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Dental Care for Children with Leukemia: Major Updates

Review Article

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Abstract

Leukemia is a haematological neoplasm that among 300 children and adolescents in Brazil. Its standard treatment consists of the use of antineoplastic based on chemotherapy or radiotherapy, these recommended therapies can provoke several side effects among them buccal alterations mainly due to the immunosupression picture. In view of the exposed this study has the objective to describe the main updates of the dental care to the child carrier of leukemia by reviewing the literature. Immunosuppression and the very fragility and stage of development of children with leukemia lead to greater vulnerability to all types of opportunistic infections and pathologies resulting from antineoplastic therapy. Currently, modern oncology requires the presence of the dentist in all phases of treatment and even before diagnosis in a sine qua non condition for management, maintenance of oral health and quality of life of the leukemic patient. The dentist besides being part of the cancer team is required both in the in-hospital environment and in daily clinical practice. Currently there is a wide range of resources and medicines to promote a satisfactory handling and quality of life for these patients.

Keywords: Child; Leukemia; Oral Health; Dental Care.

Introduction

Leukemia is a hematological and genetically acquired pathology of the hematopoietic system, originating in the bone marrow, the site of production of blood cells. Leukemia appears with a frequency of 17.0% in the first year of life, with a peak incidence of 2 to 3 years with 80 cases per million, being three times more prevalent in the Caucasian race [6].

With regard to childhood cancer, leukemia accounts for 30.0% of childhood neoplasms, is one of the most common neoplasias and most affects individuals from 0 to 15 years old, and is the main cause of childhood cancer deaths in Brazil [3].

In Brazil, the expectation of new cases is around 1 in 300 children and adolescents. The most common leukemia in children are lymphoblastic leukemias, that is, acute lymphoids (ALL), corresponding to 80.0% of the cases. Lymphoblastic leukemia originates in lymphoid cells (lymphocytes), presenting as main signs and symptoms fever in 50.0% of cases, bone and joint pain, pallor, fatigue, weight loss, subcutaneous nodules, headache, vomiting, cutaneous bleeding (epistaxis, petechiae, equizemas) and adenomegaly in 85.0% of patients [4].

The diagnosis is made through several tests, such as the hemogram, analysis of hemoglobins, which in 80.0% of cases is usually below 10 g/dl. Approximately 75.0% of leukemic patients develop platelet thrombocytopenia. The exam that defines the diagnosis of leukemia is the myelogram [3].

The standard treatment consists of use of antineoplastic-based chemotherapy or radiotherapy these therapies advocated may cause various side effects mainly due to immunosuppressive conditions [4].

The main oral alterations that affect patients taking antineoplastic drugs are craniofacial alterations, mucositis, candidiasis, xerostomia, gingival bleeding, trismus, hemorrhages, dental caries, other viral infections, dysgeusia and osteoradionecrosis, which can directly affect health, daily activities and in the quality of life of

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patients, besides being a focus for other infections [4].

When 24 children with leukemia were searched, it was found that only 28.6% of these patients had favorable oral health, the remaining 71.4% presented unfavorable oral health, with oral complications of chemotherapy such as the higher prevalence of mucositis, xerostomia, dysphagia , dysgeusia, candidiasis, gingival bleeding, cold sores and odontoalgia evidencing the need for and dental intervention [11].

Oral manifestations in pediatric patients may be expressed prior to the confirmed diagnosis of leukemia and accentuated during anti-neoplastic treatment, may be treated by the dentist with a stomatology specialization or even the generalist dentist who has a relevant role in the treatment with the medical team in the prevention, diagnosis, control and treatment of these changes in the oral cavity in modern oncology [4].

In view of the above, this study aimed to describe the main updates of the dental care of children with leukemia through literature review.

Methods

Experimental and clinical studies were included (case reports, retrospective, prospective and randomized trials) with qualitative and /or quantitative analysis. Initially, the key words were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and later verified and validated by MeSh system (Medical Subject Headings, the US National Library of Medicine) in order to achieve consistent search.

Mesh Terms

The words were included child, leukemia, oral health, dental care. For further specification, the leukemia, oral health description for refinement was added during searches. The literature search was conducted through online databases: Pubmed, Periodicos.com and Google Scholar. It was stipulated deadline, and the related search covering all available literature on virtual libraries.

Series of Articles And Eligibility

A total of 42 articles were found involving temporomandibular dysfunction. Initially, it was held the exclusion existing title and duplications in accordance with the interest described this work. After this process, the summaries were evaluated and a new exclusion was held. A total of 25 articles were evaluated in full, and 19 were included and discussed in this study.

Literature Review

Craniofacial Changes

Changes in craniofacial development can occur in two ways: direct and indirect. Direct changes affect the sites on growth or around the soft tissues. Indirect changes occur in the form of hormonal deficiency and puberty disorders caused by cranial irradiation to the hypothalamic-pituitary axis. These changes lead to anomalies in the structure of the dental roots, incomplete calcification, premature closure of apices, delay or acceleration in dental development and lesions of caries, it also results in cases of trismus, abnormal occlusal relations and facial deformities.

Children exposed to chemotherapy or radiation during the developmental stages of dental germs during the formative years (before 9 years of age) may present hypomineralization or hypomatology of enamel or short, thin and tapered root formation, with a defective enamel and dentin discolored in deformed crowns. Direct radiation to the head and neck can lead to incomplete development of the jaws, smaller teeth, stuck teeth, overlapping soft tissue atrophy, malformation of hard tooth tissues such as enamel and incomplete calcification of teeth. The younger the child, the greater the risk of craniofacial abnormalities [12].

The study of Lauritano, Petruzzi [10] with 50 children who survived leukemia, aged 8 to 15 years evaluated the possible effects of anti-leukaemic therapy on dental development are at greater risk of developing dental caries and present greater severity of dental anomalies, including V-shaped roots, dental agenesis, microdontia, enamel dysplasias. Concluding that pediatric patients with leukemia require special attention in dental care.

Radiotherapy promotes dental changes in 90 to 100% of cases, in the case of doses ranging from 20-40 Gy, it may lead to the formation of crown and short root teeth, hypocalcification, abnormal root curvature, amelogenesis and imperfect dentinogenesis.

According to Javed et al., [7] children with leukemia are more susceptible and more prevalent to changes in odontogenesis (enamel hypoplasia, halting in the development of the dental organ, anodontia, microdontiae) and rhizogenesis (short roots and sharp roots) besides agenesis.

Muscle Trismus

Muscle trismus is the limitation of mouth opening due to edema, cellular destruction and fibrosis of the muscle tissue induced by radiation, making correct oral hygiene difficult. The degree of restriction depends on factors such as radiation dose, tumor location and radiation distribution [5].

The recommended treatment includes exercises to stimulate the opening and closing of the mouth, with concomitant application of moist heat before and after exercise and administration of anti-inflammatory medication and muscle relaxants [5].

Dental Carie

It is common for the presence of caries in children with leukemia due to factors such as increased demineralization and acidophilic organisms (Streptococcus mutans), change in buccal microflora, poor oral hygiene, reduced salivary flow and loss of taste associated with a more cariogenic diet (more soft and sweet) results in rapid tooth destruction [5].

The dentist should encourage and strengthen the use of topical fluorides, promote dietary restrictions and require regular visits to the dentist every 03 months. The use of antimicrobials may help to eliminate infection [5].

The use of fluoride in the form of mouthwash and toothpaste provides additional protection against tooth decay. The den-

tist can apply concentrated fluorides and various remineralising agents in the form of topical toothpaste of phosphopeptides of amorphous calcium casein (CPP-ACP) directly into the teeth for 5-10 minutes periodically to prevent and reverse the risk of dental caries , increase remineralization [12, 17].

Candidíasis

This fungal infection caused by *Candida albicans* is one of the most common opportunistic infections in pediatric leukemic patients. It occurs in periods of immunosuppression and neutropenia, due to factors such as the use of broad-spectrum antibiotics and antineoplastic agents, inadequate oral hygiene, poor nutrition and physical condition weakened.

It can be presented in the following clinical forms: *Pseudomembranous candidiasis* presenting white plaques with a classic appearance of mucosal adhering to the mucosa that are removable by scraping, erythematous candidiasis characterized by the presence of red plaques and loss of filiform papillae and chronic candidiasis with white plaques non-removable to the scraping where the lesions show pinpoint hemorrhagic areas. The dentist conducts the treatment of candidiasis with the use of antifungal agents derived from polyene agents, imidazole and triazines including clotrimazole and ketoconazole [12].

One of the most commonly used topical medication is nystatin and its action depends directly on the time of contact with the tissues. Or it may be used the systemic drug like fluconazole and itraconazole has also been shown to be effective in antifungal therapy [5].

Javed et al., [7] also recommends the use of chlorhexidine gluconate (0.12%) and essential oils because of their bactericidal and fungicidal properties. Chlorhexidine gluconate (0.12%) forms a whitish membrane (by coagulation of serum and salivary proteins) in the inflamed mucosa, thus reducing the severity of inflammation of the oral mucosa.

Other Viral Infections

Children with leukemia may also have other viral infections such as herpes simplex, varicella zoster, cytomegalovirus, adenovirus and Epstein bar virus. Herpes simplex manifests as multiple ulcers in the corners of the mouth, lips, palate and gingiva. An erythema can also be seen around ulcerative lesions. Antiviral drugs such as acyclovir and valaciclovir are used for their treatment. In strains resistant to these drugs, foscarnet is the drug of choice [12].

Bleeding

Depending on the severity of thrombocytopenia, hemorrhages occur due to inflammation of the gingiva, ecchymosis, hematoma and the presence of petechiae. Factors such as oral hygiene, trauma associated with oral function, sharp tooth of the denture, also contribute to bleeding. The gingiva, buccal mucosa, tongue, floor of the mouth and soft palate are the most common sites of hemorrhages and petechiae. Spontaneous mucous petechiae and gingival bleeding may occur when the platelet level falls below 20,000 cells per mm^3 [12].

The dentist can prevent and reduce the risk of bleeding more efficiently by promoting the use of regular soft toothbrush or electric toothbrush at least twice a day, guiding the intake of soft or semi-solid foods. In severe cases there is a need for platelet transfusion to control bleeding [12].

Gingival Bleeding

Due to the thrombocytopenia, leukemic patients may present spontaneous gingival bleeding or traumatic brushing most commonly associated with chemotherapy. The degree of thrombocytopenia and immunosuppression increases the severity of bleeding. In these cases, regular oral hygiene is recommended, because when oral hygiene is inadequate or absent, gingival bleeding is exacerbated, making the severity of the condition possible [5]. You can also gently massage the gums with your wet finger after brushing twice a day to reduce bleeding episodes. Sometimes topical hemostatic and antiseptic substances can be used as the povidine and iodine solution to minimize gingival bleeding [12].

Mucositis

Mucositis is an ulceration that presents in the form of erythema and causes intense pain, interfering with food intake. It occurs 5-7 days after therapy, especially if drugs such as cyclophosphamide, doxorubicin, paclitaxel, 5-fluorouracil (5- FU) and methotrexate. They may be associated with mucositis, xerostomia and low neutrophil counts. The literature describes the occurrence in 50 to 54% in children undergoing cancer therapy [5].

Chemotherapy induces these lesions primarily on non-keratinized surfaces. On the other hand, radiotherapy causes focal lesions inside the mucosa where the direct radiation occurred. The main signs and symptoms of mucositis are changes in mucosal texture and staining, epithelial atrophy, mild to severe pain, cell desquamation, resulting in symptomatic ulcers, difficulty in speech and feeding depending on the degree of tissue loss and aggression of pathogens [5].

According to Goursand et al., [5] mucositis may present in 4 distinct phases: Inflammatory or vascular phase: is the initial phase, which occurs 24 to 36 hours after chemotherapy or radiotherapy. It has, as characteristics, increased vascularization of epithelial cells and tissues due to the presence of cytokines such as interleukin 1 and tumor necrosis factor; epithelial phase: occurs 4 to 5 days later, leading to a reduction of cell turnover and causing tissue damage, atrophy and ulceration; ulcerative phase: occurs after 1 week of chemotherapy or radiation therapy. Endotoxins progress to tissue damage and opportunistic bacteria, viruses and fungi can proliferate. Healing phase: begins 2 to 3 weeks, when the cells of the mucosa and leukocytes begin and renew. Healing is complete if there is no malnutrition and associated opportunistic infections [5].

Mucositis treatment is varied, palliative and includes mouthwashes, mouthwashes with 0.9% NaCl saline, 12.0% chlorhexidine, sodium bicarbonate, water, and dilute hydrogen peroxide that can provide symptomatic relief as they create an environment alkaline, interfering with bacterial colonization, but if there is a complaint of pain and burning, normal saline is recommended [12, 17].

There is also the option of using epithelial protective agents (aluminum hydroxide, magnesium hydroxide), topical anesthetics (lidocaine), topical analgesic (benzidamine) and non-steroidal anti-inflammatory drugs and the combination of antifungal and systemic antibiotics (polymyxin E, tobramycin, amphotericin B and fluconazole) but the results are only palliative [2, 5, 17].

Some studies suggest low-power infrared laser applications to promote epithelial repair, analgesia and eliminate pain on the first application. Laser energy acts on the nerve endings of the ulcer and causes the release of P-endorphin, promoting biostimulation of the tissue and facilitating a faster cure of ulceration [5, 12].

However, low-power infrared laser should be recommended on a daily basis until there is remission of symptoms. Alternatively, the applications can be carried out in a punctual way by scanning the areas with the presence of lesions [12].

In other countries it is recommended to treat oral cryotherapy (ice chip suction), which induces biological response modifiers, avoiding oral mucositis [12, 17].

Mucosal coating agents with bioadhesive agents such as hydroxypropyl cellulose, Amifostine, Topical Vitamins C, B, A and, Topical Betacarotene, Prostaglandin E (PGE2), Glutamine and Granulocyte Colony Stimulating Factor (GCSF) may also be useful as temporary physical barrier on mucosal ulcerations, thus providing relief of pain and improved healing [2, 12].

Other authors recommend that once the mucositis has developed, the dentist should perform oral assessments twice a day in the case of hospitalized patients and frequent oral care (at least every 4 hours and at bedtime) and may increase the frequency as the severity of mucositis increases and should be oriented to meticulous oral hygiene and symptom assessments [2, 12].

In severe cases, it is also recommended to perform atraumatic debridement of necrotic tissue and to clean hard soft oral tissues with a gauze wound around a finger or with a disposable sponge moistened in a diluted solution of sodium bicarbonate and water. Patients should be encouraged to use warm water with added bicarbonate of sodium to rinse the mouth several times daily in case of ulcerations and painful oral tissues [12].

According to Mathur, Dhillon, Kalra [12] complete resolution of mucositis occurs 7 to 14 days after initiation and discontinuation of therapy and sometimes, radiation-induced mucositis can remain from weeks to months and regress slowly.

Xerostomia

Xerostomia is a sensation of dryness of the buccal cavity due to dysfunction of the salivary glands, with qualitative and quantitative alterations in the salivary flow. Saliva becomes more viscous with reduced salivary amylase, IgA, buffer capacity, less lubrication and protection capacity and with a high amount of organic material and changes in coloration, from transparent to yellowish by induction of fibrosis by radiotherapy, fat degeneration and acinar, besides necrosis of the salivary glands [5, 18].

Xerostomia may occur transiently during chemotherapy (being reversed within 48 hours) or in a severe, progressive or permanent form in cases of radiotherapy (reversion may occur 4 to 12 months after therapy) [5].

Saliva shows acidic pH, and there is a change in bacterial flora from gram-positive to gram-negative in addition to inducing loss of taste, appetite, lubrication, changes in the stages of swallowing and digestion and causing some disorders such as nausea, vomiting and symptomatology leading patients to cariogenic eating habits [12].

In addition to compromising maintenance of the barrier against external injuries and tooth integrity by the process of mineralization and demineralization [5, 18]. The treatment in most cases is unsatisfactory and consists of reducing the discomfort caused by dryness of the mouth with water intake, stimulation of saliva remaining, use of artificial saliva based on carboxymethyl cellulose or salivary substitutes and sugar-free chewing gum. Pilocarpine, a parasympathetic agonist and an efficient promoter of salivary secretion, may be indicated [5, 12, 17].

The child should rinse with cold sterile water or normal saline as often as possible to keep the buccal tissues clean and wet, ensuring the removal of saliva and thick debris and reducing the risk of opportunistic infections [12].

Dysgeusia

It is the alteration of the palate is a result of the direct effect of radiation on taste corpuscles and saliva changes, reducing by 50.0% the perception of bitters and acids. Chemotherapy drugs also cause bad taste, termed the venous taste phenomenon resulting from the diffusion of the drug into the oral cavity [5, 12]. It is a transient change because the affected buttons usually regenerate, recovery of the partial or total palate occurs between two and twelve months after radiotherapy, and can be corrected with a zinc supplementation at a dosage of 220 mg twice daily [5, 12].

Osteoradionecrosis

Osteoradionecrosis damages the endothelial coatings of bone vessels resulting in hypocellularity, hypovascularisation, vasculitis followed by obliterated endarteritis, bone ischemia, fistula, and sometimes pathologic fracture of the bone leading to a radiation-induced wound healing defect and a sequence specific pathology [5, 12].

The mucosa becomes thinner with the formation of telangectasia in the irradiated area making it more susceptible to mechanical lesions. There is a decrease in collagen formation, blood flow due to vessel changes and wound healing, thus reducing nutrients and defense cells. It most commonly affects the mandible because of its relatively low vascularity and presence of teeth [12].

The ORN can be accompanied by severe pain, trismus, bone exposure and pathological fracture. Subsequent trauma to the irradiated area can cause a wound that does not heal. Breathing procedures such as exodontia or periodontal surgeries are contraindicated, and may be initial factors of tissue decomposition and ORN [5].

ORN can be minimized by the administration of hyperbaric oxygen, which improves tissue oxygenation, increases collagen synthesis and stimulates angiogenesis. It is recommended that all children be referred for oral examination one month prior to the start of chemotherapy or radiotherapy and treatment of pre-existing or associated oral diseases, pre-assessment and appropriate dental care are critical [12].

Emergency Dental Care during Leukemic Treatment

The oncologist and the hematologist should consult the dentist in case of a dental emergency. In high-risk patients (active leukemia or bone marrow suppression phase), dental intervention is limited to emergency care, but oral hygiene should be maintained with the use of mild mouthwashes and antiseptic and antimicrobial solutions, ulcers and minimize complications due to infection [19].

In the case of evidence of oral infection, the high-risk patient should receive a broad-spectrum antibiotic intravenously [9]. The neutrophil count may fall dramatically after 7 to 10 days after induction therapy leading to an increased risk of infection during that period. It is recommended to perform smaller dental procedures with a platelet count of 40,000/mm^3 -50,000/mm^3, whereas for major surgeries, it is desirable that the platelet count is at least 100,000/mm^3 [12, 17].

Platelet transfusion may be advised in case of an emergency. Only if the absolute neutrophil count exceeds 1000 per cubic millimeter, and the platelet count is appreciable, any dental treatment is performed [12, 17].

Oral Management after Completion of Leukemia Treatment

Children with leukemia during the remission phase may be treated as normal patients, although blood tests should be considered if invasive treatment is required and periodic follow-up should be scheduled to monitor oral health at intervals of 3 to 6 months [8].

Patients who have been cured of leukemia are considered low risk and can be treated with standard dental treatment regimens. Upon completion of oncologic therapy and only after two years free from the disease, orthodontic treatment that has been discontinued may be restarted [19]. Dental brushing should be recommended with fluoride toothpaste and 0.05% sodium fluoride rinse instead of chlorhexidine rinses [8].

In the case of bone marrow transplantation, after this procedure there is profound impairment of the immune function, therefore, children may not undergo dental procedures up to 1 year, except non-invasive preventive treatment, such as fluoride topical application, preventive resin restoration or fissure sealant etc. Results of blood tests are required at all visits to the dentist. The hematologist should be aware of the possible long-term side effects of chemo in the teeth, oral mucosa and craniofacial complex and should monitor the child for the same. Regular visits to the dentist should be encouraged [12].

The Performance of the Dentist in the Care of Children with Leukemia

According to Zimmermann et al., [19] modern oncology is decisively a multiprofessional approach, based on the interaction between physicians, nurses, psychologists, physiotherapists, nutritionists, pharmacists, speech therapists and dentists specialized in the field of stomatology.

However, the generalist dentist can be present in the various phases of the antineoplastic treatment, collaborating in the multiprofessional care of the patient with leukemia, performing procedures such as adjustment of the buccal environment, restorations, adjustments of prostheses, endodontics. The dental care of cancer patients has different phases, pre, trans and post chemotherapy or before, during and after anti-neoplastic therapy, remission of the disease or case of closed prognoses providing palliative care aiming at maintaining oral health, and quality of patients' lives [19].

As it is common for leukemia to present primarily oral alterations, such as gingival bleeding, petechiae, hematomas, bruises, ulcers, lymphadenopathy and gingival infection, causing the patient to seek dental treatment ends up making the dentist a fundamental part in the early diagnosis of leukemias, identifying signs and symptoms such as increase of infections, bleeding, neutropenic ulcers, and gingival and bone infiltration during routine dental care [19].

Rosso et al., [15] conducted a study with 23 patients, aged between 2 and 16 years, who had leukemia and found that 43.5% of the patients had caries, 30.4% hyperplasia, 21.7% mucositis and 30.4% of cases of xerostomia becoming clear the necessity and the intervention of the dentist to the improvement of the oral health and the quality and life of these patients.

The dentist should therefore be alert to these signs and have a duty to request a blood count to confirm or rule out the possibility that a leukemia may be the cause of these changes. The patient may be surprised by the diagnosis of leukemia during routine dental treatment, such as orthodontic treatment, and the general surgeon-dentist needs to know how to proceed in these situations [19].

Dental assessment presents different objectives according to the stage of the pathology and the treatment. Before beginning cancer therapy when the patient is already diagnosed with leukemia, he/she should receive a complete dental assessment, if possible, immediately after diagnosis and before chemotherapy, whose main objectives are: to identify specific leukemia diagnosis issues, such as leukemic infiltrate, identify and eliminate existing sources of infection (carious lesions, extensive restorations and periodontal disease) or potential as local irritants. It should focus on oral hygiene care throughout the treatment (fluoride, brushing and non-cariogenic diet) without promoting complications or delaying cancer therapy; to educate the patient, parents or caregivers about the importance of maintaining oral health, in order to reduce oral problems and discomforts before, during and after cancer treatment, and to alert about the possible effects of therapy in the oral cavity [4, 19] .

The American Academy of Pediatric Dentistry (2011) [1] also advocates dental sizing and preventive therapy, fluoride application and sealing of fissures, removal of non-restorable teeth, with periodontal pockets larger than 6mm, with acute infection, bone loss furrow exposure, mobility, symptomatic impacted and residual roots, the extraction should ideally be performed two weeks be-

fore the start of antineoplastic treatment, or at least 7 to 10 days before. If there was no dental treatment prior to antineoplastic therapy the decayed teeth should be filled with temporary fillings and the final treatment should be postponed until the patient is in remission [8].

According to Lowal et al., [8] in the case of invasive procedures, the dentist should require a detailed dental examination with radiographs; in case of tooth extraction this should be done at least 10-14 days before starting chemotherapy to allow adequate healing and to minimize the risk of oral and systemic complications.

During antineoplastic therapy, the recommended dental care is three: to maintain excellent oral health; treat any adverse side effects of antineoplastic therapy and reinforce to the patient the importance of optimal oral health to reduce problems and discomforts during chemotherapy treatment [19].

It is essential to minimize complications related to oral cavity during antineoplastic treatment. With pre-evaluation of oral health and appropriate dental management, possible oral sequelae can be prevented, reduced and relieved. Team approach is necessary to maximize results. The oncology team should clearly inform the dentist about the patient's health status and the cancer treatment plan [12].

In turn, dental staff must communicate the oral health plan before, during and after cancer therapy. The dentist should obtain information about the type, stage and prognosis of leukemia, current treatment plan, most recent hematologic reports and their implications, from the oncology team. In addition, the dentist should also communicate with the oncology team about the state of oral health, the possibilities of its link to the existing condition, the proposed treatment plan and the time required to initiate treatment [12].

Conclusion

Immunosuppression and the very fragility and stage of development of children with leukemia lead to greater vulnerability to all types of opportunistic infections and pathologies resulting from antineoplastic therapy. Currently, modern oncology requires the presence of the dentist in all phases of treatment and even before diagnosis in a sine qua non condition for management, maintenance of oral health and quality of life of the leukemic patient. The dentist besides being part of the cancer team is required both in the in-hospital environment and in daily clinical practice. Currently there is a wide range of resources and medications to promote good management and quality and a satisfactory life, as was verified in this literature review.

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