

Orofacial complaints and complications of chemotherapy

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ABSTRACT

Background: Oral complications of chemotherapy are sometimes unnoticed and if not treated, they can compromise patients' health and quality of life. **Methods:** This study aimed to assess and characterize orofacial complaints and complications, and their impact on the oral-health-related quality of life in patients undergoing cancer chemotherapy.

Results: We evaluated 28 patients with solid tumors undergoing chemotherapy, through a systematic orofacial evaluation. Eighteen patients (64.2%) developed oral complications during chemotherapy and xerostomia scored the highest incidence $n = 14$ (50%). About oral health data, gingival index revealed greater part of patients classified with moderate or severe gingival inflammation. The mean plaque index was 25.6%. The mean CPOD index was 15.48 and was worse in patients without oral complications. The patients presented higher plaque index and the oral health impact profile showed higher mean index in the patients group that developed oral complications. **Conclusion:** These data reinforce the crucial role of the dentist in the multidisciplinary team, with crucial support in the diagnosis of oral complications. Thus, a specific assistance and relieve of patient's complaints could impact positively on quality of life.

Key words: Cancer; Oral Health; Quality of life; Health

INTRODUCTION

The side effects and adverse reactions related to cancer therapies can trigger complications in the oral cavity. These effects cause acute and late toxicities that may be underreported, under recognized, and under-treated (1). Numerous studies have identified, and reported a wide range of incidence and severity for different oral complications after cancer therapies. These include: oral mucositis, xerostomia, bleeding, dysphagia, dysgeusia, caries, periodontal disease, infection (bacterial, viral, and fungal), pain, trismus, osteoradionecrosis, growth and developmental disturbances, and salivary gland dysfunction (2,3,4).

These oral complications can compromise patients' health and quality of life, and, worst of all, affect their ability to complete cancer treatment (5,6,7). Furthermore, they may lead to discomfort and even severe pain in the injured part of the body, patient's nutritional deficiency, delay in the administration of oncologic drugs or dose limitation, increase of hospitalization time and the related expenses, as well as septicemia and life-threatening diseases in some cases (5,8,9).

Among oral complications, oral mucositis stands out. Oral mucositis refers to erythematous and ulcerative lesions of the oral mucosa observed in patients with cancer being treated with chemotherapy, and/or with radiation therapy to fields involving the oral cavity (10,11). It has been consistently reported to occur in at least 75% of patients treated with irradiation for head and neck cancers, individuals receiving conditioning regimens for stem cell transplant and protocols for acute leukemia (12,13). This adverse reaction occurs in 20-40% of patients receiving conventional chemotherapy (14). Additionally, the prevalence of chemotherapy-induced mucositis has been shown to vary between 30% and 75% of patients, depending on the type of treatment (15), and the risk of developing mucosal lesions increases with the number of chemotherapy cycles and previous episodes of mucositis (16).

Oral mucositis and dry mouth were the most frequent concomitant oral manifestations associated with cancer therapies (16.33%) (6).

Xerostomia is a term used to describe the subjective symptom of a dry mouth deriving from a lack of saliva (17). It is important to note that a dry oral mucosa is friable and susceptible to trauma, inflammation, and irritation (18,19). Considering these aspects, a decrease in salivary production or changes in its qualitative properties may cause a health-related poor quality of life (20) and oral lesions (18,19).

Moreover, other oral complication associated with cancer therapy, is dysphagia. It is a symptom of swallowing dysfunction that not only deprives people of the pleasure from eating but also endangers patient health by creating a risk of aspiration pneumonia and malnutrition (21,22). It is related to a number of factors such as direct impact of the tumor, cancer resection, chemotherapy, and radiotherapy and to newer therapies such as epidermal growth factor receptor inhibitors (23). Concomitant oral complications such as xerostomia may exacerbate subjective dysphagia (23,24).

Oral candidiasis is one of the most common opportunistic infection of the oral cavity (25,26). Oral candidiasis manifests as acute or chronic disease and either superficial or disseminated systemic mycosis. It has been associated with multiple host risk factors and it is common in patients with head and neck cancers, especially during chemotherapy and radiotherapy. It usually manifests as acute erythematous candidiasis, but the diagnosis may often be missed, as it may be mistaken for radiation mucositis (27).

Last but not least, another important complication is orofacial pain. It may be caused by cancers or cancer-related therapy. The incidence of pain varies widely based on the patient population and the type of treatment. The most common etiology of cancer pain is local tumor invasion (primary or metastatic), involving inflammatory and neuropathic mechanisms. As malignant disease advances, pain usually becomes more frequent and more intense. Additional expressions of orofacial cancer pain include distant tumor effects, involving paraneoplastic mechanisms. Pain secondary to cancer therapy varies with the treatment modalities used: chemo-radiotherapy protocols are typically associated with painful mucositis and neurotoxicity. Surgical therapies often result in nerve and

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tissue damage, leading, in the long term, to myofascial and neuropathic pain syndromes (28,29).

Considering our limited understanding of the burden of illness in the oral cavity from various cancer therapies and how it impacts the quality of life of the patient undergoing cancer therapy, we performed a systematic orofacial assessment of patients undergoing chemotherapy. It is essential to act promptly through identification and treatment of oral complications, thus allowing comfort and better results after therapy in patients undergoing cancer treatment.

MATERIALS AND METHODS

Patients

This study was conducted from April 2015 to April 2016 at a local hospital after obtaining approval from the Ethics Committee (n. 1.684.653). Twenty-eight patients with cancer diagnosis were evaluated. All subjects were informed about the study's purposes and signed an informed consent. Inclusion criteria were patients with solid tumors undergoing chemotherapy. Exclusion criteria were cognitive impairment, patients undergoing radiotherapy concomitant to chemotherapy, patients who received treatment for oral complications previously, and patients with cognitive deficit.

Assessments

This study involved a retrospective analysis of data on the demographic characteristics of the study population, clinical diagnosis of cancer, as well as treatment used, which were obtained from medical records. Cross-sectional study was also performed to evaluate the stomatognathic system from dental history data, orofacial physical examination, clinical tests for dysphagia diagnostics (30), questionnaires for evaluation of xerostomia (31,32) and quality of life related to oral health (33). The socio-economic class (34) of all patients was determined. The evaluations were performed between 7-14 days after the beginning of the first cycle of chemotherapy (35). They were applied to all patients equally by an experienced and trained dentist.

Instruments of evaluation:

1. Standardized clinical form to obtain information on patient demographics, their medical history and presence of chronic diseases as covariates, type of cancer presented by each patient and treatment that was submitted (information obtained from medical records). Also, the stomatognathic system was assessed, from the data of dental history and orofacial physical examination (29). This data was studied to assess the presence of signs and symptoms of oral changes and/or oral complications of cancer treatment.
2. Oral mucositis (OM) and its severity were assessed according to the classification of the World Health Organization - WHO (36).
3. Clinical diagnostic tests for dysphagia (30), and characterization of orofacial pain, when applied.
4. Xerostomia questionnaire, consisting of eight questions, was used to evaluate feeling of dryness in the patient's mouth (31,32). Based on the severity of the symptoms, patients were classified as xerostomic or not. Xerostomia was considered for average values > 2 (37), according to the visual analogue scale (VAS).

5. Oral Health Impact Profile (OHIP) Questionnaire (33) used to measure oral-health-related quality of life. This questionnaire was developed to provide a comprehensive measurement of dysfunction, discomfort and disability attributed to oral conditions. The short form of OHIP (OHIP-14), which was used in this study, contained 14 items grouped into seven dimensions of impact: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. The participants responded to each item according to the frequency of the impact on a 5-point Likert scale (ranging from 0 to 4): never, hardly ever, occasionally, fairly often, and very often.
6. Socioeconomic ABA-ABIPEME (34) Questionnaire used to evaluation the socioeconomic class of the population studied.

Statistical analysis

A descriptive study was made for demographic, oncologic and associated comorbidities and oral complaints data. In order to relate oral complications with the patients' values of gingival index (GI), the Fisher's exact test was used; to study possible relations between oral complication and plaque index (PI), CPOD index and OHIP evaluations, the Wilcoxon test was applied.

RESULTS

Demographic data

Twenty-eight patients with solid tumors indicated to chemotherapy treatment were assessed, 05 (17.86%) men and 23 (82.14%) women, with a mean of 54.5 ± 12.46 years (ranging from 31 to 77 years). The general characteristics are presented in table 1.

Table 1. Socio-demographic and clinical data variables description of cancer patients (n=28)

Demographic data	Study Group n=28
Sex n (%)	F=23 (82.14) M=5 (17.86)
Age (mean \pm SD) (minimum-maximum)	54.5 \pm 12.46 (31-77)
Socioeconomic class	n (%)
A	0 (0)
B	13 (46.43)
C	13 (46.43)
D	2 (7.14)
E	0 (0)

n = number of patients; %=relative frequency in percentage; F=Female; M=Male; SD=standard deviation. ABA/ABIPEME: A/B Class: 59 points or up = family average income of more than US\$2,000.00 approximately; C/D/E Class: 0-58 points= family average between US\$200,00 and US\$700,00 approximately.

Cancer diseases characteristics

Breast cancer was the most frequent site of tumor n=19 (67.8%). There was predominance of adjuvant treatment n=17 (60.7%). And the most prevalent chemotherapeutic agent was doxorubicin n=20 (71.4%). Twenty-two (78.5%) patients showed comorbidity; furthermore all of them had 1 or more comorbidities. The most prevalent associated morbidity was hypertension n=13 (46.4%) and gastritis n=7 (25%). In consequence, there was predominance of use of antihypertensive drugs n=14 (50%) and antacids n=7 (25%). The cancer diseases characteristics and comorbidities of all patients are detailed in table 2.

Table 2. Cancer diseases characteristics and associated comorbidities

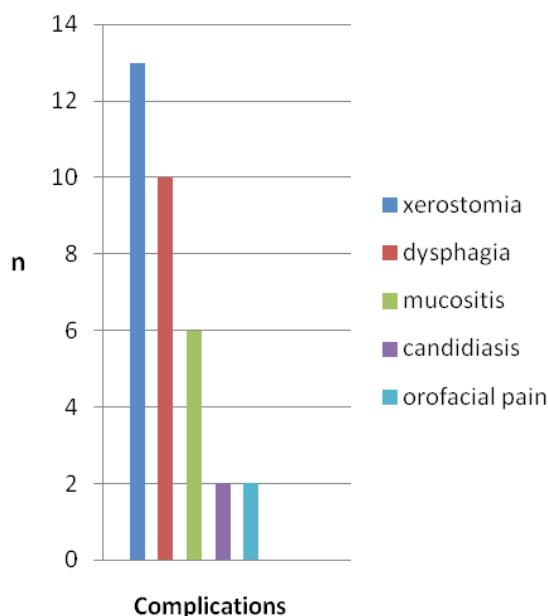
Variables	n (%)
Tumor site	
Breast	19 (67.86)
Gastrointestinal	3 (10.71)
Sarcoma	2 (7.14)
Others	4 (14.29)
Diagnostic time	
<3 months	15 (53.57)
3-6 months	9 (32.14)
6-12 months	1 (3.57)
>12 months	3 (10.71)
Treatment	
Adjuvant	17 (60.71)
Curative	4 (14.29)
Neoadjuvant	2 (7.14)
Palliative	5 (17.86)
Chemotherapeutic agent	
Doxorubicin	20 (71.43)
Cisplatin	5 (17.86)
Fluorouracil/leucovorin/oxaliplatin	3 (10.71)
Drugs*	
Antihypertensive	14 (50)
Analgesic	3 (10.71)
Antacid	7 (25)
Others	10 (35.7)
None	5 (17.86)

n= number of patients; %=relative frequency in percentage

* Patients have been used more than one drug

Oral complaints and complications detected

In this study, 18 participants (64.2%) had at least one oral complaint and/or complication resulting from chemotherapy, while 10 (36.8%) did not show any change in the oral cavity. The most prevalent oral complication was xerostomia n=14 (50%), followed by dysphagia, oral mucositis, candidiasis and orofacial pain. Figure 1 showed these data.

Figure 1. Presence of oral complications

n= number of patients

Oral Health Data

About the oral health data, gingival index 1 was the most prevalent, n=15 (52.7%) patients. The mean plaque index was 25.6% (range from 1.78 to 100%) and the mean CPOD index was 15.48 (range from 2 to 26). Observing the patients in relation to the development of oral complication, the statistical analyses indicated that the group with oral complication (n=18) and without oral complication (n=10) were different only related to CPOD index (p-value<0.05) (Table 3).

Table 3. Oral Health Characteristics

Variable	With Oral Complication (n=18)	Without Oral Complication (n=10)	P-value
Gingival Index			
0	0 (0)	1 (10)	0.6300
1	10 (55.56)	5 (50)	
2	8 (44.44)	4 (40)	
Plaque index			
Mean	25.85	25.43	0.0717
Standard Deviation	18.83	29.82	
Maximum	69.04	100	
Minimum	3	1.78	
CPOD index			
Mean	15.06	15.9	0.0006
Standard Deviation	4.90	7.42	
Maximum	24	26	
Minimum	5	2	

n= number of patients; If the p-value is inferior to 0.05 the equality between groups is rejected, if not, the equality is not rejected.

Oral health-related quality of life (OHIP-14)

In the OHIP-14 questionnaire, the patients with oral complications scored worse compared with the patients without oral complications. The questions 2 and 4, referred to change in taste and feeding discomfort, had the highest mean values noticed in both groups. These were: change in taste (0.6 versus 0.33) and feeding discomfort (0.77 versus 0.4), respectively. However, with regards to functional disability (question 12) and difficulty in performing daily tasks (question 14), there were none reported by any patients. Evaluation of oral health-related quality of life with the values of all questions for cancer patients (n=28) with oral complications and without oral complications are shown in table 4.

About all domains of the OHIP-14 questionnaire (Table 5), patients with oral complications showed mean OHIP-14 index of 0.44, while those who did not develop oral complications had mean OHIP-14 of 0.23. The domains functional limitation (0.66 versus 0.45) and physical pain (0.9 versus 0.43) showed significant differences in relation to the patients with oral complications and patients without oral complications, respectively.

DISCUSSION

The orofacial systematic clinical evaluation in patients undergoing chemotherapy is crucial to increase the knowledge about the disease's process determinants and to define therapeutic strategies for these patients. One advantage of the present study was the global systematic dental assessment performed between 7-14 days after the beginning of cancer therapy. This is the highest period of incidence of oral complications (35). The evaluations included a systematic assessment from dental history data,

Table 4. Evaluation of oral health-related quality of life (OHIP-14) in cancer patients (n=28)

Questions	With Oral Complication (n=18) M(SD)	Without Oral Complication (n=10) M(SD)	p-value
1. Had trouble pronouncing words	0.06 (0.24)	0.15 (0.25)	NA
2. Felt that sense of taste has worsened	0.6 (0.6)	0.33 (0.55)	0.2525
3. Had painful aching in mouth	0.13 (0.24)	0.03 (0.11)	NA
4. Was uncomfortable when eating foods	0.77 (0.52)	0.4 (0.56)	0.3085
5. Has been feeling self-conscious	0.3 (0.51)	0.14 (0.3)	NA
6. Has felt tense	0.18 (0.38)	0 (0)	NA
7. Diet has been unsatisfactory	0.26 (0.41)	0.1 (0.22)	NA
8. Has had to interrupt meals	0.13 (0.28)	0.1 (0.2)	NA
9. Finds it difficult to relax	0.23 (0.55)	0 (0)	NA
10. Has been a bit embarrassed	0.22 (0.42)	0.28 (0.54)	NA
11. Has been irritable with other people	0.17 (0.41)	0 (0)	NA
12. Has had difficulty during usual jobs	0 (0)	0 (0)	NA
13. Has found life less satisfying	0.07 (0.19)	0.12 (0.37)	NA
14. Has been totally unable to function	0 (0)	0(0)	NA

n= number of patients; M=mean; SD=Standard Deviation; If the p-value is inferior to 0.05 the equality between groups is rejected, if not, the equality is not rejected. NA= not applicable since number of cells with zero values was greater than 50%.

orofacial physical examination, clinical tests for dysphagia diagnostics (30) and questionnaires for evaluation of xerostomia (31,32) and quality of life related to oral health (33). Moreover, the socio-economic class of all patients was determined (34).

The most prevalent oral complication was xerostomia. Its prevalence and negative effects on the patient's quality of life requires the physician to confront the issue (21). This oral complication was found in 43.3% of examined patients, contrasting with a previous study (8) in which dry mouth was found in 10.58% of the cases and it was the second most prevalent oral complication. This contrast may be due to the lack of studies that correlate xerostomia with chemotherapy alone. In agreement with the level of scientific evidence that evaluates the various substances employed in the treatment or clinical management of patients with hypo salivation/xerostomia, more clinical studies are needed to evaluate the drugs, substances, and techniques that are presented as useful therapies for these pathologies (21). Moreover, it is important to note that xerostomia can trigger other oral complications, such as dysphagia (28,29). Furthermore, patients with oral complications showed scores of OHIP-14 slightly higher than those who did not develop oral complications, and had a mean of 0.56. This finding is in line with previous studies that showed correlations between side effects of cancer treatment and poor index of quality of life (6,7). Although the statistical analysis was not significant, this study showed a trend relating patients that developed oral complications with a worse experienced in 'functional limitation' domains of OHIP-14 when compared to patients without oral complications during the same period of evaluation, between 7-14 days of chemotherapy.

These domains refer to signs, which correspond to the trouble pronouncing words and worse sense of taste. In fact, symptoms from adverse effects involving the oral cavity are more frequently observed than signs (38). About the others domains of quality of life related to oral health, the data did not reveal any difference between the evaluated patients. Perhaps the suffering of the patient with the systemic disease (cancer) leads them to undervalue other health aspects, i.e. related to oral health.

Regarding the oral health assessment, the patients with or without oral complications showed similar gingival indexes, and the majority of patients were classified as with moderate or with severe gingival inflammation. This data is important and reinforces the crucial role of a dentist to control this treatable condition. The presence of gingival inflammation could put patients at risk of others systemic complications (39,40). The oral hygiene was similar between patients too. It is important to note that some patients presented higher index of plaque, showing the essential task of guiding patients in cancer therapy on oral hygiene care. The higher plaque index is related to oral and systemic diseases (41,42). The CPOD index was worse in patients without complication. This data is intriguing at first, however, it is possible that this group of patients have received oral care with a higher number of teeth extracted and treated.

Other aspect evaluated in this study was about the socioeconomic class of the sample studied. The results showed that most of the patients were of classes B or C. Thus, this profile of patients is characterized by lack of financial resources and worse access to health services (43). This fact is relevant, since the evaluation of the effect of oral diseases and

Table 5. Oral health-related quality of life (OHIP-14) in cancer patients (n=28)

Domains	With Oral Complication (n=18) M(SD)	Without Oral Complication (n=10) M(SD)	p-value
Functional limitation	0.66 (0.58)	0.45 (0.68)	0,0889
Physical pain	0.9 (0.54)	0.43 (0.54)	0,2525
Psychological discomfort	0.48 (0.64)	0.14 (0.3)	NA
Physical disability	0.39 (0.48)	0.2 (0.35)	NA
Psychological disability	0.46 (0.61)	0.28 (0.53)	NA
Social disability	0.17 (0.41)	0 (0)	NA
Handicap Overall	0.07 (0.19)	0.12 (0.37)	NA

n= number of patients; M=mean; SD=Standard Deviation; If the p-value is inferior to 0.05 the equality between groups is rejected, if not, the equality is not rejected. NA= not applicable since number of cells with zero values was greater than 50%.

social conditions may be of great value to researchers, health care planners, and care providers (33).

It is important to note that, the patients assessed in this study presented others comorbidities and have been used multiples drugs. This fact could contribute to worsening of oral complications (44).

In conclusion, these differences between patients who developed or not oral complications should not be underestimated, highlighting their clinical importance. Furthermore, this study reinforces the importance of the dentist in the multidisciplinary team for cancer treatment, either in the diagnostic phase or during treatment in order to provide the patients with a complete and effective treatment, contributing positively to their quality of life.

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Conflict of Interest

We declare no conflicts of interest.

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