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ORIGINAL SCIENTIFIC ARTICLE

Oral health in children with acute lymphoblastic leukaemia: before and after chemotherapy treatment

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Abstract

Aim To evaluate changes in the oral health status of children under the age of 14 years with acute lymphoblastic leukaemia (ALL) attending a cancer centre before and after chemotherapy treatment.

Materials and methods A total of 32 children with ALL without distinction of gender were selected for study. The oral cavity of the patients was evaluated before the induction stage and 17 days later. Clinical evaluation of the submandibular, submental, and cervical lymph nodes was performed. Saliva samples were collected during the early morning hours. Bacterial plaque was assessed by using the Silness and Löe plaque index (SLPI) and gingiva status was evaluated with the gingival Löe and Silness index (GLSI). The WHO toxicity oral scale was used to record the degree of oral mucositis. The resulting data were analysed with McNemar's test, *t* test (for related samples), and Wilcoxon test.

Results There were statistically significant differences for palpable lymph nodes, paleness of oral mucosa, and ecchymoseis, respectively, $P \leq 0.000$, $P = 0.03$, and $P = 0.01$, with these manifestations decreasing significantly after treatment. Incipient gingivitis had frequencies of 71.9% and 75% before and after treatment, respectively. The mean SLPI score declined significantly from 1.16 ± 0.52 (before treatment) to 0.56 ± 0.36 (after treatment) ($P < 0.000$); salivary flow increased significantly from 0.54 ± 0.34 to 1.22 ± 1.07 after chemotherapy treatment ($P < 0.00$). Oral mucositis was present in 24 children (75%) with a 1–2 severity level.

Conclusions After chemotherapy treatment, there were changes in the oral conditions of children with ALL. Some manifestations decreased after treatment, whereas in others increased.

Keywords Childhood · Acute lymphoblastic leukaemia · Chemotherapy · Oncological lesions · Oral

Introduction

Leukaemia is a disease resulting from the malignant transformation of stem cells whose proliferation begins in the bone marrow (Pinto et al. 2006). Particularly, childhood acute lymphoblastic leukaemia (ALL) originates in the T and B lymphoblasts in the bone marrow (Board 2018). ALL is the most common type of malignancy among children younger than 15 years (Howlader et al. 2017). Children suffering from ALL present oral complications due to the disease itself and other secondary effects caused by the treatment with chemotherapy. In addition, poor oral hygiene, presence of bacterial plaque, and periodontal disease can aggravate these conditions (Pels and Mielnik-Blaszczak 2012; Azher and Shiggaon 2013).

The early signs of ALL may be present at the oral cavity level due to thrombocytopenia, neutropenia, and compromised granulocytic function or to a direct infiltration of leukemic cells (Orbak and Orbak. 1997; Francisconi et al. 2016). Gingival inflammation and spontaneous gingival bleeding are common in patients with ALL (Biswas et al. 2009; Francisconi et al. 2016), becoming more frequent due to poor oral hygiene and low count platelet (Orbak and Orbak. 1997; Mazaheri

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et al. 2017). It has also been found lymphadenopathy (Hou et al. 1997), petechiae (Mathur et al. 2012), ulcers, oral mucosa paleness, and herpes on lips, oral candidiasis, and ecchymoseis (Ponce-Torres et al. 2010; Vourexakis 2015; Francisconi et al. 2016).

The treatment regimen includes multi-agent chemotherapy (three phases: induction therapy, intensification, and maintenance therapy) and central nervous system-directed radiotherapy (Dholam et al. 2014). This treatment produces immediate and late side effects and sometimes unavoidable toxic effects on healthy cells (Board 2018). Gingivitis can be intensified by haematological disorders and gingival bleeding has been reported while tooth brushing in the induction phase. Petechiae, periodontitis, and candidiasis have also been found (Morais et al. 2014; Kung et al. 2015). With regard to periodontal health, it has been observed that the gingival index of Löe and Silness (GLSI) increases significantly after chemotherapy treatment (Dholam et al. 2014). In addition, bacterial plaque presents more variation in quantity, quality and microbial complexity in the first week of treatment (Sixou et al. 1998; Wang et al. 2014).

Oral mucositis is one of the most common oral problems occurring during antineoplastic treatment (Mathur et al. 2012), which can be a "direct" and "indirect" effect of chemotherapy on the cells. It can be associated with secondary myelo-suppression, presenting different degrees of severity depending on multiple factors associated with treatment and particular characteristics of the patients (Al-Ansari et al. 2015). The prevalence of oral mucositis varies from 20 to 100% (Vanhoecke et al. 2015; Gandhi et al. 2017).

On the other hand, evidence shows that chemotherapy treatment produces decreased salivary flow rate (Gandhi et al. 2017), which is not permanent and may vary at each treatment stage (Velten et al. 2017). Daily oral hygiene, oral prophylaxis, fluoride applications, and mouth rinsing with chlorhexidine gluconate 0.12% are required to control bacterial plaque growth (Hashemi et al. 2015), with the average plaque index decreasing the implementation of these measures (Mazaheri et al. 2017).

Currently, there are no studies that compare oral health before and after chemotherapy treatment, upon 17 days at the beginning of the induction phase. Therefore, this study's objective is to assess and compare changes in oral health in patients under age 14 who have ALL attending the Institute of Cancer in Cuenca (SOLCA) before and after chemotherapy treatment. Moreover, we contrast the outcomes of this study, before chemotherapy, with outcomes found in previous studies.

Materials and methods

Ethical approval for this study was granted by the Research Ethics Committee of the University of Cuenca School of Dentistry, Ecuador, according to Memorandum Number 318 FAO-2011 and in concordance with the World Medical Association Declaration of Helsinki and conducted from August 2012 to August 2015. The children's parents signed an informed consent form allowing them to participate in the study.

This is a time-series design (i.e., before and after). The sample was calculated by taking into consideration the incidence of ALL among children under 14 years of age, who were registered at the SOLCA Tumour Department (2008–2009).

A total of 32 patients (17 female and 15 male) younger than 14 years (i.e. between 1.6 and 13.1 years) with a mean age of 5.8 ± 3 years who were diagnosed with ALL for the first time at SOLCA were evaluated before and after 17 days of the induction phase. The children were included on a non-random basis. The chemotherapy protocol used for treatment of the children was total XV (Pui et al. 2004).

Children who suffer from ALL and were receiving treatment at any stage were excluded, including those with other diseases such as chromosomal alterations, cerebral palsy and congenital heart disease. Children who received chemotherapy in the past were also excluded.

During the first stage of the study, the frequency of different oral lesions and risk indicators for dental caries and periodontal disease before treatment with chemotherapy were obtained. In the second stage upon the 17 days of initial treatment, assessments were repeated to determine whether there have been changes (because the SOLCA treatment protocols do not allow any intervention on children who have received chemotherapy before the 17th day).

Before oral dental examination, the children's medical history and outpatient notes were evaluated and reviewed, with emphasis on haemostasis.

The evaluation of oral complications was made by using the Declerck and Vinckier's criteria (1988), in which the complications are divided into three groups as follows: primary lesions are induced by infiltration of malignant cells into oral structures, such as gingiva and bone; secondary lesions are the result of the myelophthisic character of the disease, including lesions associated with anaemia, increased bleeding tendency, increased susceptibility to infection and neutropenic ulcerations, and tertiary lesions are associated with myelo-suppressive and immunosuppressive therapy.

Oncological evaluation

This evaluation was made early in the morning, with the paediatric oncologist diagnosing lesions in children suffering from ALL before and after treatment with chemotherapy. Oral examination was performed by using a tongue depressor and flashlight for signs of oral candidiasis, gingiva erythema, oral ulcers, herpes labialis, necrotic areas and mucositis, among others.

Oral mucositis was diagnosed by clinical examination and its degree of severity was evaluated using the World Health Organization criteria (1979).

Salivary flow sample

Saliva samples were collected from 23 children; unfortunately, the younger ones could not collaborate properly, because they were in early childhood development (i.e. under 5 years of age). Their cognitive level did not permit them to collaborate properly with the standard procedures for collecting saliva samples (e.g., chewing paraffin), as in several occasions, they swallowed the accumulated saliva. Furthermore, the children were under psychological stress, as they were undergoing serial blood examinations because of their diagnosis of leukaemia, and therefore, we considered improper to force them to give saliva samples under such conditions.

All saliva samples were collected early in the morning prior to tooth brushing, with children fasting and in a straight and relaxed posture. The technique of saliva stimulation with paraffin chewing was used by a trained nurse. Children chewed a piece of paraffin gum (PARAFILM M #60631, Chicago, IL, USA) for 1 min using both sides of the mandible, and then, they were asked to expectorate all the saliva into a sterile, millimetric container. The amount of saliva was divided according to time collection, expressed by millimetres per minute. This saliva collection technique usually takes 5 min (Sakeenabi and Hiremath 2011), but because of the fragile stamina observed in our children, this time was reduced to two-and-a-half minutes.

The flow of saliva is a fundamental parameter to measure the level of xerostomy and the risk of caries; values vary among children depending on their ages and cooperative behaviour. We have used the following criteria: normal secretion (0.5 ml/min and risk $\leq$ 0.5 ml/min) and pre-adolescent normal secretion (1 ml/min and risk < 0.7 ml/min) (Harris and García-Godoy 2004). In this study, the range was modified to 0.25 and 0.5, respectively.

Clinical evaluation

The clinical evaluation was conducted by a trained clinician, who performed examination and palpation for the presence of lymph node enlargement. An extra-oral examination of the head, face, and neck was performed with emphasis on lymph node chains at submental, submandibular, and cervical vertebrae levels. Oral cavity was examined in a sequential pattern from outside to the inside performing a careful exam of all its components. Children rinsed their mouths with alcohol-free 0.12% oral chlorhexidine, which was complemented with a second topic application before examination of the gingiva.

Dental and Gingival examination

For oral examination, a #5 metal mouth mirror and a blunt probe (Medro-german brand) were initially used and the Silness and Löe plaque index was assessed by taking into consideration the author's criteria as follows: 0 = no plaque; 1 = biofilm adhered to free gingival margin and adjacent area of the tooth, with plaque being seen in situ only after application of disclosing solution or using the probe on the tooth surface; 2 = moderate accumulation of soft deposits, which can be seen with naked eye within the gingival pocket, whether on the surface of adjacent teeth or on the gingival margin, or both sites; and 3 = abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin. Indicators: risk $\geq$ 1; no risk < 1 (Silness and Löe 1953).

Next, the GLSI was applied using a WHO periodontal probe (CP11—Hu-Friedy brand) and the following criteria were used: 0 = normal gingiva; 1 = mild inflammation with slight change in colour and slight oedema, but no bleeding on probing; 2 = moderate inflammation with redness, oedema, glazing, and bleeding on probing (10-s waiting period); and 3 = severe inflammation with redness, oedema, and ulceration with a tendency to spontaneous bleeding. The indicators were 0.1–1.0 (mild inflammation), 1.1–2.0 (moderate inflammation), and 2.1–3.0 (severe inflammation) (Löe 1967).

Bleeding was assessed by probing gently along the wall of the soft tissue of the gingival sulcus. Children who had erythematous lesions and gingival bleeding tendency were assigned a value of 3 and no probe was used for gingival examination to avoid bleeding. On the other hand, teeth with gum bleeding spontaneously were recorded as "teeth with gingival bleeding".

After examination, the children's parents and nurses were given instructions for implementation of their daily oral hygiene, which should be conducted with extra soft toothbrush and toothpaste with fluoride, as well as mouthwash with chlorhexidine 0.12% twice a day, one in the morning and another before bedtime. The degree of thrombocytopenia was always taken into consideration in all children.

Statistical analysis

General characteristics of the children were obtained through frequencies (percentages) and average calculations. Changes in children's dental health conditions of ALL patients, before and after treatment, were analysed using the McNemar test; the test of Kolmogorov–Smirnov was applied to evaluate the distribution of data: *t* test for related samples and Wilcoxon test. All the analyses were performed at significance level of 5%.

Results

In the present study, we have included 32 children under the age of 14 years who suffered from ALL, in which 17 (53.1%) were female and 15 (46.9%) male with mean age of 5.8 years.

Twenty children presented palpable lymph node enlargement prior to treatment and after it 18 children no longer presented it, which is a positive change at a ratio of 9:10. With regard to the 12 children presenting no lymph node enlargement before treatment, only one child presented it after treatment, a change at a ratio of 1:12.

Paleness of the oral mucosa was observed in 10 children, but none of them presented it after treatment. Concerning the 22 children who did not present pallor of the mucosae before treatment, only two children presented it after treatment, a change with a ratio of 1: 11.

Of the eight children who presented ecchymoseis in the oral cavity, seven showed a positive change after treatment. Concerning the 24 children who did not present ecchymoseis before treatment, they did not present changes afterward.

By comparing the results, we have found significant differences between the frequencies of oral manifestations before and after treatment with chemotherapy, namely: palpable lymph nodes ($P \leq 0.000$), oral mucosa paleness ($P = 0.03$), and ecchymoseis ($P = 0.01$). After chemotherapy treatment, these oral manifestations had significantly decreased, and therefore, the null hypothesis was rejected.

As for the spontaneous bleeding of the gums, an important change was observed as 13 children presented it before treatment compared to seven who did not present this condition after treatment, meaning an important change at a ratio of 7:13. With regard to the 19 children who did not present spontaneous bleeding of the gums before treatment, only two presented it after treatment, with a change at a ratio of 2:19. However, these changes were statistically non-significant ($P = 018$). Similarly, the presence of petechiae and ulcers had no significant differences, respectively, ($P = 0.88$) and ($P = 0.12$) (Table 1).

The mean SLPI score decreased after treatment from 1.16 ± 0.52 to 0.56 ± 0.36, with a statistically significant difference being found when the Student's *t* test was applied ($P \leq 0.000$). Therefore, the null hypothesis was rejected, with the mean plaque score decreasing after chemotherapy treatment. The mean GLSI scores presented a minimum variation, with no statistically significant difference ($P = 0.6$) (Table 2).

Incipient gingivitis was the most frequent condition before and after treatment (respectively, 71.9% and 75%), whereas moderate gingivitis was present before (25%) and after (18.8%) treatment. Severe gingivitis was only observed in one child before treatment (3.1%) and in two after it (6.3%).

By comparing the rates of saliva flow, there was an increase from 0.54 ± 0.34 before chemotherapy to 1.22 ± 1.07 after it. A significant difference was observed when the Wilcoxon's test was applied ($P \leq 0.000$), with salivary flow increasing after chemotherapy treatment—meaning that the null hypothesis was rejected (Table 3).

Oral mucositis was present in 24 children (75%), with 11 of them (34.4%) having grade 1 and 13 grade 2 (40.6%).

Discussion

In the present study, oral health status in children with ALL under the age of 14 years was compared before and after chemotherapy treatment (i.e., 17 days after beginning the induction phase). There are no studies making this comparison, and most refer specifically to results obtained before, during or after treatment (Pels and Mielnik-Blaszczak 2012; Kung et al. 2015; Francisconi et al. 2016).

Lesions produced by leukaemia or those which are secondary to treatment are frequently found in the oral cavity, with their frequency varying among the studies. However, in our study, the types of lesions before treatment are very similar to those reported elsewhere (Orbak and Orbak 1997; Biswas et al. 2009; Mazaheri et al. 2017).

In a study by Hou et al. (1997), the frequency of palpable regional nodes before treatment in children with ALL was 71.4%, whereas in ours, it was 62.4%. Both studies reported a significant frequency of this clinical sign, which is also the most frequent manifestation. Before treatment, 31.3% of the children showed oral mucosa paleness related to anaemia, which is a common finding in children with ALL. However, this is a figure lower than the one found in a preliminary study by Orbak and Orbak (1997), that is, 62.1%.

The presence of gingival bleeding, petechiae and ecchymoseis in the oral mucosa has been associated with thrombocytopenia, capillary fragility, and alterations in coagulation factors, all present in some children before and after treatment (Francisconi et al. 2016). Orbak and Orbak (1997) found gingival bleeding before treatment in 6.4%

Table 1 Oral health before and after chemotherapy treatment

Lymph nodes		After		Total
		Palpable	Non-palpable	
Before	Palpable	2	18	20
	Non-palpable	1	11	12
Total		3	29	32
$p \leq 0.000$				
Pale mucose membranes		After		Total
		Yes	No	
Before	Yes	0	10	10
	No	2	20	22
Total		2	30	32
$p = 0.03$				
Ecchymoseis		After		Total
		Yes	No	
Before	Yes	1	7	8
	No	0	24	24
Total		1	31	32
$p = 0.01$				
Petechiae		After		Total
		Yes	No	
Before	Yes	10	5	15
	No	8	9	17
Total		18	14	32
$p = 0.581^{NS}$				
Bleeding gingiva		After		Total
		Yes	No	
Before	Yes	6	7	13
	No	2	17	19
Total		8	24	32
$p = 0.180^{NS}$				
Ulcers		After		Total
		Yes	No	
Before	Yes	2	1	3
	No	6	23	29
Total		8	24	32
$p = 0.12^{NS}$				

McNemar test

NS non-significant ($p > 0.05$)

of the patients, and in another study carried out by Biswas et al. (2009), the frequency of gingival bleeding was 20.4%. In our study, however, gingival bleeding was observed in 40.6% of the children before treatment, most probably due to the fact that our sample presented different degrees of thrombocytopenia.

Accordingly, Orbak and Orbak (1997) found petechiae in 14.9%, whereas (Kung et al. 2015) found them in 10% of the children; our result is significantly higher than both of them, since they were detected in 46.9%. Finally, in regard to ecchymoseis in our study, 25% children presented them.

Table 2 Silness and Löe plaque index and Löe gingival indexes means before and after chemotherapy treatment

	Index	Mean value	*N*	SD	Related sample *T* test *p*
Before	SLPI	1.16	32	0.52	
After		0.56	32	0.36	0.000
Before	GLSI	0.97	32	0.56	
After		0.93	32	0.64	0.6^{NS}

SLPI Silness and Löe plaque index, *GLSI* Silness and Löe gingival index, *SD* standard deviation, *NS* non-significant ($p > 0.05$)

Table 3 Mean salivary flow rate in children before and after chemotherapy treatment

	Mean value	*N*	SD	Wilcoxon test *p*
Salivary flow before	0.54	23	0.34	0.000
Salivary flow after	1.22	23	1.07	

SD standard deviation

In our study, by comparing changes in oral health before and after the induction treatment, we have observed that some oral manifestations in children with ALL decreased after chemotherapy treatment. Significant differences have also been found between palpable lymph nodes, ecchymoseis, and paleness of oral mucosa before and after treatment. An important decrease in gingival bleeding was observed after chemotherapy, but these differences were not significant.

Incipient gingivitis was the most frequent condition observed before (71.9%) and after (75%) treatment, with the mean GLSI score being 0.97 ± 0.56 before treatment and 0.93 ± 0.56 after it, showing a slight decrease. Nevertheless, the results found by Dholam et al. (2014) showed that the GLSI scores ranged from 0.21 to 0.62 throughout the pre- and post-induction phases in 33 children in which no oral health measure was applied.

On the other hand, the bacterial plaque/biofilm is one of the etiological factors for the presence of gingivitis. Oral hygiene is a fundamental preventive practice, especially in children who suffer from ALL, requiring that both children and their parents know about oral hygiene and plan a regular dental monitoring (Mazaheri et al. 2017). In our study, the mean plaque index score before treatment was 1.16 ± 0.52, decreasing to 0.56 ± 0.36 after it, these averages values are greater than 0.59 ± 0.74 and 0.49 ± 0.67 reported by Pels and Mielnik-Blaszczak (2012). These authors investigated the plaque index 6 months after chemotherapy, whereas in our study, controls were examined on the 17th day after treatment. In both studies, the plaque index decreased possibly because of the implementation of oral hygiene regimes.

It is known that the decrease in salivary flow rate induced by chemotherapy favours the accumulation of bacterial plaque, which can cause inflammation of the gingiva if not controlled (Dholam et al. 2014). Twenty-three children had mean scores of 0.54 ± 0.34 and 1.22 ± 1.07 before and after treatment, respectively. Therefore, there was a significant increase of 0.68 in the salivary flow rate, suggesting that this response was due to the fact that the children received parenteral hydration and oral preventive measures before treatment, during the induction phase and after treatment. Similarly, Velten et al. (2017) evaluated 45 children by monitoring them for 1 month after initiation of chemotherapy, reporting that the xerostomia cases decreased after that due to the same measures described above.

With regard to the direct and indirect stomatotoxicity caused by drugs used in chemotherapy, the frequency of oral mucositis—a common finding in children with ALL after chemotherapy—varies from 20 to 100% depending on type of malignancy, chemotherapy regimen, chemotherapeutic drug type, patient's age, neutrophil count and level of oral care (Vanhoecke et al. 2015; Gandhi et al. 2017).

Mucositis may have different degrees of presentation, such as mild inflammation and ulcers, severe ulceration, pain and dysphagia or inability to swallow liquids or solid meals, and can appear as early as 4–7 days after initiation of chemotherapy, although sometimes it can be seen later (Mathur et al. 2012).

In the present study, the frequency of oral mucositis was 75%, of which 40.6% and 34.4% had severities of grade 2 and 1, respectively, according to the WHO scale. These results are close to those found by Gandhi et al. (2017), who studied 62 children receiving chemotherapy and found that 38.8% and 30.5% of them had grades 2 and 1 mucositis, respectively. However, the authors also found patients with grades 3 and 4 mucositis. Although this condition was absent in our study, it should be kept in mind that mucositis was observed on the 17th day after induction treatment rather than from the 7th to 14th days when the maximal manifestation of mucositis occurs (Al-Ansari et al. 2012). It is important to provide proper oral health before and after chemotherapy to reduce the presence of bacterial growth and, consequently, of secondary infections. The areas most affected by mucositis were the vestibular mucosa and the ventral side of the tongue.

Despite all these different results found by the above-mentioned authors and by our study as well, one can state that the effect of the treatment itself and the implementation of a preventive oral health regime can minimize the risk of associated oral complications (Pels and Mielnik-Blaszczak 2012).

Conclusions

In our study, there were changes in the oral conditions of children with ALL after chemotherapy treatment. Palpable lymph node enlargement, paleness of mucosa, and ecchymoseis decreased very significantly after treatment. An important reduction of gingival bleeding was observed after chemotherapy, but with no significant difference. The Silness–Löe plaque index (SLPI) was elevated at the initial period, but on the 17th day, it decreased significantly and the salivary flow rate increased even more significantly. Oral mucositis is the most common collateral effect of chemotherapy, with this complication affecting 75% of the children despite the fact that no child presented severe or moderate oral mucositis. We can state that the implementation of preventive oral health measures before and during treatment helped in attenuating the presence of oral lesions, which are usually present in children with ALL and those undergoing chemotherapy treatment. Therefore, we believe that professional dentists should be included in the multidisciplinary team who treat this population.

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Compliance with ethical standards

Conflict of interest All authors of this study state that they do not have conflicts of interest of any kind.

Ethical standards All procedures performed in the participants of the study were in accordance with ethical standards of the institution and/or national research committee as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All the participants signed an informed consent form to be included in the study.

References

Al-Ansari S, Zecha JA, Barasch A, et al. Oral mucositis induced by anticancer therapies. Curr Oral Health Rep. 2015;2(4):202–11.

Azher U, Shiggaon N. Oral health status of children with acute lymphoblastic leukemia undergoing chemotherapy. Indian J Dent Res. 2013;24(4):523.

Biswas S, Chakrabarti S, Chakraborty J, et al. Childhood acute leukemia in West Bengal, India with an emphasis on uncommon clinical features. Asian Pac J Cancer Prev. 2009;10(5):903–6.

Board, P. P. T. E. Childhood acute lymphoblastic leukemia treatment (PDQ®). In: PDQ cancer information summaries [Inter-net]. National Cancer Institute (US). https://www.cancer.gov/types/leukemia/patient/child-all-treatment-pdq. Accessed May 28 2018 **(PMID: 26389385)**.

Declerck D, Vinckier F. Oral complications of leukemia. Quintessence Int. 1988;19(8):575–83.

Dholam KP, Gurav S, Dugad J, Banavli S. Correlation of oral health of children with acute leukemia during the induction phase. Indian J Med Paediatr Oncol. 2014;35(1):36. https://doi.org/10.4103/0971-5851.133717.

Francisconi CF, Caldas RJ, Oliveira Martins LJ, et al. Leukemic oral manifestations and their management. Asian Pac J Cancer Prev. 2016;17(3):911–5.

Gandhi K, Datta G, Ahuja S, et al. Prevalence of oral complications occurring in a population of pediatric cancer patients receiving chemotherapy. Int J Clin Pediatr Dent. 2017;10(2):166. https://doi.org/10.5005/iD-iournals-10005-1428.

Harris N, García- Godoy F. Primary preventive dentistry. 6th ed. Upper Saddle River: Pearson Education; 2004.

Hashemi A, Bahrololoumi Z, Khaksar Y, et al. Mouth-rinses for the prevention of chemotherapy induced oral mucositis in children: a systematic review. Iran J Ped Hematol Oncol. 2015;5(2):106–12.

Hou G-L, Huang J-S, Tsai C-C. Analysis of oral manifestations of leukemia: a retrospective study. Oral Dis. 1997;31(1):31–8.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

Javed F, Utreja A, Correa FOB. Oral health status in children with acute lymphoblastic leukemia. Crit Rev Oncol Hematol. 2012; 83(3):303–9. https://www.ncbi.nlm.nih.gov/pubmed/?term=Oral+health+status+in+children+with+acute+lymphoblastic+leukemia.+Critical+reviews+in+oncology%2Fhematology%2C. https://doi.org/10.1016/j.critrevonc.2011.11.003.

Kung AYH, Zhang S, Zheng LW, et al. Oral health status of chinese paediatric and adolescent oncology patients with chemotherapy in Hong Kong: a pilot study. Open Dent J. 2015;9:21–30. https://doi.org/10.2174/1874210601509010021.

Löe H. The Gingival Index, the Plaque Index, and the retención Index. J Periodontol. 1967;38:610–6.

Mathur VP, Dhillon JK, Kalra G. Oral health in children with leukemia. Indian J Palliat Care. 2012;18(11):21. https://doi.org/10.4103/0973-1075.97343.

Mazaheri R, Jabbarifar E, Ghasemi E, et al. Oral health status, salivary pH status, and *Streptococcus mutans* counts in dental plaques and saliva of children with acute lymphoblastic leukemia. Dent Res J (Isfahan). 2017;14(3):188–9.

Morais EF, Lira JA, Macedo RA, et al. Oral manifestations resulting from chemotherapy in children with acute lymphoblastic leukemia. Braz J Otorhinolaryngol. 2014;80:78–85.

Orbak R, Orbak Z. Oral condition of patients with leukemia and lymphoma. J Nihon Univ Sch Dent. 1997;39(2):67–70. https://doi.org/10.2334/josnusd1959.39.67.

Pels E, Mielnik-Blaszczak M. Oral hygiene in children suffering from acute lymphoblastic leukemia living in rural and urban regions. Ann Agric Environ Med. 2012;19(3):529–33.

Pinto LP, De Souza LB, Gordón-Núñez MA, et al. Prevention of oral lesions in children with acute lymphoblastic leukemia. Int J Pediatr Otorhinolaryngol. 2006;70(11):1847–51.

Ponce-Torres E, Ruiz-Rodriguez MS, Alejo-Gonzalez F, et al. Oral manifestations in pediatric patients receiving chemotherapy for acute lymphoblastic leukemia. J Clin Pediatr Dent. 2010;34:275–9.

Pui CH, Relling MV, Sandlund JT, et al. Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. Ann Hematol. 2004;83:S124–6.

Sakeenabi B, Hiremath SS. Dental caries experience and salivary *Streptococcus mutans*, lactobacilli scores, salivary flow rate, and salivary buffering capacity among 6-year-old Indian school

children. J Int Soc Prev Community Dent. 2011;1(2):45–51. https://doi.org/10.4103/2231-0762.97697.
Silness J, Löe H. Periodontal disease in pregnancy. II Correlation between oral hygiene and periodontal condition. Acta Odontol Scand. 1953;2:153–62.
Sixou JL, De Medeiros-Batista O, Gandemer V, et al. The effect of chemotherapy on the supragingival plaque of pediatric cancer patients. Oral Oncol. 1998;34(6):476–83.
Vanhoecke B, De Ryck T, Stringer A, et al. Microbiota and their role in the pathogenesis of oral mucositis. Oral Dis. 2015;2(1):17–30.
Velten DB, Zandonade E, de Barros Miotto MHM. Prevalence of oral manifestations in children and adolescents with cancer submitted to chemotherapy. BMC Oral Health. 2017;17(1):49. https://doi.org/10.1186/s12903-016-0331-8.
Vourexakis Z. Oral lesions presenting as an early sign of acute leukaemia. BMJ Case Rep. 2015. https://doi.org/10.1136/bcr-2014-205100.
Wang Y, Xue J, Zhou X, et al. Oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations. PLoS One. 2014;9(7):e102116. https://doi.org/10.1371/journal.pone.0110449.
World Health Organization. Handbook for reporting results of cancer treatment. Geneva: World Health Organization; 1979. p. 15–22.