Oral Manifestations In Acute Lymphoblastic Leukemic Children Under Chemotherapy

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Leukemia is a common malignancy seen in young children and acute lymphoblastic leukemia (ALL) accounts for 75% of all leukemias. Advances in the treatment regimen include multi-agent chemotherapy and central nervous system directed radiotherapy. Immune suppression caused due to disease and therapy makes these children more prone to bacterial, fungal infections and at times reactivation of viral diseases. Hence, the present study was taken to assess, the oral conditions among ALL children during chemotherapy.
Keywords: *Acute lymphoblastic leukemia (ALL), oral manifestations.*
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INTRODUCTION

Leukemia is a malignancy with disseminated proliferation of immature or blast cells of the bone marrow, which replace the normal marrow elements and tend to accumulate in various tissues of the body.[1] Leukemia was first identified by researchers, Virchow and Bennet in the year 1845.[2] European physicians in the 19th century were the earliest observers of patients who had markedly increased white cell counts. The term "Weisses Blut" or "white blood" emerged as a designation to this disorder. Later, the term leukemia, which is, derived from the Greek word "leukos," meaning "white," and "haima," meaning blood was used to indicate the disease.[3] It is classified clinically on the basis of the duration and character of the disease (acute or chronic), the type of cell involved (myeloid, lymphoid, or monocytic) and increase or non-increase in the number of abnormal cells in the blood.[2] Acute lymphocytic leukemia (ALL) constitutes 97% of all leukemias and accounts for 75% of all acute leukemias. Peak age of its occurrence in children is aged between 3-5 years, and it occurs slightly more frequently in boys than in girls (1.2:1).[4]

The cause of ALL remains largely unknown, although many conditions may influence its development. Some of the risk factors which are important in the pathogenesis of leukemia are; ionizing radiation; chemicals; (eg: benzene, heavymetals, pesticides, petroleumdistillates), drugs (chemotherapeutic drugs agents, alkylating agents and etoposide, especially when used with radiotherapy); viral infection and genetics.[4]

Advances in the treatment regimens, including multi-agent chemotherapy and radiation therapy, have greatly increased the chances of survival.[5] The purpose of the therapy in ALL is to eradicate the invading leukemic cells and their progenitors while preserving the expressions of normal progenitors.[4] Since 1970, the rate of cure of ALL in children has increased dramatically, from less than 30% to approximately 80% with the implementation of an intensive 'Multi Centre Protocol' (MCP) 841 [Standard drug regimen for ALL children being used at several centres in India, designed in collaboration with National Cancer Institute (USA)]. Treatment of ALL progresses through four main phases according to the MCP 841 protocol. (Table I) Introduction of a standard protocol (MCP841) and improvement in supportive care led to an increase in the event-free survival (EFS) from less than 20% to 45–50% in 4 yrs.[6]

Ideally, a chemotherapeutic agent should only destroy malignant cells. Unfortunately, anticancer drugs with such sparing effect on normal tissues are not yet available and therefore, some damage to normal tissues is inevitable, particularly those in which rapid cell division normally occurs.[7] The acute toxicity induced by chemotherapy can be related to proliferation kinetics of individual cell proliferation. Most susceptible structures are tissues or organs with a high cellular turn over rate such as the oral and intestinal mucosa, bone marrow, hair follicle, testis and the liver.[8] The type of

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Table 1: Drug regimen for ALL children - MCP 841Protocol

***Induction therapy (I_1)* –4weeks**	***Daunorubicin 30mg/I.V,days1,8,15*** ***Vincristine 1.4mg/m^2 I.V days1,8,15,22,29*** ***L-Asparaginase 6000U/ m^2 IM ALTX10,2-20*** ***IT-Methotrexate12mgdays1,8,15,22***
Induction therapy with radiotherapy (I_2)* 4weeks** ***Cranial irradiation200Rads/Dose	***6-Mercaptopurine 75mg/ m^2 days1-7*** ***Cyclophospamide 750mg/ m^2 I.V,days1and15*** ***IT-Methotrexate 12mgdays1,8,15*** ***Cranial irradiation-180Cgy,x9 days(1800 Cgy)***
***Repetition of (R I_1)* 4weeks**	***Daunorubicin 30mg/I.V,days1,8,15*** ***Vincristine 1.4mg/m^2 I.V days1,8,15,22,29*** ***L-Asparaginase 6000U/ m^2 IM ALTX10,2-20*** ***IT-Methotrexate12mgdays1,8,15,22***
***Consolidation (C)* 4weeks**	***6-Mercaptopurine 75mg/ m^2 days1and1-7&15-21*** ***Cyclophospamide 750mg/ m^2 I.V,days1and15*** ***Vincristine1.4mg/m^2 I.V days1&15*** **Cytarabine 70mg/ *m^{2}SCX6 days1-3&15-17***
Maintenance (M)* 3months *x6 cycles	***Vincristine 1.4mg/m^2 I.V days1*** ***Methotrexate15mg/ m^{2}once a week*** ***L-Asparaginase 6000U/ m^2 Imdays1,35,7*** ***Daunorubicin 30mg/IV.day1*** **Prednisolone40mg/ *m^{2}days1-7***

Total duration of therapy- 2 years

chemotherapeutic agents, the dosage, and the frequency of drug administration are important therapy related factors, which affect the development of stomatotoxicity.[9,10]

Chemotherapeutic agents that have a high potential for precipitating oral mucosal damage are alkylating agents such as busulfan, cyclopospamide, procarbazine, and thiotepa; anthracyclines such as daunorubicin, doxorubicin, and epirubicin; antimetabolite such as cytocine arabinoside, hydroxyurea, 5-flurouracil, methotrxate, 6 Mercaptopurine, and 6-thioguanide; antibiotics such as actinomycin D, amsacrine, bleomycin and mitomycin; vinca alkaloids such as vinblastin and vincristine; and taxanes.[11,12]

The oral cavity is also highly susceptible to toxic effects of cancer chemotherapy, this risk is due to high cellular turnover rates for the lining mucosa, diverse and complex microflora, and trauma to oral tissues during normal oral function[13,14] predisposing the patient to mucositis and xerostomia.[15,16,17,18]

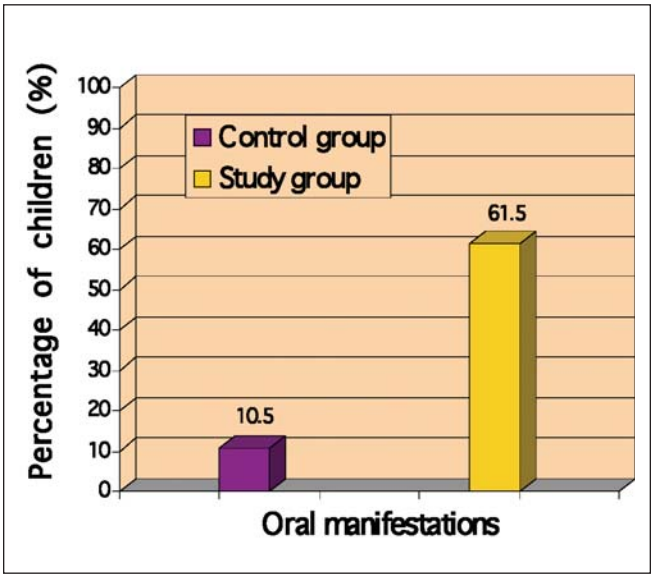
Among the opportunistic infections, the most frequent is candidiasis due to the extensive use of broad-spectrum antibiotics, chemotherapy, poor oral hygiene, malnutrition, and the general poor health of the patient. The most common viral infection in leukemia is herpes simplex, which shows atypical and prolonged evolution, usually located on the lips, palate, and tongue.[15,16,18,19] Bacterial infections result from secondary contamination of pre-existing lesions, most commonly by opportunistic gram-negative organisms.[15]

Even prior to chemotherapy leukemic children are more prone for infection of the oral cavity due to anemia, thrombocytopenia and granulocytopenia.[7]

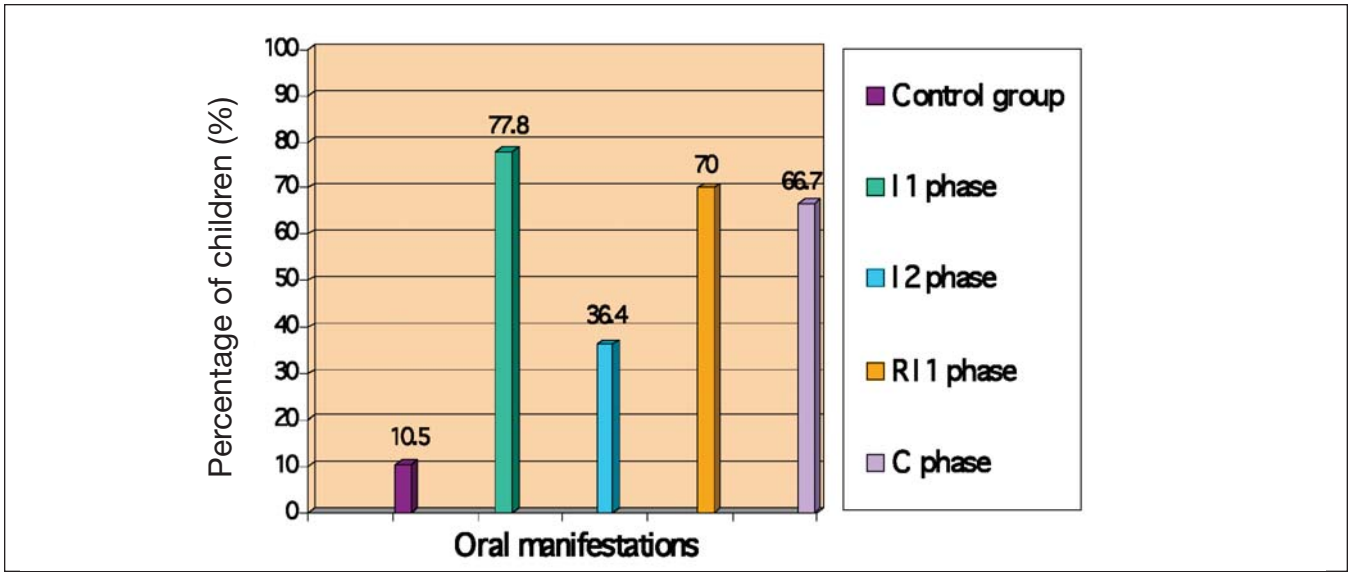
In spite of innumerable studies, which have been made on different body organs, it seems likely that the effects of leukemia on the oral cavity have not been a subject for adequate investigation.[2] Hence, the purpose of the present study was to evaluate the oral manifestations of ALL children, prior to as well as during various stages of intensive chemotherapy and to identify the most common oral manifestation and common site of occurrence.

MATERIALS AND METHODS

The present study was carried out at Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India. After obtaining approval from the institution's ethical review board, 58 children from the pediatric oncology department, diagnosed as suffering from ALL were included in the study. Of these, nineteen children who were yet to begin their chemotherapy



Graph I. Overall percentage of children with oral manifestation in the control and study groups



Graph II. Distribution of oral manifestations among children in the control and various stages of chemotherapy in the study group.

formed the control group. Thirty-nine children who were already undergoing the different phases of intensive chemotherapy formed the study group.

Among children in the study group, 9 were in the induction therapy phase (I_1), 11 were in the phase of induction therapy with radiotherapy (I_2), 10 were in the repetition of I_1 phase, ie the R I_1 phase and 9 were in the consolidation phase (C).

All relevant history including treatment regimen, medical and drug history were obtained from the hospital records. After obtaining parental consent a non-invasive oral examination was conducted using sterile mouth mirrors and disposable sterile gloves. The data obtained was subjected to statistical analysis using fisher exact test. Significance for all the statistical tests was predetermined at a p value of 0.05 or less.

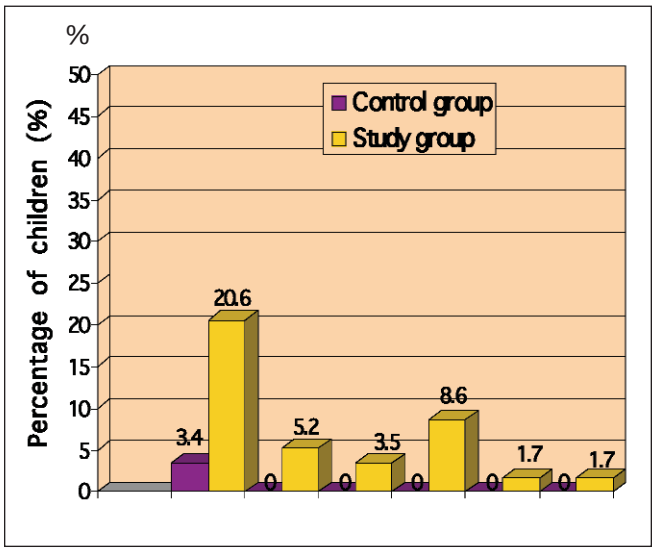
RESULTS

Among the 58 ALL children examined 37 (63.8%) were boys with a mean age of 7.14 years and 21(36.2%) were girls with a mean age of 5.33 years.

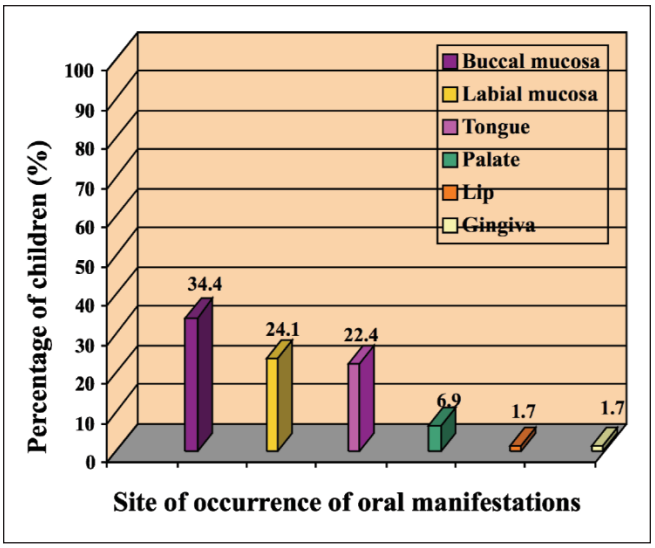
Two children (10.5%) in the control group and twenty-four children (61.5%) in the study group showed oral manifestations and the difference between these two groups was found to be statistically significant [p<0.001].

In the study group, oral manifestations were observed in 77.8%, 36.4%, 70% and 66.7% of children in the I_1, I_2, RI_1 and C phases of chemotherapy, respectively.

Mucositis was the most common manifestation seen in two children (3.4%) of the control group and in twelve children (20.6%) of the study group (photograph I). In the study group 3 (5.2%) children had mucosal ulcers (Fig. 2) and 2 (3.5%) of them had candidiasis like lesions (Fig. 3). Five children (8.6%) in the study group were observed to have



Graph III. Distribution of oral manifestations among children in the control and the study group



Graph IV. Site of occurrence of oral manifestations among the subjects.

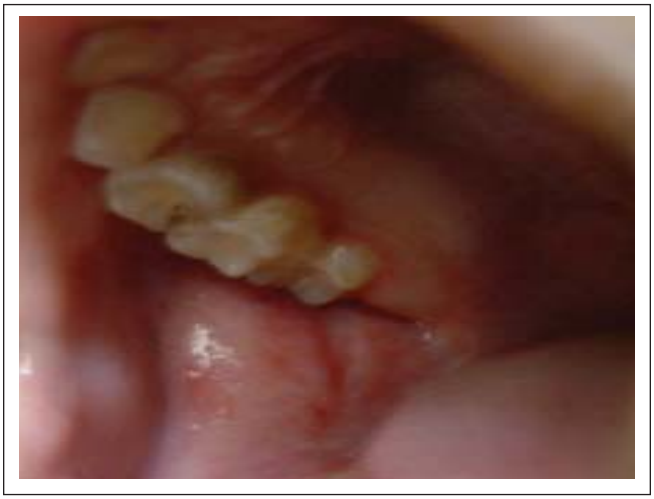


Figure 1: Mucositis

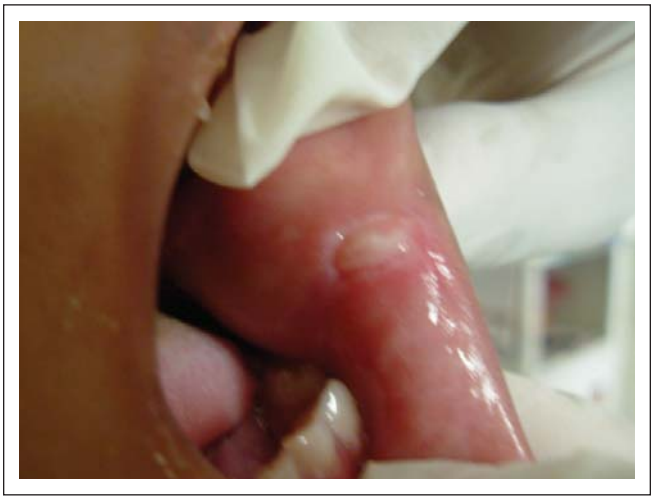


Figure 2: Mucosal ulcer

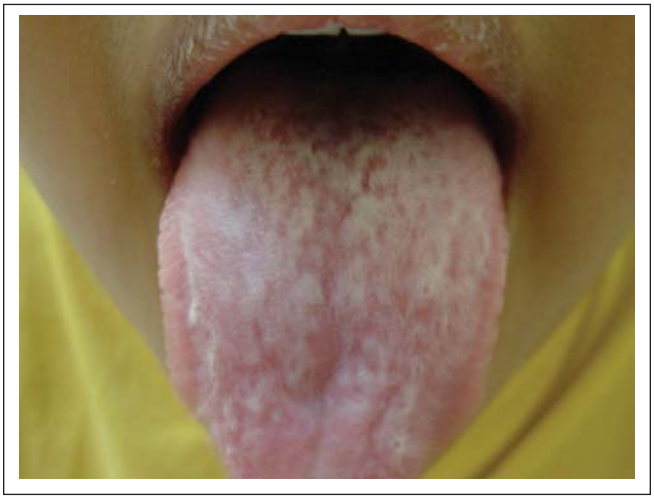


Figure 3: Candidiasis like lesions

both mucositis and mucosal ulcer. One child (1.7%) suffered from mucositis and glossitis. One child (1.7%) was observed to have both mucositis with candidiasis like lesions.

Oral manifestations were seen on the buccal mucosa of 20 (34.4%) children and on the labial mucosa of 14(24.1%) children. Lesions were seen on the tongue and palate of 13(22.4%) children and 4(6.9%) children respectively. Only one child each, showed a lip (1.7%) and gingival lesion (1.7%).

DISCUSSION

ALL is the first form of disseminated cancer shown to be curable with chemotherapy. The incidence of oral complications in ALL has been found more frequently in pediatric patients than in adults, probably due to a more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors resulting in morbidity.[20,21] On the other hand, a variety of patient related factors also appear to increase the potential for developing oral complications, including the age of the patient, nutritional status, pretreatment oral condition, oral care during treatment, and pretreatment neutrophil count.[20,22] Among the changes in the oral cavity, the more frequent are infections, as long periods of immunosupression make these individuals more susceptible. During chemotherapy there is an increase in the incidence and severity of infections seen mainly during leucopenic periods with consequent immunosupression with the patient presenting several types of infection, such as fungi, notably with candidiasis; but also viral infections, mainly herpes simplex; as well as by parasites and by saprophitic microorganisms.[23]

Forty percent of patients receiving chemotherapy have been reported to develop acute oral complications.[24] In the present study 61.5% of children who were on different phases of chemotherapy suffered from oral manifestations. Children in the I_1 phase of chemotherapy showed more oral manifestations probably due to the direct consequence of immediate toxic effects of chemotherapy, as acute oral complications can be seen as early as 3 days after initiation of chemotherapy.[25] This could also be due to higher tumor infiltrate prior to onset of therapy. The change in the drug regimen pattern in the I_2 phase of chemotherapy could probably explain the low occurrence of oral manifestations in these children. Similarly an increase in the oral manifestations was observed with a repetition of I_1 drug regimen in the RI_1 phase. In the consolidation phase of chemotherapy the disease becomes sub clinical and there is less tumor infiltrate resulting from chemotherapy. This may be the reason for children in this phase of treatment to have lesser oral manifestations.

Common oral manifestations from chemotherapy include oral mucositis, gingival bleeding, xerostomia, candidiasis, herpes simplex and bacterial infections.[7,23-26] In the present study mucositis was the most common oral manifestation, followed by mucositis with mucosal ulcer and mucosal ulcer alone. Direct stomatotoxicity develops due to the nonspecific effect of antineoplastic drugs on cells under-

going mitosis. Consequently, the renewal rate of the basal epithelium is reduced, and results in mucosal atrophy, mucositis, and ulceration. According to a recent proposal, chemotherapy-induced mucositis is no longer a simple epithelial process but seems to occur from a series of dynamic and complex molecular and cellular events which take place both in the epithelium and submucosa, resulting in microvascular injury from endothelial-cell apoptosis, increased peripheral-blood levels of tumor necrosis factor and interleukin-6, and genetically induced differences in the rates of tissue apoptosis.[24] Similar findings have been reported in five (71.4%) out of seven ALL Brazilian children with a mean age of 5 years.[26] Oral candidiasis and candidiasis-like lesions were reported in studies conducted on ALL children by various authors.[27,28,29] In the present study oral candidiasis like lesions was the least common oral manifestation observed only in the R I_1 and consolidation phases of chemotherapy. An excessive immune suppression together with gross alteration in the oral microbiota occurs during these two phases of chemotherapy. In addition, opportunistic infections arise from a decrease in normal granulocytes, inspite of severe leucocytosis constituted by nonfunctional blast cells.[15] In our study, the most common site for occurrence of oral manifestations was the buccal mucosa followed by the labial mucosa, tongue, palate, lip and gingiva. Other workers also reported similar sites.[26,27] Frequent occurrence of oral manifestations on soft and hard palate was observed by Gomes et al.[23] Oral mucosal lesions especially mucositis may also occur in the pharynx, oral floor, and lingual mucosal regions.[19] A healthy oral cavity is required to masticate food and maintain nutrition and prevent infection. Oral complications are responsible for oral discomfort, burning sensation, pain, and nutritional deficiences in acute leukemic patients. Patients with mucositis and neutropenia have a relative risk of septicemia that is four times greater than that of individuals without mucositis.[24] Patients suffering from serious, acute complications need more intensive bedside care, medications, parenteral nutritional support, and prolonged hospital stay. Oral care is essential to minimize morbidity and improve the general conditions of the patient before and during oncology treatment. Pediatric dentists should aim at preventive and therapeutic dental care during chemotherapy. There is not only a need for symptomatic relief and management of oral lesions, but also to educate parents /guardians on oral health maintenance.

CONCLUSIONS

ALL children undergoing intensive induction therapy children showed more oral manifestations than those ALL children who were not on chemotherapy.

Among the different phases of chemotherapy, ALL children in the I_1 phase showed highest percentage of oral manifestations.

Mucositis was the most common oral manifestation observed and the buccal mucosa was the frequent site of occurrence.

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