Oral health status in children with acute lymphoblastic leukemia

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Accepted 9 November 2011

Abstract

Leukemia is a malignancy of the bone marrow. Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and accounts for nearly 75% of all newly diagnosed leukemias and 25% of all malignancies in childhood. The aim of the present study was to review the oral health status in children with ALL. Databases were explored using various combinations of the following keywords: “acute lymphoblastic leukemia”, “children”, “inflammation”, “pediatric”, “periodontal disease” and “periodontitis”. Oral inflammatory conditions including chelitis, gingivitis, herpetic gingivostomatitis, mucositis, oral candidiasis, periodontitis and ulcerations are common manifestations in children with ALL.

Results: Periodontal inflammatory conditions and oral mucositis were reported to be significantly higher in children with ALL as compared to healthy controls. Tooth morphological disorders including agenesis, microdontia, short roots and developmental defects in the enamel and dentin were more often observed in children with ALL as compared to healthy controls. Children with ALL have a reduced salivary flow rate, which makes them more susceptible to dental caries as compared to healthy children. Malocclusion due to microdontia may also trigger temporomandibular joint disorders in children with ALL; however, this relationship needs further investigations.

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doi:10.1016/j.critrevonc.2011.11.003
Conclusion: Oral inflammatory conditions including mucositis and gingivitis are common in children with ALL as compared to healthy children. Tooth morphological disorders including microdontia and enamel and dentin are common manifestations in children with ALL.

Keywords: Acute lymphoblastic leukemia; Children; Dental; Pediatric; Oral, and periodontal disease

1. Introduction

The association between oral inflammatory conditions and systemic disorders is well-established [1–5]. It has been reported that children with poorly controlled type 1 diabetes (T1D) are more susceptible to periodontal inflammatory conditions as compared to those with well-controlled T1D and non-diabetic controls [1]. Likewise, in another study, Vázquez-Nava et al. [6] reported obesity to be a significant risk factor for dental caries in pre-school children. From these studies, it seems that systemic disorders may reflect in the oral cavity in the form of oral inflammatory conditions. Patients with hematological diseases receive various forms of treatments including chemotherapy, radiation, surgery, and bone marrow and stem cell transplants.

1.1. Acute lymphoblastic leukemia—etiology and epidemiology

Leukemia is a malignancy of the bone marrow and blood. It is associated with disseminated proliferation of immature or blast cells of the bone marrow that replaces the normal marrow elements and tends to accumulate in various tissues of the body. The main types of leukemia are lymphocytic leukemia (that involves an increase in lymphocytes); and myelogenous leukemia (that involves an increase in granulocytes).

The most common pediatric malignancy is acute lymphoblastic leukemia (ALL) that accounts for nearly 75% of all newly diagnosed leukemias and 25% of all malignancies in childhood [7]; however, the exact etiology of childhood ALL remains unknown for over 95% of patients who lack a pre-existing genetic disorder. The annual incidence of ALL is approximately 9–10 cases per 100,000 populations in childhood (1–10 years) [8]. The incidence of ALL has been reported to be higher in patients with a higher socioeconomic status (SES) as compared to those with an underprivileged SES [9–11]; however, the results remain debatable. Swensen et al. [12] and Dockerty et al. [13] reported that the incidence of ALL in children may not be solely accounted for by SES differences. This may probably be due to an enhanced epidermal mitotic rate or due to the presence of more epidermal growth factor receptors resulting in morbidity [14,15].

2. Rationale and objective

Since the most common pediatric malignancy is ALL [7], the objective of the present study was to review the oral health status in children with ALL.

3. Materials and methods

3.1. Eligibility criteria

The following eligibility criteria were imposed: (a) clinical studies and case-reports; (b) retrospective studies; (c) control group: children without leukemia (healthy children); (d) reference list of potentially relevant original and review articles; (e) intervention: oral health status in children with ALL; and (f) articles published only in English-language. Letters to the editor, historic reviews, and unpublished data were excluded.

3.2. Search strategies

The authors explored the PubMed/MEDLINE (National Library of Medicine, Washington, DC) and Google-Scholar databases for appropriate articles addressing the focused question—“What is the oral health status of children with ALL?” Databases were searched from 1977 up to and including August 2011 using the following terms in different combinations: “acute lymphoblastic leukemia”; “children”; “dental”; “pediatric”; “oral”, and “periodontal disease”. Titles and abstracts of articles obtained using the above described criteria were then screened by the authors and checked for agreement. The full-text of the articles judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. The second step was to hand-search the reference lists of original and review studies that were found to be relevant in the first step and once again, any disagreement between the authors was resolved via discussion. Since only a limited number of original studies addressed our focused question, the structure of the present study was customized to mainly summarize the relevant information.

4. Periodontal health status in children with acute lymphoblastic leukemia

In a recent study, Hegde et al. [16] investigated the periodontal health status in children with and without ALL. In this study [16], 120 children, aged between 4 and 10 years (90 children with ALL and 30 medically healthy controls) were included. The gingival health in children with and without ALL was assessed by a modified gingival index [17]. In this study, gingival inflammation was more often observed in children with ALL as compared to healthy controls. Gingival inflammation was also directly associated with the duration of
chemotherapy [16]. In a cross-sectional study, the prevalence of periodontal inflammatory conditions was investigated in 49 children (mean age in years: 7.34 ± 3.3) with ALL [18]. In this study, the prevalence of gingivitis and periodontitis in children with ALL were reported to be 91.84% and 16.32%, respectively [18]. Sonis et al. [19] investigated the periodontal inflammatory conditions in 69 children undergoing treatment for ALL. The results showed that the patients who received 24 grays (Gy) of cranial radiotherapy (RT) had significantly higher plaque and periodontal indexes as compared to patients who received 18 Gy of cranial RT [19]. It is known that a reduced salivary flow rate (SFR) (due to chemotherapy induced salivary gland hypoplasia) favors dental plaque accumulation, which if left uncontrolled, may trigger periodontal inflammation in immunocompromised patients [1,3,16].

5. Oral mucosal health status in children with acute lymphoblastic leukemia

Several studies [20–23] have reported an increased incidence of oral mucosal anomalies including generalized ulcers, coated tongue, fetor oris, shallow papillae, tender oral mucosa and oral mucosal infections (mucositis, candidiasis, herpes simplex, varicella/zoster and cytomegalovirus) in patients with ALL. In the study by Ponce-Torres et al. [18], the prevalence of oral candidiasis among children with ALL was reported to be 6.12%, which was comparatively lower in contrast to the prevalence reported by previous studies [21,24]. A possible explanation for this may be attributed to various factors including degree of oral hygiene maintained by the subjects, severity of immunosuppression and modifications in the drug regime patterns. Studies [25,26] have reported that administration of certain drugs, such as antifolates (methotrexate) and corticosteroids (prednisone) concurrent with the chemotherapy may influence the appearance of oral lesions. In the study by Ponce-Torres et al. [18], children with ALL undergoing chemotherapy developed mucositis and candidiasis within 1 week after antifolate and corticosteroid therapy [18]. Although Candida species (predominantly Candida albicans) are part of the conventional oral flora; they may become opportunistic pathogens under immunocompromised conditions (as in patients with ALL). Simultaneously, a dry oral environment (as observed in patients with ALL [18]) in immunocompromised patients may also trigger Candidal infections by stagnating Candida species on the oral soft tissues, particularly on the dorsum of the tongue [27].

Oral mucositis is a frequent complication of ALL and represents the main cause of pain and discomfort by promoting bacterial colonization and proliferation [28–30]. The initial presentation of oral mucositis is erythema, followed by white desquamating plaques that are painful on touch. A more pronounced form of oral mucositis is characterized by epithelial crusting and ulceration. Exposure of the richly innervated underlying stromal connective tissue is a manifestation of the most severe form of mucositis [31], and is usually seen in 5–7 days following cancer medication. Oral mucositis may occur as a result of both “direct” and “indirect” effects of chemotherapy on cells [32]. The direct effect is established by the interference of drugs in cell proliferation, maturation and replacement. On the other hand, the indirect effect has been associated with the myelosuppressive action of drugs deregulating the immune system and repair process, thereby increasing the risk of infection associated with oral mucositis [33]. Studies [34,35] have shown an increased proliferation and colonization of gram-negative bacteria including Escherichia coli, Pseudomonas aeruginosa, Klebsiella and Enterobacter species in the oral cavity of patients with ALL as compared to their healthy counterparts. Similarly, gram-positive bacteria including Staphylococci and Enterococcus have also been isolated from the oral mucosa of immunocompromised patients [36].

Oral rinses containing chlorhexidine gluconate (0.12%) and essential oil formulations are widely recommended for the treatment of oral infections [37,38]. Chlorhexidine gluconate (0.12%) exhibits bactericidal and fungicidal properties and forms a whitish membrane (by coagulation of serum and salivary proteins) on the inflamed mucosa thereby reducing the severity of oral mucosal inflammation [37,39]. A recent study [40] investigated the frequency of oral mucositis and microbiological analysis in children with ALL treated with 0.12% chlorhexidine gluconate. The results suggested that prophylactic use of 0.12% chlorhexidine gluconate reduces the frequency of oral mucositis and oral pathogens in children with ALL [40].

6. Tooth morphology in children with acute lymphoblastic leukemia

It has been reported that ALL may negatively influence the dentoalveolar complex during its formation [41]; however, this association is dependent on various factors including age of the patient at diagnosis, type of drugs used for chemotherapy and dosage of radiotherapy (if used as an adjunct to chemotherapy in severe cases) [42–47]. Chemotherapy is selectively toxic to actively proliferating cells by interfering with DNA synthesis and replication, RNA transcription and cytoplasmic transport mechanisms [43]. An ideal chemotherapeutic agent should only destroy malignant cells. However, since chemotherapeutic agents do not have a selective toxicity for tumor cells; they may also influence healthy cells at proliferation stages [42]. In humans, disorders of enamel and dentin have been reported as a consequence of chemotherapy [47]. Studies [43–45] have demonstrated that chemotherapeutic agents (such as cyclophosphamide and vincristine) interfere with the cell cycle and with intracellular metabolism thereby eliciting residual changes in dental development that may lead to microdontia, malformed teeth and changes in
the histomorphology of odontoblasts, with necrotic changes in preodontoblasts in the basal pulp region. In this regard, altered odontoblastic activity (a consequence of abnormal secretary function of microtubules and of complex changes in inter- and intracellular relationships), may negatively influence the morphology of a developing tooth [43]. Maciel et al. [46] compared the incidence of dental anomalies in shape, size, number, and structure among 56 patients treated for ALL and a control group (n = 56). In this study, the mean ages of children with and without ALL were 11.8-years and 11-years correspondingly. The results showed several dental morphological anomalies in children with and without ALL including: agenesis, enlarged pulp chambers hypoplasia, microdontia, short roots, supernumerary teeth, tapering roots and taurodontism [46]; however, agenesis, microdontia, short roots and tapering roots were more prevalent in children with ALL as compared to their medically healthy counterparts [45] (Fig. 1).

Some patients receive radiotherapy as an adjunct to chemotherapy for the treatment of ALL [48]. It has been reported that a 10 Gray (Gy) radiation dosage permanently damages the ameloblasts, whereas a 30 Gy radiation dose halts tooth development from the time the teeth are irradiated. Sonis et al. [49] investigated the dentofacial development in 97 children diagnosed with ALL. These children were treated with either: (a) chemotherapy and 18 Gy cranial irradiation, or (b) chemotherapy with adjunct 24 Gy cranial irradiation. The results showed that 94% of all patients and 100% of children younger than 5 years of age at diagnosis had dental anomalies including arrested root development, enamel dysplasias, microdontia and tooth agenesis [49]. Mandibular growth was compromised in children receiving 24 Gy irradiation as compared to those receiving lesser dosages of radiotherapy for the treatment of ALL [49].

7. Dental caries status in children with acute lymphoblastic leukemia

Dental caries is a disease of the mineralized tissues of teeth, namely enamel, dentin and cementum and is caused by the action of cariogenic bacteria on fermentable carbohydrates stagnated on the tooth surface. If left untreated, dental caries may cause demineralization of the mineral portions of teeth and disintegrate their organic matrix. Since a reduced SFR has been reported in children with ALL [16]; and that a diminished SFR favors accumulation of dental plaque on tooth surfaces, it may be hypothesized that children with ALL may be more susceptible to dental caries as compared to medically healthy children. In a recent study, Hegde et al. [16] investigated the decayed, missing, and filled teeth (DMFT) scores in 90 children with ALL and compared them to DMFT scores obtained from healthy controls (n = 30). The results showed that the DMFT scores were significantly higher in children with ALL as compared to their healthy counterparts. Similar results were reported by Nasim et al. [50]. Although the negative effects of anti-cancer therapy on SFR are well-established [16,50–52]; studies have reported that the oral mucosal inflammation induced by chemotherapy, may prevent some patients from performing daily oral hygiene maintenance regimes [51,53]. Nevertheless, controversial results have also been reported with reference to the association between ALL and dental caries. Maciel et al. [46], compared the DMFT in children with (n = 56) and without ALL (n = 56). In this study [46], no significant differences were found in DMFT scores between patients and controls that may be associated with the oral hygiene instructions that the multidisciplinary team gave these children and to the redoubled care of parents during treatment. Kinirons et al. [54] assessed the dental caries status in 54 children (aged 3–19 years) with ALL undergoing chemotherapy. The
results showed no significant differences in the dental caries experience among the subjects in relation to the duration of chemotherapy. Likewise, Cubukçu and Güneş [55], reported no significant difference in the caries experience before and after the initiation of chemotherapy in children with ALL. However, prolonged use of sugar-containing nystatin has been directly associated with the caries experience in children with ALL [54]. In results by Kinirons et al. [54] showed that children with ALL using nystatin oral rinses for over 12-months were more susceptible to develop dental caries as compared to those who had received nystatin for shorter periods [54]. A diminished SFR in children with ALL [16] may allow the sugar-containing nystatin and dental plaque to adhere to teeth surfaces and induce their fermentation. It is suggested that sugar-free anti-fungal oral rinses may contribute in reducing the occurrence of dental caries in children with ALL; however, the role of regular oral hygiene maintenance regimes in this regard cannot be disregarded. Further studies are warranted to assess the association between ALL and dental caries.

8. Disorders of the temporomandibular joint in children with acute lymphoblastic leukemia

The association between ALL and disorders of the temporomandibular joint (TMJ) has been inadequately addressed. It has been reported that dental anomalies including microdontia and hypodontia are common manifestations in children with ALL as compared medically healthy children [45–49]. In this regard, it may be hypothesized that tooth morphological disorders may result in a poor dental occlusion (poor alignment of teeth) and if remained neglected may lead to TMJ disorders. Cranial irradiation is often used as an adjunct to chemotherapy in the treatment of ALL. It is known that microdontia is a manifestation in children with ALL. Cranial irradiation has been associated with musculoskeletal fibrosis that may cause trismus and limited mouth opening in patients undergoing cranial irradiation [56]. This may explain the results by Uderzo et al. [57] where one child patient with ALL developed severe TMJ dysfunction and limited vertical mouth opening. In the study by Welbury et al. [58], mouth opening was investigated in 37 children with leukemia. The results showed no variation in mouth opening; however, it is notable that these leukemic children were not exposed to any form of radiation therapy [57]. This suggests that children with ALL undergoing cranial irradiation as an adjunct to chemotherapy are more susceptible to TMJ dysfunction as compared to children undergoing only chemotherapy for the treatment of ALL. However, due to the limited available evidence, further studies are warranted in this regard.

9. Conclusion

Oral health status is compromised in children with ALL. Oral inflammatory conditions including mucositis and gingivitis are common in children with ALL as compared to healthy children. Tooth morphological disorders including microdontia and enamel and dentin are common manifestations in children with ALL. Assessment of dental caries and TMJ disorders in children with ALL requires further investigations.

10. Recommendations

- Patient compliance is the key to success in maintaining a healthy oral cavity during cancer therapy. Therefore, it is essential to educate the healthcare provider/s and child/children about the significance of oral health care to minimize discomfort and maximize the chances for a successful outcome.
- Fluoride rinses and gels may be recommended for caries prevention.
- Multidisciplinary care, including pediatric dentistry, is important in patients with ALL, because during the initial period of treatment, the effects of the disease and the chemotherapeutic drugs can cause severe oral complications.
- For the management of oral complications related to chemotherapy, efforts should be directed to reduce the influence of secondary factors on mucositis; regular oral examinations are recommended in order to timely diagnosis and treat fungal, viral, and bacterial infections.

Conflict of interest statement

The authors declare that they have no conflicts of interest and there was no external source of funding for the present study.

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References


Biography

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