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ORAL MANIFESTATIONS ARISING FROM ANTINEOPLASTIC THERAPY IN CHILD ONCOLOGICAL PATIENTS

MANIFESTAÇÕES BUCAIS DECORRENTES DA TERAPIA ANTINEOPLÁSICA EM PACIENTES ONCOLÓGICOS INFANTIS

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ABSTRACT

In Brazil, cancer is the leading cause of death from illness in children and adolescents. The National Cancer Institute (INCA) estimates the occurrence of 8,460 new cases of cancer in children and adolescents in 2020. The objective of this study was to identify the most frequent oral manifestations in pediatric patients undergoing antineoplastic treatment. This survey included 137 children and adolescents from 0 to 18 years of age. The data included a semi-structured questionnaire to verify the most frequent oral manifestations resulting from antineoplastic therapy. The statistical tests used were the Pearson's Chi-square test and to assess the strength of the association, Odds Ratio (OR) or Ratio of Chances (RC) with respective confidence interval was obtained. The results found showed that the average age of the patients surveyed was 6.8 years; the male gender (57.7%) was predominant in the sample; the most frequent malignancy was leukemia (67.9%); 70.1% of patients had at least one oral manifestation, with mucositis being the most prevalent (56.2%), followed by dry mouth (46.7%), gingivitis (41.6%), dysphagia (35.8%), dysgeusia (35.8%), candidiasis (34.3%) and herpes (21.2%). There were 54.7% of patients with favorable oral health and 40.9% of them with unfavorable oral health. We conclude that the infant patient should be evaluated by a pediatric dentist prior to the start of chemotherapy to minimize oral complications during antineoplastic treatment.
Keywords: Oncology. Oral Health. Oral Manifestations.

RESUMO

No Brasil, o câncer é a principal causa de morte por doença em crianças e adolescentes. O Instituto Nacional do Câncer (INCA) estima a ocorrência de 8.460 novos casos de câncer em crianças e adolescentes no ano de 2020. O objetivo desse estudo foi identificar as manifestações bucais mais frequentes nos pacientes pediátricos em tratamento antineoplásico. Essa pesquisa incluiu 137 crianças e adolescentes de 0 a 19 anos de idade. Os dados incluíram um questionário semiestruturado para verificar as manifestações bucais mais frequentes decorrentes da terapia antineoplásica. Os testes estatísticos utilizados foram o teste Qui-quadrado de Pearson e para avaliar a força da associação foi obtido o Odds Ratio (OR) ou Razão das Chances (RC) com respectivo intervalo de confiança. Os resultados encontrados demonstram que a idade média dos pacientes pesquisados foi de 6,8 anos; o sexo masculino (57,7%) foi predominante na amostra; a neoplasia maligna mais incidente foi à leucemia (67,9%); 70,1% dos pacientes apresentaram pelo menos uma manifestação oral, sendo a mucosite de maior prevalência (56,2%), seguida da xerostomia (46,7%), gengivite (41,6%), disfagia (35,8%), disgeusia (35,8%), candidíase (34,3%) e herpes (21,2%). Encontraram-se 54,7% dos pacientes com saúde bucal favorável e 40,9% deles com saúde bucal desfavorável. Concluímos que o paciente infantil deve ser avaliado por um odontopediatra previamente ao início da quimioterapia para minimizar as complicações bucais durante o tratamento antineoplásico.
Palavras-chave: Manifestações Bucais. Oncologia. Saúde Bucal.

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INTRODUCTION

The World Health Organization points to cancer as a public health problem and estimates that there will be 27 new cases of cancer in the year 2030, with 17 million deaths due to the disease. According to the Brazilian *Instituto Nacional do Câncer* (INCA [National Cancer Institute]), cancer in children and adolescents is represented by a group of diseases with the uncontrolled proliferation of abnormal cells, which can occur in any part of the organism. Leukemia, lymphoma and neoplasms of the central nervous system are the most frequent in childhood and adolescence (HESPANHOL, 2010; AMERICAN CANCER SOCIETY, 2015; CAMPOS *et al.*, 2018).

The therapeutic conduct adopted for the treatment of cancer involves radiotherapy, chemotherapy and/or surgery (ALENCAR, 2011). Approximately 70% of patients with cancer undergo chemotherapy (HESPANHOL, 2010). However, antineoplastic therapy disturbs the integrity and function of the oral cavity, leading to the development of complications. The age of the patient, type of cancer, degree of malignancy, dose and duration of chemotherapy and/or radiotherapy and oral hygiene are determinants of the severity of oral complications (ALENCAR, 2011; HANNA, 2016).

Among the oral manifestations associated with the treatment of childhood cancer, the most prevalent according to the literature are mucositis (MEDEIROS, 2002; HESPANHOL, 2010; THOMAZ, 2013; VELTEN, 2014; BERGER; VELTEN, 2016; HANNA, 2016), glandular dysfunction, a change in the sense of taste, dysgeusia, pain and malnutrition.

A study conducted at an oncology center in the city of Teresina, Brazil, in 2009 involving children between six and 12 years of age found that, after mucositis, xerostomia was one of the most prevalent oral manifestations among patients who underwent antineoplastic therapy (LOPES, 2012). Xerostomia exerts an influence on the buffering capacity of saliva and can increase the level of demineralization as well at the quantity of mucin. As a result, the mucosa becomes dehydrated, unprotected from trauma and with low lubricating capacity, which hinders the formation and swallowing of the food bolus (ALBUQUERQUE, 2007a).

Pediatric patients with mucositis and/or xerostomia as oral manifestations stemming from chemotherapeutic treatment may have difficulty swallowing (dysphagia) as well as a temporary loss of taste (dysgeusia) due to the change to the taste buds, quantity and quality of saliva and oral microflora (GOURSAND, 2006).

The prevention and treatment of oral manifestations during oncological treatment are important to reducing the morbidity rate and treatment costs (OSTERNE, 2008). Therefore, the presence of a dentist and/or pediatric dentist on the oncology team of extreme importance and can reduce the occurrence of the harmful effects of antineoplastic treatment, leading to an improvement in the quality of life of the patient. The aim of the present study was to identify the most frequent oral manifestations in pediatric patients undergoing antineoplastic treatment at the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP [Prof. Fernando Figueira Institute of Integral Medicine]) in the city of Recife, Brazil.

MATERIAL AND METHODS

The present cross-sectional study received approval from the institutional review board of *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP), Recife, Pernambuco, Brazil (certificate number: 1.913.181) in accordance with Resolution 466/2012 of the Brazilian National Board of Health. Male and female patients 0 to 19 years of age diagnosed with cancer and treated with antineoplastic therapy in the pediatric cancer ward of IMIP were invited to participate in the study.

All children and their legal guardians who agreed to participate in the study signed a statement of informed consent. Patients without a final diagnosis of malignant neoplasm, those

treatment exclusively with surgery and those not treated with antineoplastic therapy were excluded from the study.

Clinical examination

The clinical examination was performed by an experienced dentist who had undergone training and calibration exercises for the diagnosis of oral lesions. Data collection was performed with the use of a clinical chart, including a self-administered questionnaire with objective and subjective questions directed at the patient and guardian that had been validated by Lopes *et al.* (2012). Data were collected on sex, age, type of cancer, signs and symptoms of oral manifestations after chemotherapeutic treatment and oral hygiene habits.

The intraoral examination was performed in the infirmary with the use of a headlamp, mirror and wooden tongue depressor. Oral status was classified based on Albuquerque *et al.* (2007a). Patients with normal oral structures and satisfactory oral hygiene were classified as having favorable oral health. Those with at least one of the conditions of interest (carious lesions, root fragments, calculus, periodontal disease, halitosis and deficient oral hygiene) were considered as having unfavorable oral health.

Statistical analysis

The data were entered onto an EXCEL spreadsheet and the Statistical Package for the Social Sciences (SPSS version 23) was used for the statistical calculations. Descriptive analysis was performed, with the calculation of absolute and relative frequencies for the categorical variables as well as mean, standard deviation and median values for age. Pearson's chi-square test was used to evaluate associations between two categorical variables. Odds ratios (OR) with respective 95% confidence intervals (CI) were used to evaluate the strength of the associations. The margin of error in the decisions of the statistical tests was 5% ($p < 0.05$).

RESULTS AND DISCUSSION

One hundred thirty-seven children and adolescents were evaluated. Males accounted for 57.7% of the sample (n = 79) and females accounted for 42.3% (n = 58). Mean age was 6.88 years. A total of 34.3% of the patents were from metropolitan Recife and most (61.3%) were from other parts of the state of Pernambuco. Just over half of the families (54.0%) earned the Brazilian monthly minimum wage (Table 1).

The most prevalent type of cancer was leukemia (67.9%), followed by tumors of the central nervous system (10.2%), Hodgkin's and non-Hodgkin's lymphoma (8.0%), neuroblastoma (5.1%), Wilms tumor (2.9%), rhabdomyosarcoma (2.2%) and hepatoblastoma, fibrosarcoma and adrenocortical carcinoma (0.7% of patients).

Regarding treatment, chemotherapy was the most frequent antineoplastic therapy (83.9%). The most frequent time ranges were zero to three months (34.3%) and more than 12 months (30.7%). "One to four doses" was the most frequent (35.0%), followed by more than 12 doses (32.1%).

Ninety-six participants (70.1%) had at least one oral manifestation stemming from chemotherapy, whereas 41 (29.9%) had not perceived any changes in the oral cavity. The most reported oral manifestation was mucositis (56.2%), followed by a sensation of dry mouth (46.7%), gingivitis (41.6%), dysphagia (35.8%), dysguesia (35.8%), candidiasis (34.3%), herpes (21.2%) and a change in the consistency of the saliva (9.5%).

Seventy-one of the patients (51.8%) had not sought a dentist prior to chemotherapy, whereas 66 (48.2%) had some dental care prior to treatment. The majority (58.4%) reported performing oral hygiene three times per day, 32.8% reported two times per day, 5.7% reported more than three

times per day and 2.9% reported performing oral hygiene once per day. The vast majority (95.6%) performed oral hygiene with toothpaste and a toothbrush and 31 (22.6%) reported using an antiseptic mouthwash.

Six of the patients (4.4%) did not undergo the clinical examination due to their debilitated health status, as the examination would cause mild discomfort. Therefore, the oral health status was determined in 131 (95.6%) of the 137 patients in the sample, 75 (54.7%) of whom were classified as having favorable oral health and 56 (40.9%) were classified as having unfavorable oral health.

Table 1 - Characteristics of children studied at an oncology treatment center according to age, sex, place of residence, family income and schooling

Variables	**n**	**%**
Total	**137**	**100.0**
Sex		
Male	79	57.7%
Female	58	42.3%
Age group (years)		
1 to 5	67	48.9
6 to 10	41	29.9
11 to 17	29	21.2
Place of residence		
Metropolitan region of Recife	47	34.3
Other parts of state of Pernambuco	84	61.3
Other states	6	4.4
Family income		
< BMMW	45	32.8
BMMW	74	54.0
2 to 3 times BMMW	17	12.4
4 or more times BMMW	1	0.7
Schooling		
None (unable to read or write)	80	58.4
Incomplete primary school	53	38.7
Complete high school	4	2.9

Note: BMMW = Brazilian monthly minimum wage
Source: Authors

Regarding associations between oral manifestations and oral health status among the pediatric patients undergoing oncological treatment, gingival bleeding was the only significantly associated variable ($p < 0.05$, OR = 2.31 and interval that excludes 1.00) for the fixed margin of error (5%). Oral health classified as unfavorable was more frequent among individuals with gingival bleeding compared to those without gingival bleeding (54.5% x 34.2%) (Table 2).

In recent years, childhood cancer has become a worldwide oral health problem due to the high mortality rate as well as the high costs related to prevention, diagnosis and treatment (INCA, 2020). IMIP, where the present study was conducted, is a reference hospital for the treatment of childhood cancer in the city of Recife, Brazil.

Cancer in children and adolescents is mainly characterized by a short latency period, a more aggressive disease and fast evolution. However, pediatric patients respond better to treatment and the prognosis is considered good. Moreover, the histopathological characteristics are unique in this population and should be studied separately from cancers that occur in adults, especially with regards to clinical behavior.

The present study found a predominance of the male sex, which is compatible with data described in studies conducted by Barbosa *et al.* (2010) and Lopes *et al.* (2012). The latter authors

evaluated oral manifestations in pediatric patients undergoing chemotherapy at an oncology treatment center in the city of Teresina (state of Piauí, Brazil), 75% of whom were male. In contrast, an equal proportion of both sexes was found in the study by Otmani *et al.* (2011). According to Velten *et al.* (2014), such a finding may indicate an association with genetic factors of predisposition linked to the X chromosome or a frail constitution in relation to the male sex.

Table 2 - Associations between oral manifestations and oral health status among pediatric oncology patients undergoing antineoplastic therapy

Alterations	**Unfavorable**		**Favorable**		**Total** [1]		**p-value**	**OR (95% CI)**
	n	**%**	**n**	**%**	**n**	**%**		
Total group	56	42.7	75	57.3	131	100		
Manifestations							$p^{(2)} = 0.382$	
Yes	42	45.2	51	54.8	93	100		1.41 (0.65 to 3.07)
No	14	36.8	24	63.2	38	100		1.00
Change in sense of taste							$p^{(2)} = 0.441$	
Yes	18	38.3	29	61.7	47	100		1.00
No	38	45.2	46	54.8	84	100		1.33 (0.64 to 2.76)
Lesions on gingiva							$p^{(2)}=0.575$	
Yes	19	46.3	22	53.7	41	100		1.24 (0.59 to 2.60)
No	37	41.1	53	58.9	90	100		1.00
Lesions on palate							$p^{(2)}=0.595$	
Yes	12	46.2	14	53.8	26	100		1.18 (0.50 to 2.82)
No	44	41.9	61	58.1	105	100		1.00
Lesions on buccal mucosa							$p^{(2)}=0.983$	
Yes	32	42.7	43	57.3	75	100		1.00
No	24	42.9	32	57.1	56	100		1.01 (0.50 to 2.03)
Consistency of saliva							$p^{(2)}=0.794$	
Yes	6	46.2	7	53.8	13	100		1.17 (0.37 to 3.68)
No	50	42.4	68	57.6	118	100		1.00
Sensation of dry mouth							$p^{(2)}=0.597$	
Yes	28	45.2	34	54.8	62	100		1.21 (0.60 to 2.41)
No	28	40.6	41	59.4	69	100		1.00
Difficulty swallowing foods							$p^{(2)}=0.150$	
Yes	24	51.1	23	48.9	47	100		1.70 (0.82 to 3.49)
No	32	38.1	52	61.9	84	100		1.00
Gingival bleeding							$p^{(2)}=0.020$*	
Yes	30	54.5	25	45.5	55	100.0		2.31 (1.13 to 4.70)
No	26	34.2	50	65.8	76	100.0		1.00
Blisters on lip							$p^{(2)}=0.501$	
Yes	10	37.0	17	63.0	27	100		1.00
No	46	44.2	58	55.8	104	100		1.35 (0.56 to 3.22)
White plaque							$p^{(2)}=0.776$	
Yes	20	44.4	25	55.6	45	100		1.11 (0.54 to 2.30)
No	36	41.9	50	58.1	86	100		1.00
Red plaque							$p^{(2)}=0.657$	
Yes	13	46.4	15	53.6	28	100		1.21 (0.52 to 2.80)
No	43	41.7	60	58.3	103	100		1.00

Note: Pearson's chi-square test.
Source: authors.

The mean age of the individuals analyzed in the present study placed the patients near the phase of early childhood (zero to six years). A similar finding was described in a study conducted in the state of Santa Catarina, Brazil (XU, 2013). However, a study conducted in the state of Piauí found a higher mean age (8.5 years), whereas a study conducted in the state of Espírito Santo reported a lower mean age (2.5 years). Age range is a factor that should be considered, as the possibility of chemotherapeutic treatment affecting the oral cavity is greater in younger patients (MILENE, 2016).

In the study conducted by Monteiro *et al.* (2016), the majority of patients were unable to read or write, which is similar to the result found in the present study. An early diagnosis of cancer and hospitalization for the administration of chemotherapeutic drugs can lead affected children to be absent from school.

Regarding family income, most children were from families that earned up to the Brazilian monthly minimum wage, which is similar to the finding described by Lopes *et al*. (2012) in the city of Teresina, Piauí, Brazil. This present result may be explained by the fact that a large portion of the patients treated at IMIP come from low-income families.

Regarding the clinical profile, leukemia was the most prevalent form of cancer in the present investigation, which is compatible with results reported in several studies in the literature (MEDEIROS *et al.,* 2002; ALBUQUERQUE *et al.,* 2007b; BARBOSA *et al.,* 2010; VELTEN *et al.,* 2014; MACHADO *et al.,* 2017). The second most common type of childhood cancer was tumor of the central nervous system, which is in agreement with data reported by Hespanhol *et al.* (2010), Lopes *et al.* (2012) and Velten *et al.* (2014).

The side effects of chemotherapy are related to the dose administered in a given period of time. The largest proportions of patients were treated for zero to three months or more than 12 months. Lopes *et al.* (2012) report similar findings. Moreover, the largest proportions of patients received either one to four doses or more than 12 doses of the chemotherapeutic drug. The administration interval of the drug is more important than the total dose, as a single dose tends to cause greater oral complications compared to the same drug administered in smaller doses over a longer period of time.

A total of 70.1% of the children in the present study had one or more oral manifestations stemming from chemotherapy, which is compatible with data described by Lopes *et al.* (2012) and Velten *et al.* (2014). According to Dias *et al.* (2007), some of the factors that contribute to the development of oral manifestations in children are the constant cellular renewal of the oral mucosa, the diverse, complex oral microbiota, the impairment of the immune system and local trauma. While 40% of all patients submitted to chemotherapy develop oral side effects, this figure can increase to 90% among children under 12 years of age.

The most prevalent oral manifestation in the present investigation was mucositis, which is in agreement with data reported in previous studies (ELTING *et al.,* 2003; FONSECA *et al.,* 2004; SONIS *et al.,* 2004; FIGLIOLA *et al.,* 2006; CARRILO *et al.,* 2010; LOPES *et al.,* 2012; MILLER *et al.,* 2012; VELTEN *et al.,* 2014). In contrast, Albuquerque *et al.* (2007a) and Monteiro *et al.* (2016) found that candidiasis was the most prevalent oral manifestation and Torres *et al.* (2010) found that gingivitis was the most prevalent.

The second most frequent oral manifestation was xerostomia, followed by gingivitis, dysphagia and dysgeusia. With the exception of gingivitis, these results are in agreement with findings described in studies conducted by Fonseca *et al.* (2004), Sonis *et al.* (2004), Figliola *et al.* (2006), Lopes *et al.* (2012) and Velten *et al.* (2014). The development of periodontal disease, such as gingivitis, is believed to be related to the presence of uncomfortable and painful oral lesions, such as mucositis, which leads to difficulty performing satisfactory oral hygiene. However, patients and their guardians should be counseled to perform adequate oral hygiene, as the buildup of plaque increases the severity of mucosal infections and predisposes the patient to gingival inflammation, which can lead to spontaneous bleeding due to possible thrombocytopenia (ALBUQUERQUE, 2007b).

Prior to the onset of oncological treatment, it is extremely important to visit a dentist or pediatric dentist to eliminate sites of infection (dental caries, periodontal disease, root fragments) that can interfere with antineoplastic treatment (MORAIS, 2014). In the present study, the majority (51.8%) of patients did not have any type of dental care prior to the onset of antineoplastic therapy. Likewise, Albuquerque *et al.* (2007a) found that approximately 85% of patients did not see a dentist prior to antineoplastic therapy.

The prevention of caries and periodontal disease can be achieved by proper brushing. In the present study, the majority of patients performed oral hygiene with a toothbrush and paste at least three times per day. The increase in access to fluoridated toothpaste and the mechanical movement of brushing, which disorganizes biofilm, reduce the risk of the development of caries and periodontal disease (PERES *et al.*, 2000; NADANOVSKY *et al.*, 2008). In contrast, the consumption of sweetened foods, salivary composition and secretion, the presence of defects in the formation of the teeth as well as the socioeconomic and cultural characteristics of the population exert an influence on the development of caries (FEJERSKOV, 2003; TENUTA *et al.*, 2012).

The majority of patients were classified as having a favorable oral health status, which is in agreement with data described in the study by Albuquerque *et al.* (2007a), who found that 36 (61%) of the 59 patients evaluated had a favorable oral health status. In contrast, Lopes *et al.* (2012) found a greater prevalence of an unfavorable oral health status, which was detected in 15 (71.4%) of the 21 patients evaluated. An unfavorable oral health status can exert a negative impact on oncological treatment, as deficient oral hygiene plays an important role in the emergence of lesions. Therefore, the health team should be capable of providing an adequate treatment protocol to avoid the negative consequences of antineoplastic treatment.

CONCLUSION

The presence of a dentist and/or pediatric dentist on the oncology team is necessary to minimize the effects of antineoplastic therapy on the oral cavity. Thus, pediatric patients should be evaluated prior to the onset of chemotherapy/radiotherapy to minimize the occurrence of oral complications during treatment. It is also important to make the children and their guardians aware of the importance of oral hygiene, as the buildup of biofilm increases the severity of mucosal infections and predisposes the patient to gingival inflammation.

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