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REVIEW

Oral alterations in children with cancer. Literature review.

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Abstract: For dentists, there is little information on malignant tumors and complications both because their natural evolution is secondary to treatment, despite cancer in children represents 3% of all cancer cases. The goal is to make a brief review of the most common neoplasm in children, to identify them and find out the oral alterations with highest incidence both as secondary to the pathology and as a side effect of treatment. This review analyses various types of malignant neoplasms which may occur in this stage of life. They are divided into haematological: leukemias, lymphomas and solid tumors. The most common leukemia is acute lymphoblastic (ALL) followed by acute myeloid and granulocytic. Lymphomas develop from the lymphatic system and are divided into Hodgkin's and non-Hodgkin's. Cancer has become a chronic disease favoring a new group of patients who achieve survival but suffer side effects due to therapies, drugs, doses and the child's characteristics. Oral complications appear in 40% of cases and the most frequent are mucositis, opportunistic infection, xerostomia, bleeding, periodontal disease and disorders in the development of teeth and jaw. Although cancer is located outside of the maxillofacial area, chemotherapy is aggressive for a developing organism. The side effects of radiation therapy affect the general and specific area to radiate as well as the surrounding organs and tissues. Recently, advances in diagnosis and treatment have increased survival from 20% to 80%, with long-term treatment.

Keywords: *Cancer, oral side effects, chemotherapy, radiation therapy.*

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INTRODUCTION.

The incidence of cancer in children is 3% of all cancers[1-3]. Recent advances in diagnostic techniques and treatment increased pediatric patients' survival from 20% to 80%. The most common cancers in children are lymphoblastic and myeloid leukemia, retinoblastoma, neuroblastoma and Ewing sarcoma. Lymphomas are divided into two types: Hodgkin's lymphoma, with greater incidence in 10 to 30-year-old people and non-Hodgkin's lymphoma which is most common in children[4,5].

In the central nervous system, there is an important diversity of cancers such as astrocytoma, medulloblastoma, glioma, ependymoma, and primitive neuroectodermal tumors[6]. Rhabdomyosarcoma is the only soft tissue sarcoma which affects the muscles in any area. It usually develops in the head, neck, pelvis and extremities, especially in male children between the ages of 2 and 6 years old. Meanwhile, the Wilms' tumor develops in children younger than 10 years old[6].

Osteosarcoma is the most common bone cancer in children. It maily appears in long bones such as the humerus, femur and tibia, in subjects between 10 and 25 years old, with a higher incidence in males[7].

Oral complications represent the main problem caused by the treatments in patients with cancer. A 40% of children who are receiving chemotherapy develop secondary oral problems, lesions and/or complications[10] as side effects due to its aggressive action on a body in full development[8-10].

CLINICAL PEDIATRIC MANAGEMENT BEFORE CANCER TREATMENT.

In a clinical context, prior to the treatment of cancer, it is necessary to consider and execute a series of activities and related procedures such as taking a thorough history, oral exploration with diagnostic tools like intra- and extra-oral X-rays, quantitative sialometric studies, apart from instructing patients in their proper oral hygiene, performing topical applications of fluoride and realization of general prophylaxis. It is also necessary to observe and treat any chronic inflammatory lesions of the jaws and to eliminate traumatic prosthesis removing unrepairable dental pieces altered by disease or trauma. Finally the extractions should be carried out at least two weeks before starting treatment[11,12].

The preventive program covers motivation for both the child and his/her family to practice oral hygiene, controlling diet, and bacterial plaque, application of fluor and sealers on pits and fissures in erupted molars, when necessary. In all cases, regular check-ups for reviewing and maintenance are needed[12].

TREATMENT.

The treatment for haematological malignancies, leukemias and lymphomas comprises induction, intensification and maintenance phases. The ones for maintenance will be held for at least two years, with frequent reassessments to detect relapses[13] (Table 1).

The acute toxicity associated with the treatment and its side effects are very important, especially because of the negative impact on children's quality of life and because they depend on the drugs used, the length of time they have been administered, the dosage and each child's specific characteristics.

Regarding the skin, the overall effects are alopecia, erythema or hyperpigmentation. On the heart, there is cardiomyopathy. Regarding the gastrointestinal tract, there is anorexia, nausea and vomiting, diarrhea, constipation, mucositis, alteration of taste and gastritis. In the liver, there is a hidroelectrolitic alteration due to increa-

Table 1. Cancer treatment in children.

TYPE OF CANCER	TREATMENT
Acute lymphoblastic leukemia	**Chemotherapy:** L-asparaginase, Vincristine and dexamethasone; a fourth drug from the anthracy cline class is added (daunorubicin and others such as methotrexate and/or 6-mercaptopurine too. **Radiation therapy** **Targeted therapy:** tyrosinekinase inhibitors (TKI) and imatinib mesylate (Gleevec).
Non-Hodgkin's Lymphoma	**Stages I and II:** BFM chemotherapy with methotrexate, 6-mercaptopurine, combination CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and COMP (cyclophosphamide, vincristine, methotrexate and prednisone). **Stages III and IV:** L-asparaginase, Vincristine and dexamethasone; a fourth drug from the anthracycline class (daunorubicin) is added and others such as methotrexate and/or 6-mercaptopurine too.
Osteosarcoma	**Chemotherapy:** Carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, ifosfamide and high-dose methotrexate with leucovorin.
Rhabdomyosarcoma	**Chemotherapy:** monoclonal antibody, dacarbazine, doxorubicin, epirubicin, gemcitabine and ifosfamide.
Astrocytoma	**Radiotherapy:** alkylating **Chemotherapy:** Carboplatin with or without vincristine, or a combination of thioguanine, procarbazine, lomustine, and vincristine (PVC); Platinum and Temozolomide, and inhibitory substances of mTOR (Everolymus, and Sirolimus). Vinblastine, Temosolomida alone or combined with irinotecan, bevacizumab, and prednisone.
Acute myeloblastic leukemia	**Chemotherapy or radiation therapy:** all-trans retinoic acid (tRA) and arsenic trioxide.
Lymphoblastic Lymphoma	**Chemotherapy:** GER-GPOH-NHL-BFM-95: prednisone, dexamethasone, vincristine, daunorubicin, doxorubicin, L-asparaginase, cyclophosphamide, cytarabine, methotrexate, mercaptopurine-6, thioguanine-6. **Radiotherapy:**GER-GPOH-NHL-FM-95

Table 1 (Cont'd). Cancer treatment in children

TYPE OF CANCER	TREATMENT
Hodgkin's Lymphoma	Chemotherapy: monoclonal antibody. Targeted radiation therapy. Extra: antibiotics and transfusion of blood products.
Histocytosis	Chemotherapy: methotrexate, Thalidomide; vinblastine, prednisone, and cytarabine; Pamidronate, Cladribine; Sx degenerative: dexamethasone, retinoic acid, IVIG infliximab, and cytarabine with or without vincristine. Radiotherapy: psoralen and longwave ultraviolet radiation (PUVA). Topical: topical steroids and nitrogen mustard.
Germ cell tumor	Early Stages (I and II): chemotherapy with cisplatin and VP-16 (etoposide) associated with bleomycin or not. Advanced stages (III and IV): chemotherapy with cisplatin combinations and VP-16 (EP) or the same combination with Bleomycin or with cisplatin, VP-16 and ifosfamide (VeIP).
Wilms' Tumor	Stage I: chemotherapy with regimen EE-4-A (Vincristine and dactinomycin, posnefrectomia). Stage II: chemotherapy with regimen EE-4-A, regimen DD-4-A (Vincristine, etoposide, doxorubicin) and regimen I (Vincristine, Doxorubicin, cyclophosphamide, and etoposide). Stage III: chemotherapy with regimen DD-4-A and regimen I. Stage IV: chemotherapy with regimen DD - 4 A and I. Stage V: chemotherapy with regimen DD - 4 A, I and EE – -4-A.

sed transaminase and bilirubin levels. Concerning the bone marrow, there is anemia and neutropenia. Besides, thrombocytopenia appears between 7 and 14 days after chemotherapy. Among the neurological effects, there is drowsiness, paresthesia, seizures, ataxia, and myalgia. As for eyes, there are alterations in the colors and visual acuity due to conjunctivitis which is caused by the direct action on the ocular conjunctiva and favored by eyelashes falling and cataracts. Although lung disorders are not the most frequent, they are the most serious, such as pulmonary fibrosis, which decreases the ability of the lung to exchange oxygen with the bloodstream, and inflammatory interstitial pneumonitis, which causes frequent manifestations of cough, dyspnea and fever. With respect to the reproductive system, there is sterility, amenorrhea and alterations of the pubertal development. Kidney disorders originate mainly because it is the route of elimination of drugs or their metabolites and injuries may occur in this track structures due to increased levels of urea and serum creatinine. Concerning the bladder, the damage is known as hemorrhagic cystitis, and patients present hematuria and dysuria. Finally, there is hypersensitivity caused by the use of corticoisteroids[14,15].

ORAL COMPLICATIONS DURING TREATMENT.

Complications associated with chemotherapy are the result of complex interactions between many factors, such as the lethal and sublethal injury in oral tissues which are produced by an attenuation of the immune system. Therefore, it is the main cause for stomatotoxicity which interferes with the normal healing process. It is frequent to observe oral mucositis, timely viral, fungal and bacterial infections, xerostomia, neuropathies, hemorrhages, periodontal disease, and alterations in the development of teeth and jaw during the stage of dental and skeletal maturation[16-18].

A) Mucositis is caused by chemotherapeutic agents and/or by ionizing radiation, which act on the cells in their multiplicative phase and form a rapid proliferation of tissue which causes lesions such as aphthous stomatitis[19].

There are two types of mucositis: erythematous and ulcerative. Erythematous mucositis typically appears between 3 and 5 days post-chemotherapy. Ulcerative mucositis is the most severe, producing inflammation and ulceration of the mucous membrane. It is painful and starts between 3 to 7 days after the beginning of chemotherapy and lasts for several days. It begins with an erythema in

the soft palate, extending to the buccal mucosa, the belly of the tongue and the floor of the mouth. Then, it is followed by an edema, ulceration with bleeding and/or pleural effusion with possibilities of secondary and opportunistic infections which can lead to anorexia, with evident dehydration and malnutrition[20].

The treatment of mucositis is based on soft mouth rinses of water containing calcium bicarbonate, 0.12% chlorhexidine and saline solution. Also, it is necessary to use drugs to protect the epithelium like aluminum and magnesium hydroxide, baking soda, diluted hydrogen peroxide and sucralfate suspension. In order to relieve pain and swelling it is required the application of topical anesthetics such as dyclonine hydrochloride 1% and lidocaine viscous 2%. It is also useful to prescribe powerful and conventional anti-inflammatory drugs and painkillers, long-term and broad spectrum systemic antibiotics, a soft diet, maintain hydration and avoid irritating foods. It is advisable to use humidifiers and vaporizers, as well as a correct brushing technique with the appropriate instrumentation[21-23].

Mucositis classification according to WHO:

Grade 0: symptoms: None.

Grade 1: symptoms: erythema.

Grade 2: symptoms: erythema, edema or ulcers. The patient can eat solid foods.

Grade 3: symptoms: erythema, edema or ulcers. The patient can only have liquids.

Grade 4: symptoms: the patient requires enteral or parenteral support.

The side effects of radiation therapy depend on the radiated area and the surrounding affected organs and tissues. They are alopecia, epitheliitis (skin flushing and tension), frequent drowsiness, headaches, dryness of the mouth, dysphagia, alterations of taste and smell as well as nausea and vomiting, skin darkening, diarrhea, and neuroendocrine toxicity, among others[24,25].

The main chemotherapeutic agents which can produce mucositis are alkylating agents, antimetabolites, arabinosidos, vinca alkaloids, anthracyclines and antitumor antibiotics among others[26,27].

B) Xerostomia appears as secondary to quantitative and qualitative salivary alterations thereby reducing salivary amylase and immunoglobulin A, which leads to an increased viscosity, burning and pain in the mouth, difficulty for swallowing dry foods, difficulty in speaking, as well as a decrease in taste sensitivity and increased liquid consumption. When associated with oral mucositis, there may be ulcerations and both pain and opportunistic infections intensify. The salivary flow can be stimulated by chewing gum and sugar-free lemon drops, or it is recommended to use saliva substitutes and sialogogues[28].

C) Secondary infections are originated due to the bone marrow suppression caused by chemotherapy, with quantitative and qualitative changes in the oral microflora, or the epithelial barrier. The most frequent are the gram-negative bacterial infections which affect both teeth and gums and oral mucosa and the symptomatology is masked by myelosuppression.

Fungal infections such as candidiasis have a pseudomembranous form characterized by patches or chronic atrophic erythematous forms and angular cheilitis. In the most serious cases, there may be sepsis caused by hematogenous spread.

Viral infections usually occur in the form of lesions caused by the herpes simplex and zoster, compromising the intraoral and perioral mucosa, accompanied by fever and lymphadenopathy[29].

D) Thrombocytopenia is a gingival hemorrhage or purpuric lesion in the oral mucosa or skin ecchymosis. In patients undergoing chemotherapy, blood studies should be carried out before any dental surgical procedure since the haematological values must be 2,000/mm^3 in leukocytes; 500/mm^3 in neutrophils and 100,000/mm^3 in platelets[21].

AFTER TREATMENT.

Late effects are caused by the disruption of the cell division during the stage of child growth. This can now be observed due to the higher survival, and they inten-

sify the lower the age of therapy initiation is. If there is an association of chemotherapy and radiation therapy or chemotherapy regimen, the alterations are the following:

A) Due to an abnormal dental development, root shortening, conoid roots, small crowns, enamel hypoplasia, intimal tear of the apical root, inhibition of the growth of the permanent tooth or only of the root, premature eruption of permanent teeth, early obliteration of the permanent apices, pulp chamber widening, root refinement, anodontia, microdontia, delay in dentition and dental shortening can be observed[30].

B) Due to rampant caries and demineralization, because of the rapid formation of cavities or dental erosion caused by a disruption of the salivary flow and consistency as well as by the quality in food, which tends to be doughy or liquid in the presence of xerostomia or mucositis[31,32].

C) Due to tooth color alteration, because of the use of tetracyclines which change the tooth color when administered during the calcification stage[33,34].

D) Due to neurotoxicity, 6% of oral complications cause discomfort and pain similar to pulpitis. It is constant and has an acute onset. It is deep, and mimics tooth pain or a burning sensation without apparent cause in the teeth or in the mucosa. It involves buccal nerves, with a higher incidence in lower molars. Nothing important can be found in the clinical examination, and in the radiographic exam, a thickening of the periodontal ligament in teeth with pulp alive can be seen[35].

In addition, in patients with head and neck cancer, radiation therapy may irreversibly damage the salivary glands, the oral mucosa, the musculature and the alveolar bone causing xerostomia, dental disease and osteoradionecrosis[36,37].

High-dose chemotherapy or when administered in continuous infusion or in frequent cycles, like therapies with methotrexate, 5-fluorouracil, doxorubicin and Actynomicine D, is more likely to cause mucositis than if it is given by the intravenous method[38].

RECOMMENDATIONS.

It is necessary to emphasize confirmation of the effectiveness of oral preventive protocols, considering them as an outline to guarantee and guide the professional before, during, and after antineoplastic treatment, since the incidence of oral complications can be reduced by eliminating the sources of infection or irritation using preventive measures during the treatment. Risk factors are an unkept oral cavity, dental pathology and faulty prostheses which must be addressed prior to therapy. In the treatment of mucositis, a correct oral hygiene like prophylaxis reduces its incidence and severity. For the recovery of the haematologic formula post-chemotherapy, it is recommended to use a granulocyte colony-stimulating factor (G-CSF). This factor produces competent granulocytes in pediatric patients under treatment with some cytotoxic for any neoplasm. Its use allows offsetting neutropenia induced by chemotherapy thus preventing secondary infections, which can sometimes be fatal.

Children must be included in the protocols of care of the pediatric preventive units of the corresponding health-care institutions using individualized tests as well as preventive programs to motivate both children and their parents to keep oral hygiene, advice them on diet, control bacterial plaque and, when required include applications of fluoride and pit and fissure sealants and schedule periodic follow-up visits.

CONCLUSION.

The pediatric dentist must have an important role both in the prevention, cure and control as well as actively participate in the detection of cancerous lesions, especially in early stages, thus avoiding the possible use of aggressive surgery treatment, radiation therapy and chemotherapy. In the presence of cancer, the patient should be referred to the specialist oncologist, and create a multidisciplinary team which normally includes an oncologist, a radiation therapist, a maxillofacial surgeon, a pathologist and a pediatric dentist to assess the patient and recommend appropriate therapy in order to grant relief and eradicate symptoms to improve their quality of life.

Alteraciones orales en niños con cáncer. Revisión del tema.

Resumen: Existe poca información para el odontólogo sobre tumores malignos y complicaciones por su evolución natural como secundaria al tratamiento a pesar de ser el cáncer en niños el 3% de todos los cánceres. El objetivo es hacer una revisión sucinta de las neoplasias más frecuentes en niños, identificarlas y conocer las alteraciones orales con mayor incidencia secundarias tanto a la patología como el efecto secundario del tratamiento. Realizamos una revisión analizando los diferentes tipos de neoplasias malignas que puede presentarse en esta etapa de vida, las cuales se dividen en hematológicos: leucemias y linfomas y tumores sólidos. La leucemia más frecuente es la linfoblastica aguda (LLA), después la Mieloide Aguda, y Granulocítica. Los linfomas se desarrollan del sistema linfático, se dividen en Hodgkin y no Hodgkin. El cáncer se ha convertido en una enfermedad crónica. Ello favorece un nuevo grupo de pacientes que logran supervivencia suficiente para que puedan producirse efectos secundarios por las terapias utilizadas, fármacos, dosis y las características de cada niño. Las complicaciones orales aparecen en un 40%, las más frecuentes: mucositis, infección oportunista, xerostomía, hemorragias, enfermedad periodontal, alteraciones del desarrollo de dientes y maxilar. Aunque el cáncer esté localizado fuera del área maxilofacial, la quimioterapia es agresiva en un organismo en desarrollo. Los efectos secundarios de la radioterapia son generales y específicos de la zona a irradiar, órganos y tejidos circundantes. Últimamente, los avances en diagnóstico y tratamiento aumentaron la supervivencia del 20% al 80%, con tratamientos a largo plazo.

Palabras clave: *Cáncer, efectos secundarios orales, quimioterapia, radioterapia.*

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