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Diagnosis, prophylaxis and treatment of oral complications in children with acute lymphoblastic leukemia. A narrative review

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignant condition defined by the proliferation of immature hematopoietic bone marrow cells, which replace the normal bone marrow elements. Furthermore, immature cells will accumulate in various areas of the body. Chemotherapeutic drugs are cytotoxic and have unwanted effects on normal cells. This toxicity is acute, or it may be chronic. Approximately 60% of survivors of ALL will suffer from one or more health problems or adverse side effects of this treatment. Oral complications are a frequent consequence of oncology therapy in pediatric patients. Xerostomia, carious lesions, gingivitis, tumors of the oral cavity, bone deformities of the jaw, temporomandibular joint disorders, trismus, and infections due to abundant microbial flora are common in these children. The risk of dental anomalies (dental or root agenesis, root malformations, enamel defects, dental hypoplasia) is higher in those who started treatment before permanent teeth erupt. All children are at risk of developing oral lesions due to poor hygiene, but children who have survived cancer are at even higher risk.

The survival rate of children diagnosed with ALL has significantly increased thanks to remarkable advances in chemotherapy. Therefore, it is important that these patients are constantly monitored by the dentist to treat complications arising from the treatments in a timely manner. In children diagnosed with ALL, oral health is of great importance as the oral environment changes as a side effect of hematological disorders and their treatments.

Treatment of carious lesions, periodontal problems and lesions of the oral mucosa must be done before starting chemotherapy by cleaning the oral cavity to eliminate any possible risk of infection. The participation of the dentist is important in improving the preventive protocols and oral examination of the pathological processes that occur in children with ALL. Interdisciplinary collaboration between physicians is essential during the treatment of pediatric cancer patients.

Keywords: acute lymphoblastic leukemia, oncological treatment, oral complications, dental treatment

INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents 75% to 80% of all childhood leukemia cases; acute myeloid leukemia (AML) accounts for 15% to 20%. Approximately 85% of all cases are due to the B lineage (B-ALL) and 15% to the T lineage (T-ALL) [1,2,3]. ALL is a malignant condition defined by disseminated proliferation of immature hematopoietic bone marrow cells, that replace the normal bone marrow elements. Furthermore, immature cells will accu-

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mulate in various areas of the body. In patients with ALL, the main factor that causes morbidity and mortality is their susceptibility to infections due to the immunosuppression medicine. Studies show that 24% of life-threatening infections occur in the oral cavity [4,5].

Leukemic cells have constellations of mutations, that can be germline are generally somatically accrued. The affected genes encode the proteins that regulate the survival of hematopoietic progenitor cells, their proliferation and differentiation. When relapse occurs, new genetic mutations may appear alongside the mutations that were detected at diagnosis. The initial mutations may also disappear in relapse. [6]. Acute leukemia usually has the 10 to 20 somatic coding single nucleotide variants and 4 or 5 structural variants at initial diagnosis, with a typical mutation rate two to three times higher at relapse [7,8,9].

ORAL COMPLICATIONS

Approximately 60% of survivors of ALL will suffer from one or more health problems or adverse side effects of this treatment. In some cases (30%), survivors' health problems are life-threatening or severe and have a great effect on their comfort. Adverse effects depend on a combination of the disease, the treatment options and a series of factors concerning the host. Chemotherapy implies administering cytotoxic drugs at the maximum does that can be tolerated by the patient's organism. These drugs have unwanted effects on normal cells that manifest as acute toxicity (occurring during treatment) or chronic toxicity (the toxic effects can persist after the treatment has ended or can appear only months or years later) [10].

All children are at risk of developing oral lesions due to poor hygiene, but children who are cancer survivors are even at a higher risk [11]. The oral cavity is frequently affected in immunocompromised patients, and complications are common during dental procedures, especially in the absence of neutrophilic granulocytes. The oral mucosa shows typical lichenoid changes with or without lesions, ulcers, or erythematous mucoceles. Hyposalivation often occurs concomitantly, which significantly increases the risk of caries, periodontitis, and oral mucosal infections [12].

The treatments used it malignancies have their own consequences and put pediatric cancer patients in increased danger of developing a variety of conditions. Dental complications are a frequent consequence of oncologic therapy in children. Xerostomia, carious lesions, gingivitis, tumors of the oral cavity, bone deformities of the jaw, temporomandibular joint disorders, trismus, and infections because of the abundant microbial flora are common in these children [13-16]. The risk of dental anomalies is higher in patients that started therapy before the eruption of permanent teeth. The most frequent anomalies are agenesis of the tooth or root, root malformations, enamel defects, and tooth hypoplasia [10].

Xerostomia

Xerostomia, or dry mouth, is caused by chemotherapy as well as by radiation around the head or neck. The salivary glands are very sensitive to radiation. Dry mouth can increase the risk of oral infections and dental caries and can cause difficulty in speaking, chewing, and swallowing, as well as sleep disturbances [17,18].

Xerostomia is caused by injury to the acini of the salivary gland. This can lead to a change in the quantity or consistency of saliva in the oral cavity, particularly a lower pH (acidic), which creates a favorable environment for the development of caries. In patients with xerostomia, the microbial flora changes from Gram-positive to Gram-negative microorganisms and tends to develop fungal infections. There are also difficulties is swallowing, chewing, speaking and changes in taste. The conditions that appear due to chemotherapy are usually self-limiting and temporary, resolving in the next 48 hours. Damage caused by radiation to the head and neck region can be long-lasting, but some patients regain salivary function 4-12 months after therapy [18].

Dental caries

Dental caries is a preventable complication in surviving children. Health professionals can limit its occurrence by early identification of risk factors [13]. Dental caries results from an imbalance between demineralization and remineralization of teeth due to the interaction between bacteria, sugar, and saliva. Only when the microbiome of the oral cavity changes, dental plaque can lead to caries. A diet rich in carbohydrates is thought to be responsible for this change. Other factor is dry mouth, poor plaque control, low fluoride exposure, as they lead to an increased number of cariogenic microorganisms [13,19].

Lactobacillus, Streptococcus mutans, and Actinomyces species are considered to be the most cariogenic [13, 19]. Saliva aids the body in slowing this process by counteracting the acidity of the environment created by the bacteria. Saliva is used to remove the food particles and glucose that the cariogenic bacteria need for their development from the oral cavity [20].

Thus, the interruption of saliva production alters the environment in the oral cavity by creating a cariogenic status. This leads to a series of severe com-

plications such as bacteremia, pain, abscess formation, and tooth loss. These complications cause decreased self-esteem, difficulties in speech and chewing, orthodontic problems and higher treatment costs [21]. Survivors have an increased risk of caries if they eat a diet high in carbohydrates and sugar. Other factors that increase the risk of caries include age when diagnosed, medications, chemotherapy, and radiation [22,23]. The salivary dysfunction secondary to chemotherapy, leading to dental plaque accumulation is associated with a higher risk of caries. Vincristine, anthracyclines, and cyclophosphamide are the chemotherapeutic agents that have been particularly associated with an increased risk of dental abnormalities and caries [13].

Patients diagnosed with cancer older than five years of age had more caries than patients diagnosed at younger ages. Patients treated before the age of five had more severe dental defects, due to the fact that immature teeth have a higher liability for oncologic treatment [13]. An important aspect in maintaining remission is oral medication. Oral medical solutions are administered in the form of capsules or tablets. They are often composed of sugar, which gives them their established role in the etiology of dental caries [24].

Gingivitis

Periodontal changes in leukemia patients are attributed to hematologic disorders or are related to chemotherapy and radiotherapy [25,26]. The inflammation and hyperplasia of the gingiva in pediatric patients with ALL is due to the infiltration of immature cells (blasts) causing a plaque-induced reaction. Significant inflammation and proliferation in the gingiva can be caused by small amounts of plaque or food debris. Chemotherapeutic agents may have destructive effects on gingival epithelium, that can lead to a greater local fragility [27,28]. Early gingivitis is the most common condition before and after treatment. Bacterial plaque is one of the etiologic factors blamed for the occurrence of gingivitis. Oral hygiene is a basic prevention method, especially in children suffering from ALL. Both parents and children need to know the importance of good oral hygiene and regular dental checkups [29].

Many side effects of oncological treatment as well as decreased self-esteem may affect the oral hygiene of children, which affects their periodontal health status. The variables analyzed by a study were bacterial plaque index, gingivitis bleeding index, histologic tumor type, age, gender, and skin color. The prevalence of gingivitis was moderately higher in children with oncologic disease, but there were no statistically significant differences considering groups divide by gender, age, skin color, or histopathologic tumor type [30].

Mucositis

The underlying disease, cytotoxic therapies, and radiation therapy predispose pediatric cancer patients to gastrointestinal mucosal changes, that subsequently create entry sites for microorganisms and cause local infections [31]. Mucositis develops in 40% of children receiving standard chemotherapy, 80% of patients receiving radiation therapy for head and neck cancer, and 75% of bone marrow transplant patients [32,33]. Oral mucositis refers to the erythematous inflammatory changes of the oral and labial mucosa, soft palate, floor of the mouth and ventral surface of the tongue in patients undergoing toxic chemotherapy or radiation. Patients characterize the condition as a sensation of tingling or burning that causes hypersensitivity to food. As mucositis progresses, chewing, swallowing, and speaking become difficult. Healing of the inflammation may be slowed if food intake is impaired because the patient refuses to eat. The delay results from a calorie and protein deprivation that causes cell migration and renewal to decrease. Injury to the oral mucosa and the epithelial barrier allows the development of infections caused by the resident flora of the oral cavity and poses a greater risk for the evolution of disseminated infections [11,18].

The physiopathology of mucositis shows us that there are four phases: an initial inflammatory or vascular phase, an epithelial phase, an ulcerative or bacteriological phase, followed by healing.

1. The inflammatory or vascular phase occurs 24-36 hours after the administration of toxic treatments, and it is characterized by the release of tumor necrosis factor and interleukin 1 (inflammatory cytokines) from the epithelial tissue. This leads to an added accumulation of cytotoxic agents deposited at mucosal level, due to the increase in local tissue vasculature.

2. The epithelial phase occurs after four to five days, and it is characterized by increased levels of local cytokines and the decrease in cell turnover in the basal epithelium. This leads to further tissue injury and atrophy. Treatment at this stage should aim to restore cell growth and decrease cytokine release.

3. The hematologic effects occur one week after treatment. The number of neutrophils decreases, and the ulcerations become exudative and erosive. This phase provides an opportunity for proliferation of viruses, bacteria, and fungi. These microorganisms produce endotoxins and may exacerbate the inflammatory cascade, thus intensifying the damage to the oral mucosa [18].

The severity of mucositis can vary between small, singular oral ulcers to large ulceration over the entire mucosal surface. A notable side effect of mucositis is acute necrotizing ulcerative gingivitis [29,31]. Pediatric patients that receive broad-spec-

trum antibiotics or have been in the hospital for a long time may develop colonization of the oral cavity with fungi or Gram-negative microorganisms. Candida, Aspergillus, or herpes simplex virus (HSV) may also appear in mucositis caused by chemotherapy. Septicemia caused by α-hemolytic streptococci can lead to complications of mucositis and has high rates of shock and central nervous system (CNS) infections [31]. Appropriate oral hygiene is crucial in decreasing the severity of oral mucositis [34,35].

Viral infections

Pediatric patients undergoing cancer treatment readily acquire opportunistic oral infections (viral, bacterial, and fungal) [34]. Typical of leukemia is the risk of reactivation of viruses, such as herpes zoster virus and herpes simplex virus (HSV). Mouth ulcers and large canker sores are common manifestations of HSV. All these infections can cause severe pain [12]. HSV most commonly occurs as a virus reactivation in a person that has been infected before. The first lesion is vesicular, located in the oral cavity or peri-oral, and then a crust forms or a yellowish ulceration persists. The infection with HSV is generally extremely aching and lead to deep edema of the oral mucosa causing pain, discomfort, hypersalivation, and difficulty swallowing [18].

Fungal infections

Candida infections are common in pediatric cancer patients. It should be noted that these infections are often resistant to the usual treatment protocol [12]. Infections caused by fungi are frequent in children because of the repetitive use of broad-spectrum antibiotics and steroids, which is exacerbated by bad oral hygiene and nutritional deficit. Candida albicans is the most frequently involved in causing fungal infections in patients with immunodeficiency. Up to 60% of people have Candida albicans in their normal flora from the oral cavity. Immunosuppressed patients often allow Candida to grow and multiply excessively, causing infection. This excessive multiplication is exacerbated by xerostomia or poor oral hygiene [18].

Dental abnormalities

The age of the child at baseline and the form, severity, and regularity of administered treatment are elements that have an important part in the onset of these dental abnormalities [18]. The development and eruption of permanent dentition occurs starting from age six up to age twelve. Abnormalities that interest the structure of permanent dentitions are more and more common after chemotherapy in children. Some of these are hypo- and microdontia, enamel hypoplasia, enlarged pulp chamber, root malformations, and lack of eruption of permanent teeth [18,36,37,38]. Risk factors include early age when starting chemotherapy, higher doses of chemotherapy, and radiation exposure. Conditioning therapies for hematopoietic cell transplantation may cause dental agenesis and root anomalies. Children that have different anomalies of the permanent dentition have a greater risk for developing carious processes due to high invasion with Streptococcus or other microorganisms [39,40].

DENTAL PROPHYLAXIS AND TREATMENT

Attention should be paid to the complications caused by oncological treatment in order to diminish the prevalence and repercussion during the remission phase and to enhance the survival rate and living standards [18]. Before starting therapy, it is recommended that a dentist performs a preventive examination to clean the oral cavity by removing dental plaque and calculus and treating existing caries. Direct restauration of teeth must be done at least three weeks prior to starting chemotherapy. Topical fluoridation is used to prevent dental caries and mucositis during radiation therapy by causing the incorporation of fluoride into the enamel and dentin and reducing the bacterial load in the oral cavity [18]. The current situation regarding the immune response of bone marrow transplanted patients should always be clarified with the specialized hematologist. If necessary, prophylactic antibiotics should be administered before dental cleaning, scaling, treatment of carious lesions, and extractions; otherwise, treatment should be postponed [12]. A panoramic radiograph must be indicated in all surviving patients to assess the growth of the roots prior to any oral procedure [41,42].

Xerostomia

Treatment of this condition involves the use of synthetic saliva alternatives, stimulating the leftover salivary tissue, by means of hygiene, and application of fluoride substances. The most common therapy used in xerostomia is administering pilocarpine for the stimulation the leftover salivary tissue [18]. The use of sugar-free chewing gums, candies, and capsules, saliva alternatives, mouthwashes that have no alcohol in their composition, and hydration help improve dry mouth syndrome. At the same time, xerostomia patients should be encouraged to drink water frequently throughout the day [32].

Dental caries

A modified diet, fluoride, sealants, oral hygiene, and periodic check-ups are the backbone of dental decay treatment, despite of the health condition of

the oral cavity. Early detection of caries is critical to avoid complications. Fluoride treatment is an important factor in caries prevention in children. The application of fluoride varnishes every three to six months is recommended [13].

Gingivitis

Surviving patients must consider more frequent dental check-ups and brushing thoroughly daily. The COG (Children's Oncology Group, 2014) suggests that children who suffer from ALL should visit the dentist every six months for checkups [41]. In contrast, the AAPD (American Academy of Pediatric Dentistry, 2016) is much more stringent and states that patients with high-risk must be examined once every three months [13].

Young children diagnosed with cancer and their caregivers should be advised to maintain proper oral hygiene, which consists of using a soft bristled toothbrush and toothpastes that contain high doses of fluoride. Dipping the toothbrush in warm water before brushing makes this action more comfortable. Families are instructed to change toothbrushes at each chemotherapy cycle and to floss daily. Soft toothbrushes, wet gauze or sponges used when the patient has thrombocytopenia or neutropenia provide proper oral hygiene and minimize the possibility of gum trauma. It is essential to rinse the oral cavity with saline or sodium bicarbonate after each meal and before bedtime. Careful clinical examination must be done at every check-up to find possible oral issues ahead of time [18,23]. Saliva alternatives and mouthwashes are the ideal treatment choice for these patients. Mouthwashes high in sodium bicarbonate must be used in order to overturn the acidic pH of the mouth and reduce dental plaque. Chlorhexidine mouthwashes are utilized in the course of active and post-treatment stages in cancer patients [13].

Mucositis

1. Inflammatory or vascular phase

Keeping ice cubes in the oral cavity during chemotherapy causes local vasoconstriction and decreases the comeback of toxic elements in the mucosal cells. Ice cryotherapy is beneficial in lessening the intensity of mucositis in phases 1 and 2 of treatment with ebetrexate and carboplatin. This is the only effective mucositis prevention measure suggested in the Cochrane Oral Health Review publications.

2. The epithelial phase

A variety of medications were studied in clinical trials, such as sucralfate and oral glutamine, and are still tested now, as well as new substances like cytokine mouth rinses that have been shown to be useful in this epithelial phase.

3. Ulcerative or bacteriological phase

Research that talks about using topical antimicrobic substances and antiseptic mouthwashes show that elements such as chlorhexidine or capsules containing polymyxin B, tobramycin, and amphotericin B are useful for treating this phase.

Analgesic premedication is required for the cooperation of kids who present ulcers when eating and during toothbrushing. Topical anesthetics like lidocaine, dyclonine, and mouthwashes that contain diphenhydramine are commonly recommended in pediatrics. When topical analgesics do not work or are not feasible because local pain does not allow absorption of medication and food, parenteral administration is chosen. In some more severe cases, parenteral or enteral nutrition may be required. Healing begins after two to three weeks during which oral mucosal cells and leukocytes, which renewal at the same pace, recover in conditions of proper nutrition and without infections caused opportunistic microorganism present [18].

Viral infections

Patients who were exposed to HSV infection are treated using oral or parenteral hydration in conjunction with symptomatic treatment.

Fungal infections

When oral candidiasis develops in children treated with toxic agents, nystatin is optimal choice of treatment which a clinician should consider, even if it is not always useful against the infection. Amphotericin B or other antifungal substances such as amphotericin B or isavuconazole are administered prophylactically and curatively [43-45]. Dental protocols for children receiving toxic treatment, such as regular checkups, decay control, and avoidance of gum disease, may reduce or dispose of complex dental therapy in children who are cancer survivors [46-49].

CONCLUSIONS

The survival rate of children diagnosed with ALL has increased significantly due to remarkable advances in chemotherapy treatment. Therefore, it is important that these patients are cared for and constantly monitored by the dentist in order to treat the complications resulting from the administered treatments in a timely manner. In this way, dental abnormalities, orthodontic problems, and secondary tumor processes in the oral cavity can be detected early.

Oral health care is of great importance in children diagnosed with ALL. This importance arises from the changes that occur in the mouth as hematological diseases and toxic treatments.

The treatment of carious processes, periodontal problems and lesions of the oral mucosa must be done before starting chemotherapy by cleaning the oral cavity to eliminate any possible risk of infection.

The dentist has a crucial part in improvement the preventive approach and dental examination of the pathological processes that occur in children with ALL. Interdisciplinary collaboration between physicians is essential in all phases of treatment of children diagnosed with tumor pathologies.

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REFERENCES

1. An Q, Fan CH, Xu SM. Recent perspectives of pediatric leukemia - an update. *Eur Rev Med Pharmacol Sci.* 2017 Oct;21(4 Suppl):31-36
2. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro Oncol.* 2017 Nov 6;19(suppl_5): v1-v88
3. Gholman RR, El Meligy OA, Felemban EH. Dental Rehabilitation of a Child with Acute Lymphocytic Leukemia: A Case Report. *International Journal of Clinical Pediatric Dentistry,* 2019, 12(6):582-6.
4. González García H, Garrote Molpeceres R, Urbaneja Rodríguez E, Gutiérrez Meléndez P, Herráiz Cristóbal R, Pino Vázquez MA. Differences in incidence and survival to childhood cancer between rural and urban areas in Castilla y León, Spain (2003-2014): *A Strobe-compliant study. Medicine* (Baltimore). 2018 Oct;97(41): e12797.
5. Kapoor G, Goswami M, Sharma S, Mehta A, Dhillon JK. Assessment of oral health status of children with Leukemia: A cross-sectional study. *Spec Care Dentist.* 2019 Nov;39(6):564-71.
6. Ma X, Edmonson M, Yergeau D, Muzny DM, Hampton OA, Rusch M, Song G et al. Rise and fall of subclones from diagnosis to relapse in pediatric B-acute lymphoblastic leukaemia. *Nat Commun.* 2015 Mar 19;6:6604
7. Farrar JE, Schuback HL, Ries RE, Wai D, Hampton OA, Trevino LR, Alonzo TA et al. Genomic Profiling of Pediatric Acute Myeloid Leukemia Reveals a Changing Mutational Landscape from Disease Diagnosis to Relapse. *Cancer Res.* 2016 Apr 15;76(8):2197-205.
8. Ding LW, Sun QY, Tan KT, Chien W, Mayakonda A, Yeoh AEJ et al. Mutational Landscape of Pediatric Acute Lymphoblastic Leukemia. *Cancer Res.* 2017 Jan 15;77(2):390-400.
9. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *N Engl J Med.* 2015 Oct 15;373(16):1541-52.
10. Jenkins A. Late effects of chemotherapy for childhood cancer, Paediatrics and Child Healh, 2013, 23(12):545-9.
11. Gawade PL, Hudson MM, Kaste SC, Neglia JP, Constine LS, Robison LL et al. A systematic review of dental late effects in survivors of childhood cancer. *Pediatr Blood Cancer.* 2014 Mar;61(3):407-16.
12. Ramseier AM, Passweg J, Waltimo T. Oral Problems in Patients Undergoing Haematology or Oncology Treatment. In Neuhaus KW, Lussi A. Management of Dental Emergencies in Children and Adolescents, Wiley, 2019:245-54.
13. Horner AJ, Nativio DG. Unique Factors Affecting the Management and Prevention of Caries in the Childhood Cancer Survivor. *J Pediatr Health Care.* 2019 Jan;33(1):53-57.
14. Docimo R, Anastasio MD, Bensi C. Chemotherapy-induced oral mucositis in children and adolescents: a systematic review. *Eur Arch Paediatr Dent.* 2022 Aug;23(4):501-11.
15. Bensadoun RJ, Riesenbeck D, Lockhart PB, Elting LS, Spijkervet FK, Brennan MT. Trismus Section, Oral Care Study Group, Multinational Association for Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of trismus induced by cancer therapies in head and neck cancer patients. *Support Care Cancer.* 2010 Aug;18(8):1033-8.
16. Hong CH, Napeñas JJ, Hodgson BD, Stokman MA, Mathers-Stauffer V, Elting LS et al. Dental Disease Section, Oral Care Study Group, Multi-national Association of Supportive Care in Cancer (MASCC)/ International Society of Oral Oncology (ISOO). A systematic review of dental disease in patients undergoing cancer therapy. *Support Care Cancer.* 2010 Aug;18(8):1007-21.
17. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN et al. Salivary Gland Hypofunction/Xerostomia Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Support Care Cancer.* 2010 Aug;18(8):1039-60.
18. Belfield PM, Dwyer AA. Oral complications of childhood cancer and its treatment: current best practice. *Eur J Cancer.* 2004 May;40(7):1035-41;
19. Rathee M, Sapra A. Dental Caries. 2022 Jun 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. PMID: 31869163.
20. Krol DM, Whelan K. Section on oral health. Maintaining and Improving the Oral Health of Young Children. *Pediatrics.* 2023 Jan 1;151(1):e2022060417
21. Kagihara LE, Niederhauser VP, Stark M. Assessment, management, and prevention of early childhood caries. *J Am Acad Nurse Pract.* 2009 Jan;21(1):1-10.
22. Rapone B, Nardi GM, DI Venere D, Pettini F, Grassi FR, Corsalini M. Oral hygiene in patients with oral cancer undergoing chemotherapy and/or radiotherapy after prosthesis rehabilitation: protocol proposal. *Oral Implantol* (Rome). 2017 Feb 14;9(Suppl 1/2016 to N 4/2016):90-97.
23. Ritwik P. Dental Care for Patients with Childhood Cancers. *Ochsner J.* 2018 Winter;18(4):351-357.
24. Gupta A, Marwaha M, Bansal K, Sachdeva A, Gupta A. Dental Awareness among Parents and Oral Health of Paediatric Cancer Patients Receiving Chemotherapy. *J Clin Diagn Res.* 2016 May;10(5):ZC92-5.
25. Lauritano D, Petruzzi M, Fumagalli T, Giacomello MS, Caccianiga G. Oral Manifestations in Children with Acute Lymphoblastic Leukemia, European Journal of Inflammation. 2012;10(2):65-8.
26. Quispe RA, Aguiar EM, de Oliveira CT, Neves ACX, Santos PSDS. Oral manifestations of leukemia as part of early diagnosis. *Hematol Transfus Cell Ther.* 2022 Jul-Sep;44(3):392-401.
27. Azher U, Shiggaon N. Oral health status of children with acute lymphoblastic leukemia undergoing chemotherapy. *Indian J Dent Res.* 2013 Jul-Aug;24(4):523.
28. Sampaio MEA, Ribeiro ILA, Santiago BM, Valença AMG. Perception of Pediatric Oncological Patients and Their Parents/Guardians about a Hospital Oral Health Program: A Qualitative Study. *Asian Pac J Cancer Prev.* 2022 Feb 1;23(2):451-7.
29. Parra JJ, Alvarado MC, Monsalve P, Costa ALF, Montesinos GA, Parra PA. Oral health in children with acute lymphoblastic leukaemia: before and after chemotherapy treatment. *Eur Arch Paediatr Dent.* 2020 Feb;21(1):129-36.
30. De Oliveira JC, Do Nascimento MCP, Varela KM, Da Silva VCR, Godoy GP. Prevalence of Gingivitis in Oncology Pediatric Patients, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2017;124(2): e122.
31. Ardura MI, Koh AY. Infections in children with cancer. In: Sarah Long S, Charles Prober C, Marc Fischer M 5th eds. Principles and Practice of Pediatric Infectious Diseases. Elsevier; 2018. p. 586-92.

32. Hong CH, daFonseca M. Considerations in the pediatric population with cancer. *Dent Clin North Am.* 2008 Jan;52(1):155-81
33. Curra M, Soares Junior LAV, Martins MD, Santos PSDS. Chemotherapy protocols and incidence of oral mucositis. An integrative review. Einstein (Sao Paulo). 2018;16(1): eRW4007.
34. Glenny AM, Gibson F, Auld E, Coulson S, Clarkson JE, Craig JV et al. Children's Cancer and Leukaemia Group (CCLG)/Paediatric Oncology Nurses Forum's (CCLG-PONF) Mouth Care Group. The development of evidence-based guidelines on mouth care for children, teenagers and young adults treated for cancer. *Eur J Cancer.* 2010 May;46(8):1399-412.
35. Velten DB, Zandonade E, Monteiro de Barros Miotto MH. Prevalence of oral manifestations in children and adolescents with cancer submitted to chemotherapy. *BMC Oral Health.* 2017 Jan 20;17(1):49.
36. Lauritano D, Petruzzi M. Decayed, missing and filled teeth index and dental anomalies in long-term survivors leukaemic children: a prospective controlled study. *Med Oral Patol Oral Cir Bucal.* 2012 Nov 1;17(6):e977-80.
37. Avşar A, Elli M, Darka O, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007 Dec;104(6):781-9. 104(6):781-9.
38. Nemeth O, Hermann P, Kivovics P, Garami M. Long-term effects of chemotherapy on dental status of children cancer survivors. *Pediatr Hematol Oncol.* 2013 Apr;30(3):208-15.
39. Effinger KE, Migliorati CA, Hudson MM, McMullen KP, Kaste SC, Ruble K et al. Oral and dental late effects in survivors of childhood cancer: a Children's Oncology Group report. *Support Care Cancer*. 2014 Jul;22(7):2009-19.
40. Cubukcu CE, Sevinir B, Ercan I. Disturbed dental development of permanent teeth in children with solid tumors and lymphomas. *Pediatr Blood Cancer.* 2012 Jan;58(1):80-4.
41. Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GM, Huang JT et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. *Biol Blood Marrow Transplant.* 2016 May;22(5):782-95.
42. Hoogeveen RC, Hol MLF, Pieters BR, Balgobind BV, Berkhout EWER, Schoot RA et al. An overview of radiological manifestations of acquired dental developmental disturbances in paediatric head and neck cancer survivors. *Dentomaxillofac Radiol.* 2020 Mar;49(3):20190275
43. Morgan JE, Hassan H, Cockle JV, Lethaby C, James B, Phillips RS. Critical review of current clinical practice guidelines for antifungal therapy in paediatric haematology and oncology. *Support Care Cancer.* 2017 Jan;25(1):221-8.
44. Ruhnke M, Cornely OA, Schmidt-Hieber M, Alakel N, Boell B, Buchheidt D et al. Treatment of invasive fungal diseases in cancer patients-Revised 2019 Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Mycoses.* 2020 Jul;63(7):653-82.
45. Zimmermann P, Brethon B, Roupret-Serzec J, Caseris M, Goldwirt L, Baruchel A et al. Isavuconazole Treatment for Invasive Fungal Infections in Pediatric Patients. *Pharmaceuticals* (Basel). 2022 Mar 19;15(3):375.
46. Francisconi CF, Caldas RJ, Oliveira Martins LJ, Fischer Rubira CM, da Silva Santos PS. Leukemic Oral Manifestations and their Management. *Asian Pac J Cancer Prev.* 2016;17(3):911-5.
47. Gandhi K, Datta G, Ahuja S, Saxena T, G Datta A. Prevalence of Oral Complications occurring in a Population of Pediatric Cancer Patients receiving Chemotherapy. *Int J Clin Pediatr Dent.* 2017 Apr-Jun; 10(2):166-71.
48. Ritwik P, Chrisentery-Singleton TE. Oral and dental considerations in pediatric cancers. *Cancer Metastasis Rev.* 2020 Mar;39(1):43-53.
49. Ferrández-Pujante A, Pérez-Silva A, Serna-Muñoz C, Fuster-Soler JL, Galera-Miñarro AM, Cabello I et al. Prevention and Treatment of Oral Complications in Hematologic Childhood Cancer Patients: An Update. *Children* (Basel). 2022 Apr 15;9(4):566.