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ORIGINAL ARTICLE

Occurrence of oral mucositis in women during oncological treatment of breast cancer in the Brazilian Northeast

Ocorrência de mucosite oral em mulheres durante tratamento oncológico de câncer de mama no Nordeste brasileiro

Ricardo Barbosa-Lima[1,*], Simone Yuriko Kameo[2], Bruno Ferreira Amorim[3], Maria Júlia Oliveira Ramos[4], Jéssica dos Santos Costa[4], Pabliane Matias Lordelo Marinho[5], Namie Okino Sawada[6] e Glebson Moura Silva[4]

[1]*Department of Dentistry, Federal University of Sergipe (UFS). Lagarto, Sergipe, Brazil.*
[2]*Department of Health Education, Federal University of Sergipe (UFS). Lagarto, Sergipe, Brazil.*
[3]*Department of Medicine, Federal University of Sergipe (UFS). Lagarto, Sergipe, Brazil.*
[4]*Department of Nursing, Federal University of Sergipe (UFS). Lagarto, Sergipe, Brazil.*
[5]*School of Nursing of Ribeirão Preto, University of São Paulo (USP). Ribeirão Preto, São Paulo, Brazil.*
[6]*School of Nursing, Federal University of Alfenas (UNIFAL). Alfenas, Minas Gerais, Brazil.*

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KEYWORDS

Breast neoplasms
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ABSTRACT

Objective: To describe the occurrence of oral mucositis (OM) in women undergoing cancer treatment for breast cancer (BC).
Methods: This is a retrospective, quantitative, and analytical study in medical records of women diagnosed with BC in an oncology service. Clinical data were collected regarding the occurrence and severity of OM according to the World Health Organization criteria and the cancer treatment experienced by the participants.
Results: 196 women were included. Of these, 97 (49.5%) developed OM, 43.4% of which were grade 1 or 2 (low or moderate). The occurrence was higher in white women (OR 1.93; 95% CI 1.04 - 3.57; p = 0.035), with metastatic breast cancer (OR 5.46; 95% CI 1.79 - 16.64; p = 0.002) and who experienced taxane agents at some point during chemotherapy (OR 2.26; 95% CI 1.12 - 4.56; p = 0.02). The mean severity of OM in the entire sample was 0.8 ± 1.0, and in the affected women was 1.7 ± 0.7. The difference in the severity of OM by the variables was observed only among women with grade 2 and grade 3 fatigue (p = 0.03).
Conclusions: OM is a common mucocutaneous toxicity in women with BC. Despite the low severity observed, care for women with BC undergoing cancer treatment must consider the possible risks and complications associated with OM, adopting strategies to prevent, monitor, and treat them.

*Corresponding author:
Departamento de Odontologia de Lagarto, Universidade Federal de Sergipe.
Av. Governador Marcelo Déda, 13. São José. Lagarto, SE, Brazil | CEP 49400-000
E-mail: ricardoblima17@gmail.com (Barbosa-Lima R)

The study was carried out at University of São Paulo (Ribeirão Preto, São Paulo, Brazil) and Onco Hematos (Aracaju, Sergipe, Brazil).

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PALAVRAS-CHAVE

Epidemiologia
Mucosite oral
Neoplasias da mama

RESUMO

Objetivo: Descrever a ocorrência de mucosite oral (MO) em mulheres em tratamento oncológico para câncer de mama (CM).
Métodos: Trata-se de um estudo retrospectivo, quantitativo e analítico em prontuários de mulheres com diagnóstico de CM em um serviço de oncologia. Dados clínicos foram coletados quanto à ocorrência e gravidade da MO de acordo com os critérios da Organização Mundial da Saúde e o tratamento oncológico vivenciado pelas participantes.
Resultados: Foram incluídas 196 mulheres. Destas, 97 (49,5%) desenvolveram MO, sendo 43,4% grau 1 ou 2 (baixo ou moderado). A ocorrência foi maior em mulheres brancas (OR 1,93; IC95% 1,04 – 3,57; p = 0,035), com câncer de mama metastático (OR 5,46; IC95% 1,79 – 16,64; p = 0,002) e que experimentaram agentes taxanos em algum momento da quimioterapia (OR 2,26; IC95% 1,12 – 4,56; p = 0,02). A gravidade média da MO em toda a amostra foi de 0,8 ± 1,0 e nas mulheres afetadas foi de 1,7 ± 0,7. Diferença na gravidade da MO pelas variáveis foi observada apenas entre as mulheres com fadiga grau 2 e grau 3 (p = 0,03).
Conclusões: MO é uma toxicidade mucocutânea comum em mulheres com CM. Apesar da baixa gravidade observada, o cuidado à mulher com CM em tratamento oncológico deve considerar os possíveis riscos e complicações associadas à MO, adotando estratégias para prevenir, monitorar e tratá-las.

INTRODUCTION

Oral mucositis (OM) is considered a common adverse event related to the treatment of cancer with antineoplastic agents and ionizing radiation. The occurrence of this condition in patients with cancer varies according to the chemotherapy and radiotherapy protocols, considering the individual organic responses[1,2]. Mucocutaneous toxicities that affect the oral cavity, including OM, can occur in up to 75% of patients irradiated in the head and neck or treated with high-dose chemotherapy, being frequently under-investigated and underreported in low-risk patients treated on an outpatient basis[3].

OM is a tissue lesion in the oral cavity caused by cancer treatment, whose progression involves pain, erythema, ulcerations and bleeding[4]. The processes that trigger OM in patients with cancer are multifactorial and involve DNA damage, changes in the proliferation cycle of basal cells and increased expression of pro-inflammatory cytokines, in addition to the interactions between the damaged mucosa and the oral biofilm, where bacteria colonize the lesions and induce more inflammatory response mediated by tissue macrophages[3].

Oral ulcerations appear more quickly when treatment with antineoplastic agents is initiated and the course of the disease begins after seven days and ends after three weeks of the appearance of ulcerations[3]. However, when associated with radiotherapy, the course of OM can be longer and last 90 days or more[2].

The occurrence of OM may be associated with several outcomes in patients with cancer. The limitations imposed by the presence of inflammation and ulcers in the oral cavity can result in difficulties in oral intake and hygiene in the affected patients. These two limitations trigger other difficulties for cancer treatment, such as weight loss, nutritional deficiencies, weakness and susceptibility to oral and systemic infections. Adding the limitations inherent to OM with its consequences, whether associated with chemotherapy or radiotherapy, it is common to observe the need to reduce therapeutic doses, increase the length of hospital stay or interrupt the cancer treatment[1-4].

In addition, there is evidence that OM can reduce the functionality and quality of life of patients undergoing cancer treatment affected by this disease. Beyond the local and systemic complications, the presence of OM can compromise the communication and interaction capacity of individuals in society, characterizing the biopsychosocial impacts of this condition and reinforcing the need to investigate it in several spheres and in an integrated approach[5].

Oral changes associated with breast cancer treatment are common. Although radiation-induced OM is not considered a problem, women who experience chemotherapy protocols involving taxanes (especially paclitaxel or docetaxel), anthracyclines (especially doxorubicin) or 5-fluorouracil (5FU) develop OM more frequently[6].

The detection of risk factors for the occurrence of OM in patients with cancer undergoing chemotherapy is important to promote scientific support for prevention and treatment strategies, allowing the reduction of complications associated with the oral mucosa, maintaining antineoplastic therapy and avoiding comorbidities[7]. Although it is an extensively studied condition, there is still a lack of scientific clarity about risk factors related to the emergence of OM[3]. Thus, this study describes the occurrence of OM in women undergoing oncological treatment for breast cancer.

METHODS

This is a retrospective, quantitative and descriptive study of medical records of women. The study population was patients undergoing cancer treatment at a Brazilian northeastern private oncology service. The study's place was chosen due to the number of people undergoing cancer treatment with data available for analysis. The proposed study was approved by the Research Ethics Committee of the School of Nursing of Ribeirão Preto - University of São Paulo (approval number 531.146; CAAE: 20834513.0.0000.5393). Informed Consent Form was dispensed due to the study's documentary nature with secondary data.

When the study started, 560 patients were under treatment. The medical records of these patients were initially screened, and all women who met the proposed inclusion criteria were included. As inclusion criteria, female patients over 18 years old, with histopathological diagnosis of breast cancer undergoing antineoplastic treatment between February 2014 and February 2015 were included, resulting in one year of analysis and collection. Each medical record included was analyzed in a single moment, without longitudinal monitoring. Of these patients, only the records filled correctly were included, excluding incomplete, doubtful, or illegible, considering they were non-electronic medical records (filled out manually by the professionals of the service studied).

In addition to OM, the variables chosen were age, race, origin, time since diagnosis, histopathological type, surgical procedures, radiotherapy, antineoplastic agents, and symptoms associated with cancer treatment (fatigue, weight gain and loss). The classification adopted for fatigue, weight gain, and loss during cancer treatment was based on the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), considering the 4.0 version published in May 2009[8].

The occurrence of OM in the sample was qualitatively registered by professionals from the private oncology service studied. Two oncology researchers collected this information from medical records and attributed the severity according to the criteria proposed by the World Health Organization (WHO). The WHO criteria are considered adequate for OM research and are widely used in clinical practice in oncology because they consider clinical and functional characteristics[5].

OM was classified as grade 1/mild (asymptomatic or mild pain associated with erythema), grade 2/moderate (erythema or painful ulceration with the maintenance of the ability to eat solid food), grade 3/severe (painful ulcerations with restricted solid food intake, liquid diet only) and grade 4/life-threatening (oral food intake impossible).

Data collection in medical records was performed by two independent researchers using a specific form built based on the variables of interest. The analysis of medical records occurred on days previously scheduled according to the availability of the service. The data obtained were processed in tables using Google® Sheets tool for subsequent statistical analysis.

Statistical analysis was performed using PAST: Paleontological Statistics Software Package for Education and Data Analysis (v. 4.0, Oslo, Norway, 1999). Summary measures and descriptive statistics were operated to verify the occurrence of the outcomes. Inferential statistical approaches were operated using Pearson's Chi-square test and Fisher's exact test (expected values less than five in the contingency tables), including the odds ratio (OR) with a 95% confidence interval (95% CI) when p-values were less than 0.05.

Also, to compare means, Lilliefors test (*L*) was used to test the sample's normality. The analysis of the means between groups was based on the normality and quantity of samples, adopting the Mann–Whitney test (*U*) for two samples, Kruskal-Wallis test (*H*) for three or more, and Dunn-Bonferroni post hoc tests. The significance of 95% ($\alpha = 0.05$) was considered.

RESULTS

Of the 560 medical records initially assessed, 196 patients (35%) met the proposed inclusion criteria and were included (n = 196). Most of the sample were black or mixed women (68.9%), with a mean age of 52.9 ± 11.2 years old, 94.9% from the Brazilian Northeast. The most common histopathological diagnosis was invasive ductal carcinoma (85.2%), followed by invasive lobular carcinoma (8.2%). Besides, 97.4% were unilateral breast tumors, 59.7% received the diagnosis more than one year ago, 75.5% had locoregional, and 20.9% had a distal spread. All patients underwent diagnostic biopsy, 65.3% to radical mastectomy, and 21.4% to lumpectomy (partial mastectomy). Also, all participants underwent chemotherapy, and 33.7% to radiotherapy.

Table 1 describes the stratified occurrence of OM in the sample. There were no cases related to complications of OM that threatened life or led to death. Most patients experienced moderate pain that did not compromise their food intake, requiring only dietary modifications to adapt patients to oral changes caused by mucositis, stratified in grade 2. Half of the patients (50.5%) were not diagnosed with oral inflammation or ulceration during breast cancer oncological treatment. The mean grade of OM in the affected sample (grade 1 to 3) was 1.7 (SD: ±0.7), while in the complete sample (grade 0 to 4) was 0.8 (SD: ±1.0).

Table 1 - Stratified occurrence of oral mucositis according to the clinical classification.

Classification	n	%
Grade 0	99	50.5
Grade 1	40	20.4
Grade 2	45	23
Grade 3	12	6.1
Grade 4	0	0
Total	196	100

Table 2 describes the occurrence of OM concerning the variables analyzed. It also describes and compares the mean grade of OM in each variable considering only women affected by OM (n = 97; 49,5%). This choice was made because the number of patients without OM (grade 0) in the compared groups would be a confounding factor when assessing OM's severity.

The corrected *p*-value was significant among patients with grade 2 (fatigue not relieved by rest, limiting daily instrumental activities) and grade 3 (fatigue not relieved by rest, limiting self-care daily activities) fatigue ($p = 0.03$). Table 3 describes other symptoms associated with breast cancer treatment and their relationship with the occurrence of OM. In addition to fatigue, the occurrence of OM was significantly higher in white women (OR: 1.93; 95%CI 1.04 – 3.57; $p = 0.035$),

with systemic metastasis from breast cancer (OR: 5.46; 95%CI: 1.79 - 16.64; p = 0.002) and who used taxane chemotherapeutic agents at some point in their cancer treatment (OR: 2.26; 95%CI: 1.12 - 4.56; p = 0.02).

Table 2 - Occurrence and mean grade of oral mucositis according to variables investigated.

Variables	Group with oral mucositis		Group without oral mucositis		*P*-value (X^2)	Mean grade	*P*-value (*U* or *H*)
	n	%	n	%			
Age (years)							
≤ 49	41	20.9	37	18.9	0.483	1.6 ± 0.7	0.993
> 49	56	28.6	62	31.6		1.6 ± 0.6	
Race							
White	37	18.9	24	12.2	0.035*	1.8 ± 0.7	0.179
Black or mixed	60	30.6	75	38.3		1.6 ± 0.6	
Time since diagnosis							
1 year or less	41	20.9	38	19.4	0.579	1.6 ± 0.6	0.127
More than 1 year	56	28.6	61	31.1		1.8 ± 0.7	
Histopathological type							
Invasive ductal carcinoma	84	45.9	83	45.4	0.981	1.7 ± 0.7	0.884
Invasive lobular carcinoma	8	4.3	8	4.3		1.7 ± 0.7	
Tumoral dissemination							
Absent	3	1.5	4	2.0		1.7 ± 0.6	
Locoregional spread	73	37.3	75	38.3	0.002*†	1.7 ± 0.7	0.999
Distal spread	21	10.7	4	2.0		1.7 ± 0.7	
Surgical procedures							
Biopsy only	11	5.6	15	7.7		1.7 ± 0.8	
Lumpectomy	26	13.3	16	8.2	0.175	1.8 ± 0.8	0.974
Radical mastectomy	60	30.6	68	34.7		1.7 ± 0.6	
Radiotherapy (sessions)							
≤ 20	3	4.5	6	9.1	0.483†	1.7 ± 0.6	0.745
> 20	28	42.4	29	43.9		1.9 ± 0.8	
Fatigue							
Absent	5	2.6	13	6.6		2.0 ± 0.7	
Grade 1	11	5.6	19	9.7	0.010*	1.5 ± 0.5	0.025*
Grade 2	46	23.5	49	25.0		1.5 ± 0.7	
Grade 3	35	17.9	18	9.2		1.9 ± 0.6	
Weight gain							
Absent	55	28.1	68	34.7		1.6 ± 0.6	
Grade 1	30	15.3	25	12.8	0.196	1.8 ± 0.7	0.216
Grade 2	11	5.6	6	3.1		1.9 ± 0.7	
Grade 3	1	0.5	0	0.0		-	
Weight loss							
Absent	77	39.3	81	41.3		1.7 ± 0.7	
Grade 1	12	6.1	13	6.6	0.665	1.5 ± 0.5	0.243
Grade 2	8	4.1	5	2.6		2.0 ± 0.5	
Grade 3	0	0.0	0	0.0		-	
Antineoplastic drugs							
Exposed to taxanes	82	41.8	70	35.7	0.020*	1.7 ± 0.7	0.860
Not exposed to taxanes	15	7.7	29	14.8		1.7 ± 0.6	
Exposed to anthracyclines	84	42.9	83	42.3	0.586	1.7 ± 0.7	0.180
Not exposed to anthracyclines	13	6.6	16	8.2		1.5 ± 0.5	
Exposed to 5FU	19	9.7	19	9.7	0.944	1.6 ± 0.6	0.382
Not exposed to 5FU	78	39.8	80	40.8		1.7 ± 0.7	
AC protocol	12	6.1	14	7.1		1.7 ± 0.6	
AC-T protocol	49	25.0	55	28.1	0.787	1.8 ± 0.7	0.421
FAC protocol	19	9.7	16	8.2		1.6 ± 0.6	
Other protocols	13	6.6	18	9.2		1.5 ± 0.5	

n: absolute frequency; %: relative frequency; X^2: Pearson's Chi-square test; *p-value < 0.05; † Fisher's exact test; *U*: Mann-Whitney test; *H*: Kruskal-Wallis test; AC: adriamycin + cyclophosphamide; AC-T: adriamycin + cyclophosphamide with sequential taxane (paclitaxel or docetaxel); FAC: 5FU + adriamycin + cyclophosphamide.

Table 3 - Sign and symptoms associated with breast cancer treatment associated with the occurrence of oral mucositis.

Variables	Group with oral mucositis		Group without oral mucositis		*P*-value (X^2)	Mean grade	*P*-value (*U* or *H*)
	n	%	n	%			
Pain	82	41.8	83	42.3	0.893	1.7 ± 0.7	0.268
Absence of pain	15	7.7	16	8.2		1.5 ± 0.6	
Nausea or vomiting	42	21.4	39	19.9	0.578	1.6 ± 0.7	0.341
Absence of nausea or vomiting	55	28.1	60	30.6		1.8 ± 0.7	
Anxiety symptoms	68	34.7	62	31.6	0.268	1.7 ± 0.7	0.191
Absence of anxiety symptoms	29	14.8	37	18.9		1.8 ± 0.6	
Depression symptoms	51	26.0	50	25.5	0.771	1.7 ± 0.7	0.535
Absence of depression symptoms	46	23.5	49	25.0		1.8 ± 0.7	
Changes in self-image	29	14.8	37	18.9	0.268	1.6 ± 0.7	0.167
No changes in self-image	68	34.7	62	31.6		1.8 ± 0.6	
Changes in self-esteem	20	10.2	29	14.8	0.160	1.6 ± 0.7	0.659
No changes in self-esteem	77	39.3	70	35.7		1.7 ± 0.7	
0 to 2 combined symptoms	43	21.9	37	18.9		1.8 ± 0.7	
3 to 4 combined symptoms	33	16.8	38	19.4	0.612	1.6 ± 0.6	0.239
4 to 6 combined symptoms	21	10.7	24	12.2		1.6 ± 0.7	

n: absolute frequency; %: relative frequency; X^2: Pearson's Chi-square test; *U*: Mann-Whitney test; *H*: Kruskal-Wallis test.

DISCUSSION

Half of the patients had already manifested OM at the time of data collection. Most clinical and epidemiological factors were not significantly associated with the occurrence or severity of OM. However, a small portion manifested significant functional impairment (grade 3 or 4), indicating low severity.

Fatigue is a symptom strongly associated with cancer treatment and prevalent in women with breast cancer. The functional impact of this condition significantly worsens patients' quality of life and may be associated with the chemotherapeutic agents used[9,10]. One of the hypotheses to elucidate the cause of cancer-related fatigue considers pro-inflammatory cytokines, especially tumor necrosis factor (TNF-α) and interleukin (IL-1β). In vitro and in vivo studies associate the increase in these cytokines' serum levels with the development of fatigue and other signs and symptoms of cancer treatment, including pain[11].

Although the authors did not find any study that evaluated the influence of these cytokines on OM and fatigue simultaneously, there is evidence that the damage caused by chemotherapeutic agents to DNA causes the positive regulation of genes encoding TNF-α and IL-1β and contributes to the pathogenesis of OM[12], allowing an initial link to be established between these two pathologies. Furthermore, inhibition of the production of TNF-α and IL-1β by pharmacological agents can reduce the severity of OM in patients with cancer[13].

However, an epidemiological study with women diagnosed with metastatic breast carcinoma brought interesting results compared to our findings. Of patients with adverse reactions, including fatigue and OM, the occurrence of grade 3 toxicities for both conditions was considered rare. However, grade 1 or 2 fatigue and grade 1 mucositis were significantly associated with reduced quality of life. In this study, one of the groups was composed of women who were exposed to taxane agents[14].

Considering this population, another study reported that 87.6% of women with metastatic breast cancer were white, more than 78% were diagnosed with ductal carcinoma, and 88% underwent palliative chemotherapy throughout the disease, demonstrating the high exposure of women with advanced breast cancer to antineoplastic agents and their adverse reactions[15].

Furthermore, the literature reports several chemotherapy protocols related to OM in women with breast cancer, although the ideal protocol remains undetermined in metastasis cases. Taxane agents, such as paclitaxel and docetaxel have broad antitumor activity in vivo, although their cytotoxic potential is notorious. Doxorubicin (anthracycline) and cyclophosphamide have also been used frequently, and the combination of these three drugs with 5-fluorouracil constitutes the main chemotherapy regimen for breast cancer: AC (doxorubicin + cyclophosphamide), AC-T (doxorubicin + cyclophosphamide with a subsequent taxane) and FAC (5-fluorouracil + doxorubicin + cyclophosphamide)[16].

Considering the occurrence of OM caused by chemotherapy agents in women with metastatic breast cancer, a meta-analysis conducted in 2016 concluded that there was no significant difference in overall stomatitis incidence, considering eight different

protocols involving taxanes, doxorubicin, cyclophosphamide and 5-fluorouracil[16].Corroborating these findings, another epidemiological study published in 2017 observed that the occurrence of OM in women with metastatic breast cancer treated in protocol AC-T or AC without taxane was low and tolerable, with less than 1.1% of occurrences classified into grade 3 or 4[17].

Previously, the risk of OM during AC protocol was estimated in 13.6% of patients, while for women undergoing AC-T and FAC, it was 2.8% and 3.3%, respectively[6]. Despite this estimate, our results differ and suggest a higher occurrence of OM in women exposed to taxanes. Comparing AC and FAC, a study of women undergoing chemotherapy after mastectomy indicated that OM's risk was more significant in the FAC group, where 80% of patients developed the condition[18].

Although we did not find a significant occurrence in our results, the literature reports that patients with OM undergoing chemoradiotherapy are frequently affected by anxiety and depression symptoms that can accentuate negative outcomes related to cancer[19]. Finally, it is worth considering that women with breast cancer with professional oral hygiene support may develop OM less frequently and severely compared to women who perform oral self-care[20].

The dentist who attends cancer patients should examine pre-existing oral conditions and treat them before chemotherapy, as well as remove foci of infection, instructing and motivating the correct oral hygiene. When OM is installed, several therapeutic options are available, including low-level laser, cryotherapy, antioxidant drugs, growth factors, and PTA (polymyxin, tobramycin and amphotericin B)[21].

CONCLUSION

OM is a common mucocutaneous toxicity in women with breast cancer. In our findings, approximately half of the patients developed this condition with low or moderate severity. Despite this, care for women with breast cancer undergoing oncological treatments must consider the possible risks and complications associated with OM, adopting strategies to prevent, monitor, and treat them. The occurrence of simultaneous OM and fatigue during cancer can be investigated *in vitro* and *in vivo* to verify common pathogenic aspects.

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