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ORAL MANIFESTATIONS ARISING FROM CHEMOTHERAPY IN CHILDREN

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Abstract: Introduction: Pediatric antineoplastic treatment culminates in systemic and oral changes. Therefore, the presence of the dental surgeon is necessary throughout the chemotherapy treatment for the correct prevention, identification, guidance to those responsible and treatment of lesions that not only cause discomfort to the patient, but also influence the quality and effectiveness of cancer treatment. Objective: to identify the oral manifestations in children resulting from chemotherapy, as well as to present the importance of the Dental Surgeon within the multidisciplinary team directed to pediatric onco treatment. **Materials and methods:** A scientific search was carried out for articles in the following Databases: Scielo, Pubmed and Bereme. by scientific articles published from 2017 to 2022. **Conclusion:** The insertion of the dental surgeon in the multidisciplinary hospital team is essential, providing adequate oral treatment and the necessary guidelines to maintain oral health and thus guaranteeing the quality of life of pediatric patients.
Keywords: Manifestations mouthpieces; pediatric oncology; Multidisciplinary team; Chemotherapy; pediatric dentistry.

INTRODUCTION

Cancer, also called Malignant Tumor or Neoplasms, corresponds to the set of heterogeneous diseases characterized by disordered, aggressive and uncontrollable growth of cells, which may affect different types of tissues and organs, neighboring or distant. In Brazil, cancer is the second main factor of mortality, reaching 600 thousand new cases every year (NATIONAL CANCER INSTITUTE, 2020).

Childhood cancer affects people from 0 to 14 years of age and is considered a public health problem because it is a highly prevalent disease that requires a high financial cost attributed to the diagnosis and especially to the treatment, which consists of an extensive treatment. (NATIONAL CANCER INSTITUTE, 2017).

In Brazil, Cancer is already the first cause of death in children, equivalent to 8% of the total. The National Cancer Institute estimates that for each year of the 2020/2022 trigeminal period, more than 8,460 cases of childhood cancer are diagnosed, with 4,310 cases being more prevalent in males and 4,150 in females (NATIONAL CANCER INSTITUTE, 2020).

In children, risk factors according to environmental exposure for the detection of cancer are still undefined, as there may be several ubiquitous risks and in small degrees during childhood. However, the most accepted condition in the etiology is obesity and exposure during intrauterine life. (NATIONAL CANCER INSTITUTE, 2016).

When the mutation in the genetic material occurs, the cells do not progress normally and continue with similar aspects of the embryonic cell, resulting in an inadequate multiplication in a rapid, disorganized way and with short latency periods. This results in a rapidly proliferating tumor, but on the other hand, it has a good prognosis for responding better to treatment. (COSTA, et al., 2021).

The most recurrent categories of cancer among children are leukemias, central nervous system tumors and lymphomas, the most common being leukemia, especially acute lymphocytic leukemia (ALL), comprising about one-third of all childhood cancers. al., 1995) Tumors of the central nervous system represent 20% of childhood tumors and among them the most reported in childhood are medulloblastoma and astrocytoma with a higher incidence in males on average at 10 years of age and Lymphoma is the third type of malignant neoplasms most common in childhood, especially for non-Hodgkin (CAMARGO; LOPES, 2000) surgery and

radiotherapy (CAIELLI; MARTHA; DIB, 1995). The development of oral manifestations resulting from chemotherapy affects about 40% of patients, and in children younger than 12 years, this percentage rises and can reach 90%, since chemotherapeutic agents act in a non-specific way on proliferating cells (MARTINS; HUNTER; GAETI, 2002).

Antineoplastic treatment (CT) in pediatric patients has a greater impact on oral tissues due to the high rate of epithelial cell renewal (HESPANHOL et al., 2010; LOPES; NOGUEIRA; LOPES, 2012). Thus generating oral complications, which can cause changes in the shape, aesthetics and functionality of the patient's stomatognathic system. (PERES, et al., 2013).

During cancer treatment, the participation of a multidisciplinary team is necessary, considering that the treatment encompasses the patient in its entirety. In this context, the dental surgeon acts directly, providing well-being to the patient through preventive and curative therapy (SILVA; CARNEIRO; CRUZ, 2008). This present study aims to identify the oral manifestations in children resulting from chemotherapy, as well as to present the importance of the Dental Surgeon within the multidisciplinary team directed to pediatric oncology treatment.

MATERIALS AND METHODS

A search for articles was carried out in the following databases: PubMed, Scielo and Bereme. The search used the following keywords: Dental Surgeon, pediatric oncology, chemotherapy, Hospital Dentistry, oral manifestations, Oral diseases, Multidisciplinary Team, oral manifestations, Antineoplastic treatment, Oncological morbidity, chemotherapy in children, oncological children, totaling 16 articles, within of the inclusion criteria, the Boolean operators were also used: And, Our and Not. The following filters were used: articles published in Portuguese and English, from the year 2017 to the year 2022, from March to June 2022. Original articles and other reviews were included in the work.

LITERATURE REVIEW

Chemotherapeutic treatment corresponds to the use of specific chemical substances aimed at eliminating malignant neoplasms. Chemotherapeutic agents are introduced by different routes of administration. However, the best choice is intravenous, where it integrates with the bloodstream, spreading throughout the body, thus being considered a form of systemic treatment (JENSEN, et al; 2007; GOMES, et al., 2013).

Antineoplastic drugs affect both common and neoplastic cells. However, the specific effect of the drug predominantly affects malignant cells, due to small quantitative particularities in the midst of the metabolic and biochemical stages that differentiate them from normal cells. (ALMEIDA, et al., 2005; BRASIL, 2014). The difference in the composition of chemotherapeutic agents results in different levels of toxicity to the patient. Currently, the most used in antineoplastic treatment are: Vincristine, Adriamycin, Taxol, Cytarabine (ara C), Cyclophosphamide, Methotrexate, 5-fluorouracil and Cisplatin. There was a strong impact on the oral mucosa from the last four drugs mentioned (CHENG, et al. 2012).

During drug administration, some factors such as dosage and frequency directly imply the emergence of complications in the patient's clinical condition, which may originate or attenuate systemic disorders, such as: Heart failure, nephrotoxicity, hormone disorders, impairment in the child's growth and changes mouthpieces (EFFINGER, et al., 2014; ZU-BOWSKA, et al., 2013). These oral alterations have a multifactorial etiology, which may be

due to poor oral hygiene, nutritional change, immunosuppression and the destruction of healthy cells in the oral mucosa (COSTA, et al., 2021). This cell damage is a result of the high rate of cell proliferation in this region, which is also one of the specific characteristics of the antineoplastic agent's action (HAMERSCHLAK, 2008). During chemotherapy, several oral manifestations can be considered, including mucositis, recurrent aphthous stomatitis, viral infections, xerostomia, changes in the dental germ, gingivitis, changes in taste, among others (PERES, et al., 2013).

MUCOSITIS

Oral mucositis is characterized as inflammation and ulceration of the mucosa with painful symptoms. It occurs in four well-defined stages: Inflammatory, epithelial, ulcerative and scarring. It usually appears within the first 10 days of treatment initiation and its regression only occurs on average after 3 weeks of completion of anticancer treatment (BELLM et al., 2000; AMARAL et al., 2012). Diagnosing this lesion in advance is essential, seeing that the evolution may favor dehydration and malnutrition of the patient, which may interfere with the dosage of chemotherapy when in an aggravated condition. (HESPANHOL et al., 2010).

XEROSTOMIA

Xerostomia is a disorder of the salivary glands altering the quality and quantity of salivary flow. Its main etiology within oncology comes from adriamycin, a chemotherapeutic agent (SONIS et al., 1996). This change influences nutritional quality by hindering food intake, impairs communicability by interfering with the psychosocial state, provides an increase in the incidence of carious lesions, due to a reduction in the salivary buffer effect and an increase in Streptococcus mutans, favors the installation of a pathogenic microbiota, generating from periodontal infections as well as viral infections such as candidiasis. (CARE UNIT, 2009; CAMARGO et al., 2004).

HERPES

Herpes lesions are caused by the herpes simplex virus and can occur both in the intraoral and perioral mucosa. Characterized by the appearance of papules that rapidly evolve to blisters with citrine interior exudate (CONSOLARO, 2009). Generally, the etiology of this viral infection is due to chemotherapy that causes immunosuppression in patients and also suppresses the bone marrow and altering the oral microbiota (HESPANHOL et al., 2010).

CARIES

Caries during antineoplastic treatment can manifest for three main reasons, due to the direct action of radiation on the dental elements, due to hyposalivation and xerostomia, also due to the sudden change in food, patients tend to adopt a sweeter diet during chemotherapy. Therefore, this diet associated with Streptococcus mutans causes an accelerated destruction of dental tissue. (GOURSAND et al., 2006)

RECURRENT APHTHOUS STOMATITIS (CANKER SORE)

Recurrent aphthous stomatitis erupts in non-keratinized tissue. Pre-injury symptoms involve the appearance of erythematous macules, burning and local itching. This macula progresses to a lesion covered by a fibrinopurulent membrane, yellowish-white and circumscribed by an erythematous halo (FÁVARO, 2004). The most recurrent sites are the cheek and labial mucosa, tongue belly and vestibule fundus (NEVILLE et al., 2009). It has

a multifactorial cause, which can be of systemic or local origin. The degree of aggravation of these injuries varies from patient to patient, diversifying their location, extent and amount (FRAIHA; BITTENCOURT; CE-LESTINO, 2002).

GUM BLEEDING

Gingival bleeding may be one of the most common oral manifestations resulting from chemotherapy. This is because most antineoplastic drugs have the potential to affect the bone marrow, resulting in thrombocytopenia, which affects the amount of platelets, reducing it and favoring spontaneous or post-traumatic hemorrhage. This bleeding can also be related to an inflammatory process already installed, such as gingivitis, and can be potentiated by aggravating the chemotherapy condition (VARELLIS, 2005).

Another factor that may favor bleeding events is linked to drugs that may be associated with the patient undergoing chemotherapy, as they somehow impair hemostasis, such as antiepileptics (phenytoin) and immunosuppressants (cyclosporine). These hemorrhagic conditions can result in anemia and failure in the healing process (COSTA; SILVA; MACEDO, 2011)

HEMATOMAS ECCHYMOSES AND PETECHIAE

When there is a decrease in platelets, vulnerability of blood capillaries and coagulation disseminated within the vessels, caused mainly by some anticancer drugs, some signs in addition to gingival hemorrhage can occur in the form of hematomas, ecchymoses and petechiae. These types of injuries occur due to submucosal hemorrhage, where there is no extravasation of blood and it is contained under the tissue, and can arise more easily and be aggravated when there are elements that can cause injury such as biofilm, calculus, orthodontic components, exfoliation of deciduous teeth, tongue bite, among other factors considered traumatic (SASADA et al., 2015; KROETZ; CZLUSNIAK, 2003; CARNEIRO; SILVA; CRUZ, 2008).

GINGIVITIS

The inflammatory process that affects the protective periodontium that surrounds the teeth, that is, the gum is called gingivitis. It has microbial origin and is caused by the accumulation of bacteria, bacterial biofilm, which adheres to the tooth surface and when not removed through oral hygiene, persisting in the place, causes injury to the gingival tissue. This infectious-inflammatory pathology presents redness in the marginal gingiva, common bleeding and/or probing and swelling, thus changing the appearance and quality of the gingiva (GUEDES-PINTO; BONECKER; RODRIGUES, 2010; XAVIER et al., 2007).

Gingivitis when associated with chemotherapy occurs mainly due to the decrease in the quantity or quality of brushing to the patient, erroneously administered when the patient presents sensitivity in the oral scope, caused by xerostomia and increased gingival bleeding caused by anticancer drugs. (GOURSAND et al., 2006; CAMARGO; BATISTELLA; FERREIRA, 2004).

THE IMPORTANCE OF THE DENTAL SURGEON IN THE HOSPITAL TEAM

Scientific studies correlate cancer treatments and oral lesions, being directly linked. The severity of the lesions depends on some factors such as: the location and staging of the malignancy, the dosage of chemotherapeutic agents, age of the patient, durability of chemotherapy, diagnosis and the quality

of oral hygiene (HESPANHOL et al., 2010; LOPES et al, 2012). In the multidisciplinary oncology team, the dental surgeon plays an essential role in dental analysis and diagnosis, as these directly influence the planning of the dental treatment that will be proposed. Communication with the responsible physician is essential for choosing an effective treatment plan (ALBUQUERQUE; MORAIS; SOBRAL, 2007).

The role of the CD in the analysis is carried out following three steps: Antineoplastic pre-treatment: Oral clinical examination and adequacy of the oral environment; during antineoplastic treatment: Instructions to those responsible for correct oral care and hygiene and periodic preventive and/or curative consultations; Antineoplastic post-treatment: Curative approaches to sequelae and possible complaints (LITTLE et al, 2007; ELAD et al., 2015). After the diagnosis of cancer, the dental examination must be performed instantly, removing the foci of dental infections, with priority in acute interventions. Elective treatments are contraindicated at this time, and must be extended after the completion of chemotherapy (ALBUQUERQUE, 2007).

During antineoplastic treatment, patients are expected to have immunosuppression and for this reason they are more susceptible to oral complications. Always reinforcing the importance of maintaining proper oral hygiene. Dental intervention in the face of the side effects of chemotherapy is essential preventing a progression of systemic infections (TONG, ROTHWELL, 2000). Adapting the oral environment favors the patient in several ways, promoting a better quality of life for the patient, allowing him to eat without discomfort, perform brushing without worrying about feeling pain, thus directly influencing the progression of the antineoplastic treatment, the systemic picture of the patient and emotional and social well-being (GANDHI et al, 2017).

Even with the completion of chemotherapy, the dental approach must remain, aiming at a therapeutic intervention of the repercussions arising from the anticancer treatment. Post-treatment anticancer follow-up must be done with quarterly consultations in the first year and subsequently in six-monthly periods. For patients undergoing bone marrow transplants, dental treatment is not recommended in the first year (MASSLER, 2000). Regardless of when the dental procedure will be performed (before, during or after), the execution requires examinations regarding the patient's hematological index (ZIMMERMANN et al., 2005).

Clinical studies have shown treatment protocols for various oral manifestations that affect children undergoing chemotherapy. These protocols are based on the clinical conditions of each patient as well as the specifics of each cancer treatment. Table 1 describes the main oral conditions and their respective treatments.

CONCLUSION

During chemotherapy, the treatment of oral manifestations as well as early diagnosis and prevention must be considered of paramount importance to reduce the morbidity rate and possible future costs Children undergoing antineoplastic treatment are more likely to develop lesions in the oral cavity, such as mucositis, xerostomia, viral infections, herpes, ecchymosis, recurrent aphthous lesions and gingivitis, which directly affect the systemic health and well-being of the patient. Evidencing the need for the performance of the Dental Surgeon inserted in the Multidisciplinary team, highlighting prevention and health promotion measures, helping in the attempt to improve the patient's clinical condition and their quality of life during hospitalization.

Alteration	*Time of Manifestation*	*Treatment*
Caries According to GOURSAND et al, 2006.	Even dental intervention appropriate to the case.	Atraumatic restoration technique (ART): Removal of carious tissue + insertion of ionomeric cements.
Ecchymosis and Petéqueas According to KROETZ; CZLUSNIAK, 2003.	It usually appears as a result of trauma and lasts for about 1-3 weeks.	Preventive: Remove possible causes of trauma.
Recurrent aphthous stomatitis According to FÁVARO, 2004 and NEVILLE et al, 2009.	When it occurs, it lasts an average of 7-15 days.	Use of protective creams, pastes and ointments containing: - Carboxymethylcellulose gelatin (Orabase); - Salicylates; - Topical anesthetic; Corticosteroid creams and ointments; - Betamethasone valerate 0.1%; -Triamcinoloma 0.1% - 0.5%; - Fluocinanide 0.5% gel or ointment - Clobatasol propionate 0.05%.
Gingivitis According to ABREU et al, 2010.	Since gingivitis is a biofilm-dependent disease, it lasts until there is rehabilitation and continuous adaptation of the oral environment.	Correct oral hygiene even in the face of painful symptoms and adequacy of the oral environment and adequacy of the oral environment especially before the beginning of chemotherapy treatment.
Herpes According to CONSOLARO, 2009.	When it occurs, it lasts an average of 7-15 days.	Topical use of Acyclovir ointment 5 times a day for 3 days; Administration of Acyclovir 200 mg tablet, take 2 tablets (400 mg) every 4 hours for 7 days; Lasertherapy 660nm, 100mW, 2J, 20J/cm².
Mucositis According to AMARAL et al, 2012.	It usually appears within the first 10 days of chemotherapy treatment and may last even after 2-3-3 weeks of completion.	Preventive treatment: Low power laser (660nm, 100Mw, E=1J, 10J/cm²) During: Low power laser (660nm, 100Mw, 2j, 20j/cm²). Mouthwash with chamomile tea; cryotherapy Topical use of 0.12% aqueous chlorhexidine gluconate Careful oral hygiene guidelines even with painful symptoms (opt for multiple bristle brushes and as a last resort use foam brushing).
Gingival bleeding According to VENTRIGLIA; DINIZ; AZNAR, 2014.	From the moment the administration of antineoplastic drugs begins (cause) and during their use, the patient is more susceptible to the occurrence of hemorrhage.	Preventive: Oral hygiene guidance, Mouthwash and dressing with medicine macerated with antifibrinolytic, During: Oral hygiene that includes chlorhexidine, use mouthwash that contains antifibrinolytic.
Xerostomia According to ROSALES et al, 2009.	Can last even after anticancer treatment.	Stimulation of the salivary glands through sugar-free chewing gum; Administration of artificial saliva (gel or spray): Saligel, BioXtra, On care, Odomed Pro Gel.

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