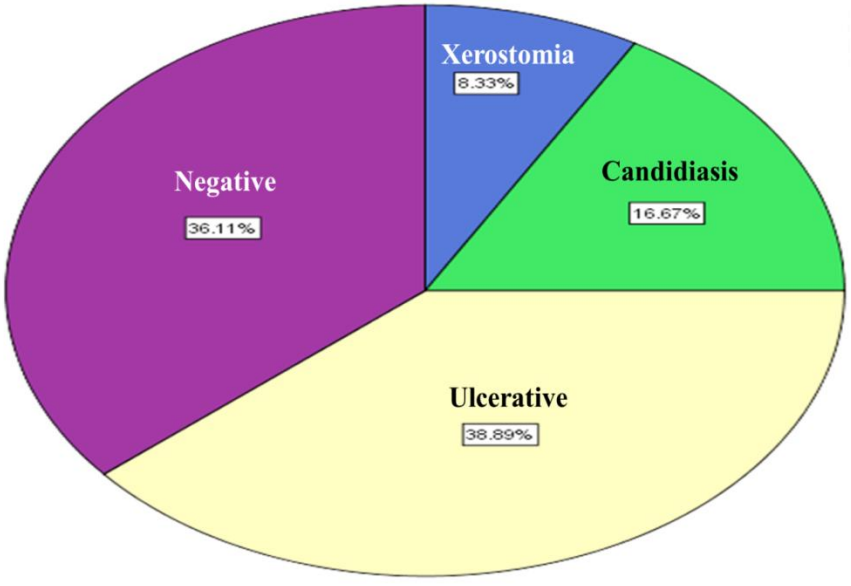

Figure 1: Distributions of patients based on OM type.

Table 2. Distribution of the patients according to the type of cancer

Type of cancer	NO.	%
CA- Lung	2	5.6
CA-Mandible	6	16.7
CA-Stomach	5	13.9
CA-Gastric	6	16.7
CA-Bronchus	2	5.6
CA-Colon	2	5.6
CA-Ovary	3	8.3
CTX=3	3	8.3
CA-Rectal	2	5.6
CA-Uterus	2	5.6
CA-Rectum	1	2.8
CA-Breast	2	5.6
Total	36	100.0

Table 3. Distribution of the patients according to the CT protocol

Chemotherapy protocol	No.	%
Etoposide	3	8.3
Cisplatin	7	19.4
Oxaliplatin with 5-FU	6	16.7
Carboplatin with 5-FU	4	11.1
Paclitaxel with Oxaliplatin with 5-FU	1	2.8
Paclitaxel with Carboplatin	3	8.3
Oxaliplatin with Irinotecan with 5-FU	2	5.6
Bleomycin with Cisplatin with Etoposide	1	2.8
Endoxan	3	8.3
Caelyx	1	2.8
Irinotecan with 5-FU	2	5.6
Holoxan	1	2.8
Paclitaxel with Oxaliplatin+5-FU	1	2.8
Carboplatin	1	2.8
Total	36	100.0

3.2 Association of OM with different variables

Table 4 shows the correlation between different variables and types of OM detected after CT treatment, in which we noticed that age of the patients was highly significantly correlated with the presence of OM, followed by weight and gender. As shown in Figure 2b, the results confirmed that patients with ages ranging from 36-45 and 26-35 years are more likely to show ulceration and candidiasis respectively, after receiving CT treatment. In this study, the highest prevalence of ulceration and candidiasis was found in patients aged 36-45 years, and it is possibly due to high cellular turnover [14]. Further, patients with a weight of 66-75 kg showed a high level of ulceration, followed by patients weight of 56-65 kg with ulceration and candidiasis (Figure 2c), and we also noticed that all OM types (ulceration, candidiasis, and xerostomia) were higher among males than the female

(Figure 2a). Further, based on types of cancer, gastric, stomach, bronchi, colon, and mandibular cancer have developed ulceration and candidiasis and the rest developed xerostomia (lung, mandibular) as shown in Figure 2d. The results suggest that most male gastric cancer patients aged 36-45 and weights between 66 to 75 kg suffer ulceration in the oral cavity after receiving CT.

Table 4. Distribution of patients by types of OM and different variables associated with it

Correlations

	Gender	Age	Weight	Oral mucositis
Gender		0.741**	0.744**	**0.741****
Age	0.741**		0.872**	**1.000****
Weight	0.744**	0.872**		**0.872****

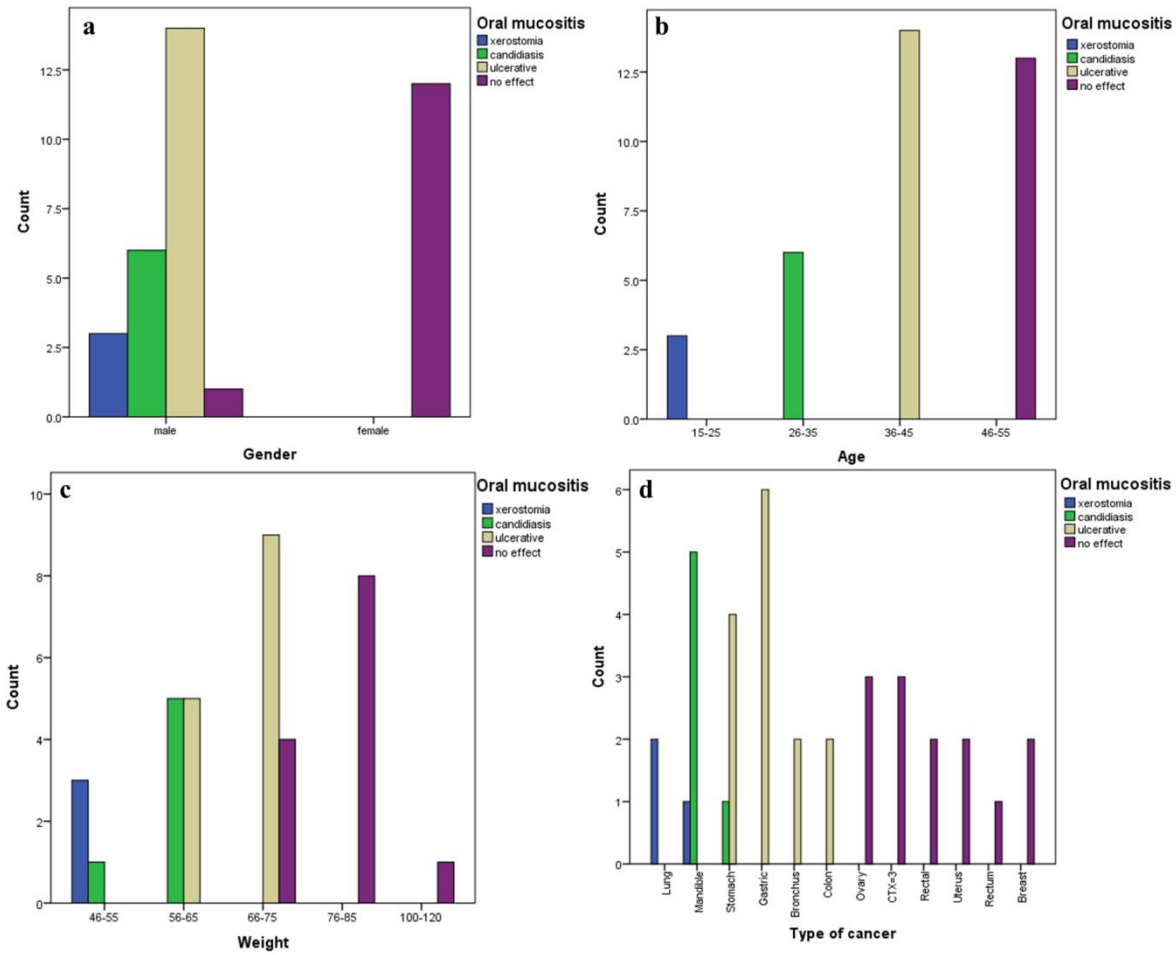

Figure 2. Associations between OM and different variables in patients receiving CT: (a) gender, (b) age, (c) weight, (d) type of cancer.

4. Discussion

The chemotherapies showed many adverse effects including oral side effects that need specific oral care. The oral manifestations symptoms determined in this study after receiving CT are similar to that reported in previous studies including mucositis, ulceration, xerostomia, dysphagia, mouth and lip dryness, dysgeusia, gingival bleeding, candida infection, and the loss of ability to talk [8, 9, 15–18]. Further, CT oxaliplatin and carboplatin

combined with 5 fluorouracil (5-FU), showed an increase in OM from mild to moderate [19]. In patients dealing with CT alone or combined with radiotherapy, the entire gastrointestinal tract may be affected. Weight loss is common, and patients might also additionally require gastrostomy or parenteral feeding. Severe OM might also additionally cause dose reductions and unplanned interruptions of cancer therapies [20]

In this study 36 patients were examined for oral manifestations, 13 out of 36 examined patients didn't show any oral manifestation after receiving CT for 1 or 2 weeks, while 23 (63.9 %) patients showed oral manifestations symptoms including ulcerative, candidiasis, and xerostomia. However, the prevalence of OM in the study of Tonkaboni and Batebi [21] (36.2%) was lower. The ulcerative showed the largest percentage (38.86 %), followed by candidiasis (16.67 %), and xerostomia (8.33 %). These manifestations may be associated with reduced salivary flow, mucositis severity, and neutropenia [9]. These differences in OM symptoms may be attributed to cancer types differences and CT protocols [14].

Ulceration is characterized by the disruption of the integrity of the epithelial tissue or underlying connective tissue and causes a major danger issue for systemic infectious, specifically in neutropenic or immunocompromised patients. Oral ulcerative can be classified based on the duration and number of lesions into 3 main groups: recurrent, acute, and chronic ulcers and into 5 subgroups: multiple chronic, multiple acute, solitary acute, solitary chronic, and solitary/multiple ulcers [22]. Candidiasis is the most common mouth fungal infection caused by *Candida albicans*. The most common type of candidiasis is the pseudomembranous presentation, followed by erythematous candidiasis and angle cheilitis. Candidiasis can develop into sepsis and lead to death if not probably diagnosed, especially when caused by *Candida tropicalis* [23]. The low percentage of oral candidiasis is likely due to the use of antifungal drugs that act both locally and systemically during treatment for most patients [17].

Xerostomia causes speech difficulty, mouth pain, affects the patient life, and an alteration in salivary gland functions and may be resolved shortly after the finish of treatment or dose reduction [9]. Increased levels of amylase and peroxidase are observed. The simultaneous decrease in the amount of IgA and IgG accompanies the CT. In fact, oral manifestations are the most common side effects reported in acute myeloid leukemia (AML) patients during receiving CT for one week which include bleeding (56 %), mucosal ulceration (53 %), gingival enlargement (36 %), or necrosis, high prevalence of caries, pallor of the mucous membrane, herpetic opportunistic infections, candidiasis, temporomandibular arthritis, osteolytic lesions of the lower jaw, palatal pigmentation, toothache, hemorrhagic bubbles on the tongue, chapped lips, swelling of the parotid gland may appear, and chin anesthesia [8, 24].

However, patients must follow a diet that is essential to prevent the increase or emergence of oral symptoms. For instance, cigarettes, alcohol, coffee, tea, and spicy food must be avoided [8]. On the other hand, oral hygiene habits play an important role in maintaining or improving a patient's oral health, and involving dentists in multidisciplinary oncology teams is essential in inhibiting or alleviating complications of antineoplastic [9]. This dentist can help prevent the development of a more severe clinical course, which can lead to the suspension of antineoplastic therapy [17]. Teeth and oral tissue disease could have been prevented by following good oral hygiene protocol and a high-fluoride toothpaste.

5. Conclusions

After completion of the examination procedures for patients receiving CT at Al-Sadr teaching hospital, most of their symptoms were mucositis, ulcerative, candidiasis, and xerostomia. In this study, we concluded that OM was the predominant lesion of the mouth after CT. Thus, having an oral and maxillofacial specialist working in coordination with the medical team is important for patient care before and after CT. Scientific progress and additional research are necessary to help the human race overcome cancer, such as a simple disease

6. Recommendations

Educating patients about the importance of strict adherence to oral care guidelines during applying CT protocols is recommended to minimize oral side effects and can improve the patient's life and also reduce the urgency of stopping CT due to these oral side effects.

Conflict of Interest

The authors declare that they have no conflict of interest.

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