



REVIEW ARTICLE

Oral manifestations resulting from chemotherapy in children with acute lymphoblastic leukemia[☆]

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KEYWORDS

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Abstract

Introduction: Acute lymphocytic leukemia is a type of cancer most common in children and it is characterized by excessive and disordered immature leukocytes in the bone marrow.

Aim: Identify most frequent oral manifestations in children with acute lymphocytic leukemia under chemotherapy treatment.

Methodology: The research was conducted on the electronic database PubMed/Medline, Science Direct, Scielo and Scopus. It has been sought papers with full presentation, wrote in Portuguese, English and Spanish, published between January 1992 and April 2013.

Results: From studies primarily selected, only eight met the criteria of inclusion. All studies performed intraoral examinations to diagnose oral lesions. According to results, the most frequent lesions were mucositis, candidiasis, periodontitis and gingivitis. The oral health condition from acute lymphocytic leukemia carriers varied according oral hygiene of the patient.

Conclusion: The results of studies identified such a great part of patients with ALL presented some lesion in oral cavity during or after chemotherapy treatment. The dentist surgeon needs to recognize oral manifestations and intervene in the oral health of patients with ALL, contributing and helping with treatment.

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Manifestações orais decorrentes da quimioterapia em crianças portadoras de leucemia linfocítica aguda

Resumo

Introdução: A leucemia linfocítica aguda é um dos tipos de câncer mais comuns em crianças e é caracterizada pela produção excessiva e desordenada de leucócitos imaturos na medula óssea.

Objetivo: Identificar as manifestações orais mais frequentes em crianças portadoras de leucemia linfocítica aguda sob o tratamento quimioterápico.

Metodologia: A pesquisa foi realizada nas bases de dados eletrônicas PubMed/Medline, Science

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Direct, Scielo e Scopus. Procurou-se por artigos apresentados na íntegra, escritos em português, inglês e espanhol, publicados entre janeiro de 1992 e abril de 2013.

Resultados: Dos estudos selecionados primariamente, apenas oito atenderam aos critérios de inclusão. A população avaliada foi um grupo de crianças portadoras de leucemia linfocítica aguda. Todos os estudos realizaram exames intraorais para o diagnóstico das lesões bucais. De acordo com os resultados, as lesões mais frequentes foram mucosite, candidíase, periodontite e gengivite. A condição de saúde bucal dos portadores de leucemia linfocítica aguda variou de acordo com a higiene bucal do paciente.

Conclusão: Pacientes com LLA podem apresentar alguma lesão na cavidade oral durante ou após o início da quimioterapia. O cirurgião dentista necessita reconhecer as manifestações orais e intervir na saúde bucal do paciente com LLA, contribuindo e auxiliando no seu tratamento.

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Introduction

Leukemia is a disease characterized by progressive and excessive production of leukocytes in the bone marrow, whose immature forms start circulating in blood.^{1,2} The disseminated proliferation of blasts leads to a substitution of normal bone marrow elements, resulting in the accumulation of immature cells in the blood. The etiology of leukemia is still uncertain, but many studies point to causal factors such as viral infection and radiation and chemical exposure. There are three different subtypes of lymphocytes, and thus there are different types of leukemia, which are classified according to the cell involved, as well as the duration and characteristics of the disease.¹⁻⁴

Acute lymphoblastic leukemia (ALL) represents approximately 80% of leukemias, and occurs mostly in children.¹ ALL results in uncontrolled and excessive production of lymphoid blasts, hindering the normal production of red and white cells, as well as platelets. The chances of survival have increased with advances in anticancer treatment modalities.^{2,3}

The first signs of leukemia can regularly occur in the oral cavity, especially in the acute phase of cancer, as common lesions at this stage of the disease that can be observed and recognized primarily by the dentist.^{4,5} The most common manifestations of leukemia in the oral cavity are gingival bleeding, hyperplasia, opportunistic infections, and bone alterations.

During the antineoplastic treatment, the lesions become even more severe, since chemotherapy acts on poorly differentiated or high-metabolism cells, affecting not only blast cells, but also normal body cells.^{3,4}

The dentist needs to be aware of lesions caused by leukemia and the anticancer treatment in order to improve the patient's oral health. Thus, this study aimed to perform a systematic review of the literature on oral complications secondary to chemotherapy performed in children with ALL.

Methods

A systematic search of articles in English, Portuguese, and Spanish published between January of 1992 and April of 2013 was performed in the PubMed/MEDLINE, Science Direct, Scopus, and SciELO databases. Studies whose the target population was children aged 2 to 18 years with ALL and that evaluated the complications of anticancer treatment in the oral cavity were selected.

The search used the following terms: oral manifestations, Leukemia, Acute Lymphoblastic Leukemia, ALL, chemotherapy, and children, as well as the corresponding words in Portuguese and Spanish. The Boolean operators AND, OR, NOT were used in the databases, when possible. The search strategies are shown in Table 1.

Table 1 Search strategies and number of articles found in the databases.

Strategies	A	B	C	D
(Oral Lesions OR Oral Manifestation OR Mouth Lesion OR Mouth Manifestation OR Oral Pathology) AND Leukemia AND Chemotherapy AND Children	0	88	32	801
(Oral Lesions OR Oral Manifestation OR Mouth Lesion OR Mouth Manifestation OR Oral Pathology) AND Acute lymphocytic leukemia AND Chemotherapy AND Children	0	37	0	128
(Oral Lesions OR Oral Manifestation OR Mouth Lesion OR Mouth Manifestation OR Oral Pathology) AND Acute lymphocytic leukemia AND (Chemotherapy OR antineoplastic agents) AND Children	0	34	1	134

A, Scielo; B, Science Direct; C, Scopus; D, PubMed/Medline.

After the initial search and retrieval of abstracts, four independent evaluators selected the relevant studies according to the inclusion and exclusion criteria. Longitudinal or cross-sectional controlled clinical trials that assessed oral manifestations in children with ALL were included in the systematic review. Studies in languages other than those primarily chosen, *in vitro* studies, animal studies, literature reviews, case reports, and studies not associated with the target population or the oral manifestations of the disease were excluded.

The first step in study selection was performed by analyzing the titles and abstracts. Subsequently, all studies whose titles or abstracts were considered relevant were obtained in full and thoroughly analyzed. Finally, the articles reviewed and selected through consensus of the five evaluators were included in the data systematization.

Results

Among the initially selected studies, 18 showed potential to be included in the systematic review; however, after thorough analysis of the studies, only eight met all the inclusion criteria. Among the selected studies, five had been performed in developing countries and three in developed countries; the methods and results of the studies are summarized in Tables 2 and 3.

Regarding the profile of the studies, the sample size ranged between 17 and 156 children, with a total sample size of 472 children aged 2 to 18 years. The selected studies were published between the years 1992 and 2012. Of the selected studies, seven were cross-sectional; only the study by Williams et al.¹¹ was longitudinal. The main objective of all selected studies was the evaluation of oral complications due to chemotherapy in patients with ALL.

The studies by Torres et al.⁶ and Subramaniam et al.² evaluated the incidence of oral manifestations between genders. In the study by Torres et al.,⁶ of the 49 children studied, 26 (53%) were males and 23 (47%) females. In the study by Subramaniam et al.,² of the 58 children, 37 (63.8%) were males and 21 (36.2%) females. The authors did not establish an association between gender and the frequency of oral manifestations. The remaining studies included in this systematic review did not assess their patients according to gender. In all selected studies, the intraoral examination was used to establish the diagnosis of oral lesions during chemotherapy.

Of all evaluated studies, only Pels et al.⁷ reported the performance of intraoral clinical examination before the start of chemotherapy. Among the variables analyzed by the authors were chemotherapy, type of drugs used by the children with ALL, use of chlorhexidine gluconate, oral hygiene, and place of residence.

Table 2 Methodology and objectives of the selected studies.

Study	Objective	Number of patients / age / study groups.	Oral health assessment	Variables analyzed (risk factors)
Subramaniam et al. (India, 2008) ²	To evaluate the oral manifestations in children with ALL during chemotherapy	58 (49 in the study group and 19 control children), age not reported	Performed through intraoral examinations	1. Oral health; 2. Compare outcomes between the study groups; 3. Most common sites of oral manifestations; 4. Gender; 5. Chemotherapy phase
Torres et al. (Mexico, 2010) ⁶	To determine the prevalence of oral manifestations in pediatric patients with ALL receiving chemotherapy, and to evaluate risk factors	49 children aged 2 to 14 years	Performed through intraoral examinations	1. Oral health; 2. Gender; 3. Age; 4. Time and type of treatment; 5. Chemotherapy phase
Pels and Blaszczyk (Poland, 2012) ⁷	To assess the state of oral hygiene in children with ALL during anti-cancer treatment	156 (78 in the study group and 78 in the control group), aged 2 to 18 years	Intraoral examination (simplified oral hygiene index (OHI-S)/ plaque index and gingival index). Period of examinations: First test: one month before chemotherapy; Second test: one to five months after the start of treatment; Third test: six to 18 months of treatment	1. Oral hygiene; 2. Gingival disease; 3. Compare outcomes between the study groups; 4. Treatment used

Table 2 Methodology and objectives of the selected studies (cont.).

Study	Objective	Number of patients / age/ study groups.	Oral health assessment	Variables analyzed (risk factors)
Sonis et al. (USA, 1995) ⁸	To evaluate the prevalence of dental caries and periodontal disease in children with ALL, comparing three treatment modalities	64 children: first group (chemotherapy), Second group (chemotherapy associated with 1,800 cranial cGy), Third group (chemotherapy combined with 2,400 cranial cGy). Age < 5 years	Performed through intraoral examinations. (DMF-T, OHI-M, IG-M)	1. Oral health; 2. Dental caries; 3. Bacterial plaque; 4. Gingival disease; 5. Compare outcomes between the study groups; 6. Treatment used
Pinto et al. (Brazil, 2006) ⁹	To evaluate the clinical aspects of oral mucosa in children with ALL and determine the effect of chlorhexidine 0.12% in the prevention of oral complications in these patients	33 children. Group I (23 children): oral solution of chlorhexidine 0.12%, twice a day; Group II (ten children): did not receive this solution. Aged 2 to 15 years	Clinical examination of the oral cavity/ digital palpation of the oral mucosa, and cytological smears (obtained from the oral mucosa at the beginning of chemotherapy intensification)	1. Presence of mucositis; 2. Effects of chlorhexidine 0.12%; 3. Compare outcomes between the study groups
Soares et al. (Brazil, 2011) ¹⁰	Evaluation of changes in the oral mucosa and qualitative alterations of the microbiota in children with ALL undergoing chemotherapy	17 children, aged 2 to 12 years	Clinical examination of the oral mucosa for the detection of oral lesions	1. Presence of mucositis; 2. Effects of chlorhexidine 0.12% on oral microbiota
Williams MC. (England, 1992) ¹¹	To investigate the incidence of alterations in the oral mucosa in a group of children during the first six months of anticancer treatment	24 children (12 children in the study group and 12 in the control group). Age not reported	1. Intraoral examination aimed at assessing the oral manifestations; 2. Salivary flow; 3. Presence of <i>Candida</i> in the oral mucosa; 4. Hematological examination	1. Oral health; 2. Amount of saliva; 3. Amount of <i>Candida</i> ; 4. Number of neutrophils; 5. Compare outcomes between the study groups
Mendonça et al. (2012, Brazil) ¹²	To evaluate the association of HSV-1, <i>Candida</i> spp. and oral bacteria on the severity of oral mucositis in children with ALL	71 patients, age not reported	Oral examinations aimed at assessing the presence of oral manifestations in children.	1. Oral health; 2. Evaluate the presence of <i>Candida</i> spp. and the severity of mucositis in patients with ALL

Although six^{2,6-9,12} of the eight articles mentioned the drugs used for chemotherapy, no clear correlation was established between oral complications and type of drug used. Pels et al.⁷ established an association between the phase of chemotherapy and oral complications; oral manifestations were more common in the induction phase.

The most frequent oral lesions were mucositis,^{2,6,9-12} candidiasis,^{2,6,12} periodontitis,⁶⁻⁸ and gingivitis.⁶ The most common sites of oral manifestation involvement were the oral mucosa and labial mucosa, according to the study by

Subramaniam et al.² The oral manifestations and most common sites of the selected studies are presented in Table 3.

The prevalence of oral manifestations was related to patients' poor oral hygiene⁶ and antineoplastic treatment;^{2,8} in the selected studies, no specific drug was related to the presence of oral manifestations. Another important factor related to oral manifestations was the quality of life and social class of the patients with ALL,⁶ as the presence of HSV and *Candida* spp. was associated with increasing severity of mucositis in children with ALL.¹²

Table 3 Outcomes obtained from the studies selected in the search.

Study	Most frequently found oral manifestations in the study group	Most frequent sites of oral manifestations	Outcomes obtained
Subramaniam et al. (India, 2008) ²	Mucositis (20.6%) - most common; Ulcerations (5.2%); Candidiasis (3.5%);	Jugal mucosa, 20 (34.4%); Labial mucosa, 14 (24.1%); Tongue, 13 (22.4%); Palate, four (6.9%)	All children undergoing chemotherapy showed oral manifestations more frequently when compared to children in the control group. Oral manifestations are more common in the induction phase.
Torres et al. (Mexico, 2010) ⁶	Gingivitis, 91.84%; Caries, 81.63%; Mucositis, 38.77%; Periodontitis, 16.32%; Cheilitis, 18.36%; Repeated herpes, 12.24%; Gengivostomatitis, 2.04%; Other manifestations: dry mouth, mucosal pallor, mucosal petechiae, and ulcers/oral candidiasis, 6.12%	Not mentioned in the study	It was observed that ALL combined with poor oral hygiene are important risk factors for the development of candidiasis and gingivitis
Pels and Blaszczyk (Poland, 2012) ⁷	The gingival index was higher in children with ALL compared to control children	Not mentioned in the study	Although children with ALL had better oral hygiene, higher rates of gingival diseases were observed in children with ALL, compared to control children
Sonis, AL et al. (USA, 1995) ⁸	There was no difference in the prevalence of dental caries among children in the control group and the test group. Patients who received 2,400 cGy presented higher risk of developing periodontal disease when compared to the control group	Not mentioned in the study	The results of this study suggest that children with ALL treated with chemotherapy did not have a higher risk of developing caries. There was a higher risk of developing periodontal disease among children from the test group
Pinto et al. (Brazil, 2006) ⁹	Mucositis was observed in six children from Group I and in eight from Group II, and was characterized by the presence of edema, erythema, and ulcers	Not mentioned in the study	Chlorhexidine showed to be beneficial in the reduction of oral manifestations in children
Soares et al. (Brazil, 2011) ¹⁰	Mucositis was the most common oral manifestation, affecting five children	Not mentioned in the study	The prophylactic use of 0.12% chlorhexidine gluconate reduces the frequency of oral mucositis and oral pathogens in children with ALL undergoing chemotherapy
Williams (England, 1992) ¹¹	The main oral manifestation was the presence of ulcerations	Not mentioned in the study	The main oral problem was ulceration, which was associated with the low number of neutrophils
Mendonça et al. (2012, Brazil) ¹²	Candidiasis showed to be associated with mucositis	Not mentioned in the study	The presence of HSV and <i>Candida</i> spp. is associated with increasing severity of mucositis in children with ALL

Discussion

The selected studies in this systematic review evaluated the oral manifestations in patients with ALL. The studies by Torres et al.⁶ and by Subramaniam et al.² estimated the incidence between genders, but did not establish an association between gender and frequency of oral manifestations; no other study showed such association.

In the study by Subramaniam et al.,² oral manifestations were observed in 77.8%, 36.4%, 70%, and 66.7% of children, divided according to the groups in the study. In the study by Torres et al.,⁶ approximately 95% of patients had some type of oral manifestation. These results corroborate the findings from other studies.^{13,14}

Chemotherapy can be directly toxic and affect the oral mucosa through the systemic circulation. Moreover,

the drugs used are often secreted through the saliva, which results in drug exposure in the oral cavity.¹⁵ However, among the studies selected, only six^{2,6-9,12} mentioned the drug combinations used in chemotherapy, and none directly correlated the oral manifestations to a specific type of drug.

Among the drugs most often associated with oral manifestations, teniposide, paclitaxel, methotrexate, idarubicin, epirubicin, doxorubicin, cisplatin, and cytarabine are associated with mucositis, xerostomia, gingival bleeding, and other diseases of the oral cavity.^{16,17} Methotrexate, bleomycin, doxorubicin, cisplatin, vinblastine and vincristine are drugs that produce direct toxicity of some of their antimetabolites and other synthetic agents, such as hydroxyurea and procarbazine hydrochloride, which lead to glandular degeneration, changes in collagen, and epithelial dysplasia.^{15,18} Drug combinations used during chemotherapy in the studies are shown in Table 4.

Mucositis was the most common oral manifestation in the study by Subramaniam et al.,² affecting 20.6% of patients with leukemia, whereas among children who were not undergoing treatment, only 3.4% had mucositis. For most researchers, mucositis is caused by chemotherapy and occurs due to a dynamic process, resulting in the destruction of the basal cells; the same is stated by Sonis,¹⁹ in a study published in 1998, who also mentioned that tissue damage was caused by direct contact with the antineoplastic agents. In the study by Torres et al.,⁶ mucositis was not the most frequent disease; nevertheless, it affected approximately 38.7% of children.

In the study by Pels et al.,⁷ although children with ALL had better oral hygiene, they had more oral manifestations than children from the comparison group; oral mucositis was the most common lesion among patients undergoing chemotherapy. Pinto et al.⁹ concluded that good oral hygiene associated with the use of 0.12% chlorhexidine glu-

Table 4 Chemotherapeutic drugs used and phases of chemotherapy.

Study	Chemotherapeutic drugs used	Phases of chemotherapy
Subramaniam et al. (India, 2008) ²	Induction therapy - daunorubicin 30 mg, vincristine 1.4 mg, L-asparaginase, methotrexate 12 mg Induction therapy with radiotherapy - mercaptopurine 75 mg, cyclophosphamide 750 mg, methotrexate 12 mg Repetition - daunorubicin 30 mg, vincristine 1.4 mg, L-asparaginase 6000 U, methotrexate 12 mg Consolidation - mercaptopurine 75 mg, cyclophosphamide 750 mg, vincristine 14 mg, cytarabine Maintenance - vincristine 1.4 mg, methotrexate 15 mg, L-asparaginase 6000 u, daunorubicin 30 mg, prednisolone 40 mg	Four phases
Torres et al. (Mexico, 2010) ⁶	All patients were treated according to the chemotherapy protocol used and time of treatment: Zero to seven weeks - doxorubicin, vincristine, prednisone, L-asparaginase, and methotrexate Seven to 14 weeks -high doses of methotrexate, dexamethasone, cytosine arabinose, cytarabine, and cyclophosphamide 14 weeks to 3 years - methotrexate, 6-mercaptopurine, cyclophosphamide, cytarabine, or a combined therapy: prednisone, vincristine, and cytosine arabinose	Three phases
Pels and Blaszcak (Poland, 2012) ⁷	The Berlin-Frankfurt-Münster protocol was used ¹³	Not mentioned
Sonis et al. (USA, 1995) ⁸	Chemotherapy protocols were used in the treatment according to the neoplasia stage ^{14,15}	Three phases
Pinto et al. (Brazil, 2006) ⁹	The protocol proposed by the Brazilian Society of Pediatric Oncology for the treatment of acute leukemia was used. ¹⁶ Methotrexate was one of the drugs used in this therapy. Chlorhexidine gluconate 0.12% was administered for ten consecutive days after each infusion of methotrexate during chemotherapy intensification	Not mentioned
Soares et al. (Brazil, 2011) ¹⁰	Not mentioned	Not mentioned
Williams (England, 1992) ¹¹	Not mentioned	Not mentioned
Mendonça et al. (Brazil, 2012) ¹²	The protocol for the treatment of acute leukemia proposed by the Brazilian Society of Pediatric Oncology was used ¹⁶	Not mentioned

conate prevented oral manifestations in children with ALL, especially mucositis, due to its capacity to interfere with microorganism adhesion, when used as an antiseptic in the oral cavity.

The study by Soares et al.¹⁰ showed similar results to the study of Pinto et al.⁹ children who used chlorhexidine gluconate had fewer oral manifestations when compared to the control group. A microbiological analysis showed a reduction in pathogenic microorganisms in the oral cavity, and mucositis, the most frequent oral manifestation, was observed in five children (29.4% of the sample). Other studies also evaluated the use of chlorhexidine in patients with ALL, with positive results in reducing oral manifestations caused by chemotherapy.^{20,21}

In the study by Torres et al.,⁶ the most common oral manifestation was gingivitis, affecting 91.84% of the sample; the high rate of gingivitis in this study was associated to poor oral hygiene, in addition to chemotherapy. The chemotherapy phase also showed an association with the onset of gingivitis. In the study by Subramaniam et al.,² the rate of gingivitis was lower: less than 2% among patients. This difference may be due to the better oral hygiene of the children participating in that study,² corroborating the findings of Trindade et al.,¹⁴ who demonstrated that oral hygiene should be encouraged at any stage of treatment, since it can prevent oral and systemic manifestations.

The study by Sonis et al.⁸ concluded that patients with ALL treated with chemotherapy had the same probability of dental caries as children from the control group. For the authors, the presence of caries was associated with poor oral hygiene of the participants. These results corroborate the findings of Sepet et al.,²² who assessed the presence of caries among children in the maintenance phase of chemotherapy and in a group of healthy children, observing no correlation between the presence of caries and the use of chemotherapeutic drugs.

Primary herpetic gingivostomatitis was observed in 2.04% of the patients in the study by Torres et al.,⁶ and recurrent herpes in 12.24%. The presence of herpes in that study could have been caused by the participants' low immunity, associated with exposure to the virus; this result corroborates other studies that also reported the presence of herpetic stomatitis in children with ALL.^{23,24}

In the longitudinal study by Williams et al.,¹¹ all patients had ulcerations in the oral mucosa, whereas oral candidiasis was observed in 10% of tests performed during the study period. The presence of the disease was associated with the low number of neutrophils of leukemia patients in combination with low salivary flow caused by chemotherapy. In the study by Mendonça et al.,¹² oral candidiasis was also associated with the presence and severity of mucositis; antifungal prophylaxis was suggested in patients with ALL with mucositis. This same suggestion was made in the study by Pine et al., published in 2010.²⁵ Other oral manifestations observed in these studies were dry mouth, gingival bleeding, oral erythema, toothache, and primary herpetic stomatitis.

Conclusion

The oral health status of patients with ALL varies according to a number of factors. The results of the studies demonstrated that most patients with ALL had some lesion in the

oral cavity during or after the start of chemotherapy. The dentist is responsible for recognizing these lesions and intervening in the oral health of these patients, thereby contributing to their treatment and quality of life improvement. New studies are required to better elucidate the subject, especially regarding the prevention and control of these oral manifestations.

Conflicts of interest

The authors declare no conflicts of interest.

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