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RECENT UPDATE IN THE MANAGEMENT OF ORAL COMPLICATIONS FOLLOWING CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Mucositis is an unavoidable oral complication during chemotherapy in acute lymphoblastic leukemia. It decreases pH of saliva thereby increases oral infections. Chlorhexidine mouth wash, fluoride toothpaste prevents these complications. Zinc helps in mucous membrane stabilization; regulate taste perception having cofactor alkaline phosphatase within taste bud membrane. Dry mouth, decrease salivation is prevented by sibs of water, chewing gum, and cholinergic drugs. Leukemic children should rinse their mouth with baking soda for cleaning and lubrication. Benzydamine hydrochloride mouth wash prevents dental caries, xerostomia, and mucositis. Ice chips decreases poor entry of drugs to oral mucosa, vasoconstriction, poor blood flow, reduces severity of mucositis. Growth factors stimulate epithelial cell proliferation, decrease mucositis. Sucralfate checks oral infections and pain. Oral exercises are helpful to prevent trismus in leukemic children. Low dose laser therapy may be a choice to prevents secondary infections. Amifostine, Topical Vitamin E, Topical Beta-carotene, Prostaglandin E Lozenge, Glutamine, Granulocyte Colony Stimulating Factor provides a temporary physical barrier or lubricating agents.

KEYWORDS: Acute leukemia, Mucositis, Chemotherapy, Mucosal barrier, Oral complictions, Chlorhexidine mouth wash.

INTRODUCTION

Leukemia is defined as the malignant switch of hematopoietic precursor cells categorized into lymphoid and myeloid lineages based on the type of cell and acute or chronic condition of disease.[1-2] The most common types of cancer based on the rate of incidence in children are acute lymphoblastic leukemia (ALL), central nervous system tumors, and lymphoma respectively constituting half of the total malignancies. It is commonly seen in children but can be found at any age.[1,3] In Bangladesh, though the exact incidence is unknown, there appears to be an increase in the case of childhood malignancies. Yet, if we take the cognizance of incidence of other countries of this region we can presume that 5 to 6 thousand new cases should be diagnosed each year.[4] Pediatric ALL is the most common yet curable childhood malignancy within the pediatric cancers group children.[5-6] It is the most common childhood malignancy and potentially curable.[7] ALL in children is a highly curable disease. Now a day's, cure rate in the western countries between 70-80% and also in Bangladesh.[8] Initial signs and symptoms of acute leukemia appear in the mouth due to infiltration of leukemic cells or decrease in normal marrow elements.[9] The children present with anemia, gingival bleeding, gingival hyperplasia, petechiae, hemorrhages, and ulcerative lesions.[10] When signs and symptoms suggest that patients have leukemia physician should perform blood, bone marrow examination and relevant investigations. Blood and bone marrow examination are the guidance of diagnosis and treatment. Blood samples are taken from a vein in the patient's arm and marrow samples are usually taken from the hip bone. They should have complete blood count (CBC) with differential, bone marrow aspiration**,** and biopsy**,** blood chemistry, coagulation profile, flow cytometry, cytogenetics, lumbar puncture, computed tomography (CT) scan, ultrasonography, and echocardiogram.

The children are treated by multi-agent chemotherapy according to **induction of remission** with Vincristine, Prednisone, L-asparaginase, Daunorubicin, triple-intrathecal methotrexate; **central nervous system directed therapy** with high dose methotrexate; **intensification therapy** to minimize drug resistance by killing any residual cancer cells; and **maintenance therapy** to suppress leukemic cell proliferation in blood by the administration of methotrexate and 6-mercaptopurine for 2.5 to 3 years based on initial cell count and other risk factors.[11] Consequently, leukemic

patient develops mucositis, oral ulcerations and other complications.[12-14]

The complications of chemotherapy are sore throat, laryngeal pain, gingival bleeding, mucositis, mucosal ulcerations, dry mouth, and decreased salivary secretion.[15-16] Fungus is being increasingly recognized as an important determinant of survival in immunocompromised patients. Fungal infections in Bangladesh are diverse and studies have documented their frequency. Among superficial Candida infections, oral thrush is the most common with a prevalence rate of 11.5-14%.[17-18] Chemotherapy causes immunosuppression of normal hemopoietic and secretory cells in rapidly growing oral tissues results mucositis. The ALL children are found with trismus, xerostomia, dysgeusia, epithelium desquamation, malnutrition, fungal, bacterial, and other opportunistic infections.[19]

Chemotherapy

Induction of Remission: Induction is given with 6 or 8 drugs for 28 days: vincristine 1.5mg/m^2 intravenously weekly; prednisone 60mg/m^2 orally 28 days, L-asparaginase 6,000 IU/m^2 from 3rd day for nine doses intramuscularly, Daunorubicin 60 mg/m^2 on day 7, 15, 21 and 28 intravenously, triple intrathecal methotrexate (methotrexate-12.5mg, hydrocortisone-25 mg, cytarabine-30mg) four to six doses weekly. With these regimens cure rate is about 95%. Remission (less than 5% blast cell in bone marrow and no blast in peripheral blood film) is a known prerequisite for prolonged survival. ***CNS Directed Therapy:*** Intensive therapy is required to treat central nervous leukemia. Astrocytes cause chemotherapeutic agents not readily cross the barrier. This acts as a sanctuary site for leukemic infiltrates, as chemotherapeutic agents not able to cross the barrier. So, cranial irradiation and or weekly triple intrathecal methotrexate, cytarabine, and hydrocortisone are usually practiced. ***Intensification:*** Intensification is usually advocated to minimize drug resistance through the killing of any residual leukemic cells. ***Maintenance:*** Maintenance therapy is designed to suppress leukemic cell proliferation in blood by administration of methotrexate and 6-mercaptopurine for 2.5 to 3 years depending on initial cell count and other risk factors (Serum LDH, mediastinal mass, hypo or hyper diploidy, cytogenic abnormalities, etc). Blood counts begin to fall within five to seven days after each cycle of chemotherapy and remain low for 2 to 3 weeks.[11] Pediatric dentists, nurses, and health care providers are required to assess the condition of patient before, during, and after chemotherapy.[20] Protocol-based oral care management are required to reduce the risk of infections and systemic complications.[21]

Complications

Primary: Starts from leuke
mic cells infiltration in the gingiva and oral bone results gingival hypertrophy. **Secondary:** Associated with direct effect of chemotherapy results anemia, infections, thrombocytopenia causing bleeding, infection, oral ulcer. **Tertiary:** Mucositis, ulcerations, skin desquamation, gingival bleeding, altered test sensation, xerostomia, candidiasis, dysphagia, decrease salivary flow, caries tooth, and opportunistic infections.[22-23]

Hematologicl

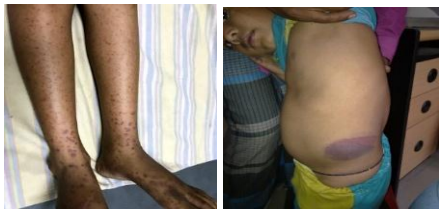
Thrombocytopenia, neutropenia, or impaired functions of neutrophil are due to effects of chemotherapy. Leukemic cell induces oral mucosal change including pain, gingival swelling, bleeding, ulceration, and infections. All these features are associated with changes of hematological parameters like, platelet counts below 10,000 to 20,000/mm^3.[24-27]

(1) Absolute Neutrophil Count Absolute neutrophil count >1,000/mm^3, no need of a prophylactic antibiotics;[21] some authors suggest antibiotic support,[28] when absolute neutrophil count (1,000-2,000/mm^3)[29] Antibiotics are usually practiced with neutropenia. If there is an infection, vigorous antibiotic is needed. When absolute neutrophil count <1,000/mm^3: elective oro-dental care is withheld until absolute count rises. Neutropenia in acute leukemia is prone to develop infections. Before chemotherapy hematological and other relevant investigations and appropriate management is important.

(2) Platelet Count: Platelet count>75,000/mm^3: Dentist and other related personnel should be prepared for the management of prolonged bleeding. When platelet count is 40,000 to 75,000/mm^3: platelet transfusions should be considered before and 24 hours postoperatively. Prolonged bleeding following local procedures are requiring sutures, homeostatic agents, pressure packs, or gelatin foams. When platelet counts <40,000/mm^3: elective oro-dental care is avoided. Supportive measures like; platelet transfusions and control of bleeding hospital admission should be confirmed before the procedure.[21] Hematological investigations (platelet count) are necessary to assess bleeding which should be managed by transfusion of platelet concentrate.

Petechia and Purpura

Petechiae and purpura in acute leukemia are manifested in oral cavity as multiple bleeding areas.[30-31] This is found in leukemic children as a tiny, purple, red, or brown spot in skin (Figure 1A). This can be hemorrhagic diathesis or coagulation disorders. Children taking anticoagulants may present with oral petechiae in buccal mucosa or tongue which may be injured while chewing food. Petechiae in oral mucosa may also be encountered in liver cirrhosis and end-stage renal disease undergoing dialysis.[32-34]



(A) (B)

Figure 1: Petechiae: tiny purple, red, or brown spots on the skin (A); ecchymosis: flat, blue or purple patch measuring 1 centimeter or more in diameter (B)

Ecchymosis

ALL patients on chemotherapy often show signs of bleeding or hemorrhage from the skin and oral cavity. Ecchymosis varies from minor bleeding to hematoma of inflamed gingiva, or hemorrhage due to severity of thrombocytopenia, oral hygiene status, and sharp tooth. Gingiva, buccal mucosa, tongue, floor of the mouth, hard and soft palates are most common sites of ecchymosis. It is commonly found on the tongue in leukemic children. Trauma associated with oral infections also induces hemorrhage. Spontaneous ecchymosis is found as a flat, blue, or purple patch measuring 1 centimeter or more in diameter (Figure1B) when platelet count falls below 20,000 per mm.[3] The intraoral bleeding is alarming to patients and caregivers;[22] bleeding from gum following brushing require platelet transfusion when platelet count around 50,000 per mm.[3]

Gingival Hypertrophy

Gum swelling is usually caused by local inflammations, food impaction, or mouth breathing. Hormonal changes, drug (cyclosporine), or tumor infiltrates causes gingival swelling.[35-36] This may be secondary to infiltration of gingival tissue characterized by progressive enlargement of interdental papillae and gingiva. In leukemic children crowns of teeth are covered by infiltrative growth. Gum is swollen, devoid of stippling, and pale red to deep purple in color predisposes to bleed.[30] Gingival hyperplasia resolves completely or partly with chemotherapy.[30,32] Gum hypertrophy is caused by poor oral hygiene, medications, systemic illnesses, genetic, and idiopathic.[37-41] Leukemic infiltrations[42-43] causes swelling of gum (Figure 2) influences to hypoxia of oral tissues. Mild touch to gum causes bleeding in the infected area. Dental plaque increases hypertrophy and induces manifestations of systemic diseases. Periodontal treatment is required when systemic signs and symptoms are controlled by chemotherapy.[43] Mild to moderate gum inflammations[44] cases a significant deterioration of gingiva,[45] is associated with duration of chemotherapy.[46]

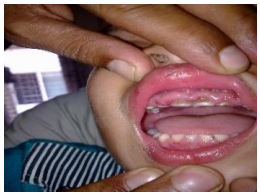


Figure 2: Painless discrete, fibrous gingival swelling between upper right central incisor and left canine due to leukemic infiltrations.

Gingival Ulceration

Gingival ulceration is often present atypical dental abscess as soft tissue necrosis without swelling, and recrudescence. Herpes simplex virus infection presents with widespread lesions affecting both keratinized and non-keratinized tissue with colonization by *Candida albicans*.[32,47] The oral colonization of *Candida albicans* is invariably found in children with ALL.

The gingival ulcerations are secondary neither to leucopenia nor to neoplastic infiltrations.[48] Gingival mucous membrane ulceration is found with other associated clinical conditions.[49-50] Increased incidence of ulcers, coated tongue, fetor oris, shallow papillae, tender oral mucosa, and mucosal infections are common.[51-54] Soft palate, oropharynx, buccal and labial mucosa, the floor of the mouth, ventral and lateral surfaces of the tongue are affected.[23] Administration of antifolates and corticosteroids with concurrent use of other chemotherapy influence oral lesions.[55-56] The manifestation of infiltrations are found as chloroma.[24-25] Various intensities of mucositis and pathological lesions are observed during 48 hours to 6 months of chemotherapy because of abnormal hematological parameters related to the intensity of chemotherapy.[57] Gingival ulceration and neutropenia are found three to four days of high dose methotrexate ($5gm/m^2$),[58] which require folic acid antagonist (folinic acid) to rescue. This causes more rapid epithelial mitotic rate because of epidermal growth factor receptors.[22] This causes eating difficulty, weight loss, anorexia, cachexia, and dehydration,[59] and require proper management.

Infections

Of all oral infections 51.5% are fungal, 33.1% bacterial,15.1% viral, and 19.1% polymicrobial.[60] *Fungal:* Fungal infections causing death in bone marrow aplasia.[61] Risk factors for disseminated or invasive fungal infections are therapy-induced mucositis, hyperalimentation. Repeated blood transfusions cause iron overload and impaired iron utilization which invites fungal infections. Indwelling catheters are associated with fungal infections by *Candida parapsilosis* and cardiac involvement by disseminated fungal infections,[62] although *Candida* species are conventional oral flora in immunocompromised children. Dry oral cavity triggers infections by *Candida* species; the most common opportunistic infections in oral soft tissues.[63] *The Candida* spp. are attached to the epithelial surface via extracellular polymeric materials that

penetrate by the release of enzymes. A soft white adherent erythematous painful eroded patch is found in oral mucosa as pseudomembranous candidiasis. Oral thrush traditionally a classical "curdled milk appearance"; scraping shows the lesions as pinpoint hemorrhagic areas.[64] Appearance is due to atrophy of oral mucosa and increased vascularization.[65] Acute pseudomembranous candidiasis progresses to angular cheilitis. The prevalence of oral candidiasis is 6.12%,[66] less than previous observations,[26,67] but this is found in every patient with ALL.

Bacterial: Oral infections or poor oral hygiene lead to a significant decrease in pH of saliva (5.7 ± 0.58 vs. 6.19 ± 0.56) in ALL. With low salivary pH cumulative effects of other risk factors are increased.[68] Poor oral hygiene and scurvy are associated with gum bleeding.[69] There are increased proliferation and colonization of Gram-negative bacteria including *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella*, and *Enterobacter* species.[70-71] *Staphylococcus* and *Enterococcus* have been isolated from oral mucosa in immunocompromised patients.[42] The oral cavity is a source of bacterial and fungal septicemias.[72] Other infections (tuberculosis and pneumonia) are also reported.[22] ALL children are found with Gram-negative, obligatory aerobes, rod-shaped bacteria (*Burkholderia cepacia*).

Viral: A high prevalence of Herpes Simplex Virus infection is found with chemotherapy which is reactivated ulcers rather than primary infection.[73] The immunocompromised ALL children are very much susceptible to viral infection. Herpes simplex, varicella-zoster, cytomegalovirus, adenovirus, and Epstein-Barr virus are observed. Herpes simplex virus infection manifest as multiple ulcers at the corners of the mouth, lips, palate, and gingiva. Erythema is seen around the ulcerative lesions.

Movement Restriction

Long term chemotherapy destroys joint causing pain and restricted movement in temporomandibular joint (TMJ).[74] Tenderness, mucositis, high decay missing-filled are common in long term chemotherapy. Acute leukemia and TMJ association has been inadequately addressed,[45] but it is found after chemotherapy. Restricted movement in TMJ causes edema, cellular destruction, and muscular fibrosis.[22] Inadequate oral hygiene hamper oral health status or infection leads to restricted mouth opening. Bad oral hygiene predisposes to infection causing fibrosis of joints. Long-term chemotherapy causes weakness of periodontal structures, gum infections, and loosening of teeth. Restricted mouth opening, dental caries, periodontal disease, and occlusion difficulties generally are not found without chemotherapy.[75]

Dysgeusia

Dysgeusia is found either due to ALL or therapeutic interventions affect daily activities lead to malnutrition, weight loss.[76-77] Chemotherapy causes dysgeusia by insulting gustatory cells and damage of mucous membrane of mouth. High viscosity and minimal salivary flow, eatable substances do not reach taste buds situated in the posterior part of tongue cause dysgeusia or bitter and sour. Enough fluid intake is advised which washesout debris and improve taste sensation. Dysgeusia is often temporary because affected buds regenerate normally within 2-12 months after myelosuppressive therapy.[78] The turnover rate of normal human taste bud cells is 10 days, and life span of olfactory receptor cells is about a week. Chemotherapy kills the cells with high turnover rates. The rapidly growing cells are more vulnerable to chemotherapy and dose adjustment is very important. Dysgeusia that leukemic patient's experiences are extraneous substances produced by poor oral hygiene, infections, postnasal drip, gastrointestinal reflux, and mucositis.[79] Chemotherapy decreases the life span of olfactory receptors which results in abnormal taste sensation. Regular fluid intake is advised to keep oral cavity moist and free from infections.

Salivary pH

Oral infections in ALL cause decrease pH of saliva which increases the chance of infections. In low salivary pH cumulative effects of other risk factors are increased.[68] Low salivary pH causes accumulation of dental plaque, increased frequency of gingivitis, and xerostomia which required treatment.[22,68] Maintenance of oral hygiene from the beginning should be performed because low pH of saliva leads to gingival infections. Chemotherapy cause saliva changes quantitatively, qualitatively, increase viscosity and proportion of organic material. The inhibitory effects of cytotoxic drugs on salivary glands contributed to low salivary pH.[80] Buffering capacity and electrolyte levels of saliva are changed in leukemic children. Low pH causes oral flora to shifts from Gram-positive to Gram-negative. [23] Saliva contains a wide range of organic and inorganic buffering agents that neutralizes acidic products of oral bacteria. It is a major determinant of an individual's susceptibility to dental caries.[46,80-83] Low salivary pH remains stable even years after recovery from the disease.[84] Decreased salivary flow and increased viscosity results in speech difficulty, chewing and swallowing. It also increases the prevalence of candidiasis, periodontal disease, and caries. Low pH hampers function of taste buds resulting in taste alteration, dislike of food which complicates episodic nausea, vomiting, pain, and discomfort.[22] Decrease salivary flow causes decrease levels of phosphorous and calcium ion.[51] Saliva in healthy children helps easy chewing and swallowing. Blockage in salivary flow invites infections and leading to periodontal infections, anorexia, and vomiting.

Oral Status

An oral lesion in children causes painful ulcerations leads to poor nutrition, dehydration, and threatening to life. Inappropriate oral hygiene invites infections,

increases the duration of therapy.[85-90] After chemotherapy oral cavity becomes dry, ulcerated, chance of dental decay due to reduced salivary flow and buffering capacity. Leukemic children suffer from oxidative stress which results in inflammation by oral pathogens.[46]Chemotherapy modifies oral environment and increases plaque and gingival indices.[91] Maintenance of an infection-free oral cavity is required to minimize the negative effects.[44] Children maintaining good oral hygiene are found with favourable condition during chemotherapy.[92] Debilitating disease becomes a difficult job to maintain oral hygiene practice.[93] Plan wise assessment of mucositis and maintenance of optimum oral hygiene is essential during treatment.

Mucosa membrane dueing chemotherapy are found pale, ecchymosed, hematoma,[94] pain and discomfort.[95-97] Erythema, mucosal lesion, and desquamating plaques causes pain.[98-99] Previous viral infections cause oral pain, dental ache, mucosal ulceration, and bad oral smell. The direct and indirect effects of chemotherapy affect rapidly growing cells in the oral mucosa membrane.[100] Direct effects are due to chemotherapeutic agents on the cell proliferation, maturation, and replacement. The renewal rate of basal epithelium in oral cavity is decreased which results in ulcer, atrophy, and mucositis. Indirect effects cause myelosuppression which regulates immune system and repair process; results infection and mucositis.[101]

Dental Caries

Chemotherapy affects the salivary gland and oral microflora.in the mouth cavity.[22] It changes the pH of saliva by decreasing parotid gland secretion. Decrease salivary flow leads to accumulation of bacteria, viruses in mouth cavity which infect gum, and loosening of teeth. The leukemic children are found with a high prevalence of caries tooth, high decayed, missing and filled teeth.[45-46,102] The number of decayed teeth in primary dentition is more than permanent dentition due to inadequacy in manual dexterity in early stage and prolonged time of exposure of primary teeth by bacterial plaque.[44] Early and prolong period of chemotherapy causes decayed teeth in the primary dentition.

Decayed, missing, and filled teeth scores are found no significant difference between leukemic children,[103] due to maintenance of oral hygiene. Caries' teeth before and after chemotherapy are found no significant difference.[104] Prolonged antifungal drugs cause caries tooth,[105] sugar-containing nystatin results decrease salivary flow. Dental plaque is attached to the dental surface cause fermentation and infections.[46] Chemotherapy causes an inflammatory change in oral mucosa thus preventing maintenance of oral hygiene.[106-07] Children should be prohibited from the use of mechanical dental cleansing aids as it triggers bleeding tendencies. Alkaline saline rinses warm water with salt and sodium bicarbonate are useful.[108] The children should maintain oral hygiene by Chlorhexidine mouth wash during the period of chemotherapy.

Dental Anomalies

During chemotherapy the dento-alveolar complex is affected at the time of its formation.[109] The association depends on age at diagnosis, type, and doses of chemotherapy.[110-15] Chemotherapy affects healthy cells at proliferative stages of the growing tooth buds. The younger age children have more destructive effect than older. Higher the dose more toxic effect to dento-alveolar complex. It interferes with DNA synthesis, replication, RNA transcription, and cytoplasmic transport mechanisms. It also causes hypomineralization or hypomaturation of the enamel of tooth and formation of short, thin, tapered root.[110] Defective enamel and dentin are found as deformed, discolored crowns.[115] Dental anomalies during chemotherapy are 82%[116], 80%[117], and 28%.[118] The dose, duration, and drugs should be approptiately adjusted before treatment.

Prolonged Effect

The age of the child is important during odontogenesis.[119-21] The changes are microdontia, agenesis, change in crown or root, defective mineralization, and late eruption. There is alteration in tooth size, shape; growth center maturation of facial bones.[122] Children before 5 years are found with more severe dental defects and immature teeth than after 5 years.[19] Delay in dental development, hypoplasia, and microdontia are found in children who received a prolonged period of chemotherapy.[116]

Dental Maturation

Cyclophosphamide causes more malformed teeth than vincristine because of increased secretory activity on microtubules and microfilaments during developmental stage. Long term chemotherapy causes soft tissue deposits, severe gingivitis and periodontal involvement, dentofacial and tooth abnormalities or agenesis, and root hypoplasia.[91] Hypodontia are common with prolonged therapy that affect growing tooth buds and developing tooth.[45] The effect on bone, soft tissues, and blood vessels are less in growing children.[110] Dental development, microdontia, malformed teeth, changes in histology of odontoblasts, basal pulp are observed.[111-13] Dental agenesis, microdontia, taper roots, short roots teeth, enlarged pulp chambers, hypoplasia, supernumerary teeth ate also reported.[117] The odontoblastic activity alters the morphology of a developing tooth.[111,123] Hypoplastic teeth are associated with the duration of treatment.[124] The craniofacial abnormalities are more common in younger age children.[125] Chemotherapy causes microdontia, tooth agenesis, and enamel dysplasia.[126] Root tapering or narrowing, blunting of root apex, and loss of root length are also reported.[127] Colchicine, vinblastine, and cyclophosphamide alter odontogenesis.[128] We have also four some patient with such anomalies. The younger age is prone to have root stunting, microdontia, hypodontia,

taurodontia, and retention of primary dentition than older.[129] The maturation defect is found before 5 years.[128-30] The secretory over activity of chemotherapeutic agents in developing tooth buds causes loss of tooth structure that leads to hypoplasia of mandible, short root teeth. The enamel hypoplasias are more common in anterior than posterior teeth. These are found when exposed to cytotoxic therapy and results altered ameloblasts during secretory or postsecretory phase,[130-34] immature teeth are more commonly affected than mature teeth.[135]

Principle of Management

Parents should be well informed to maintain oral hygiene practice of their child throughout therapy.[136] Health care providers should educate regarding good oral hygiene schedule.[137] Early initiation of antifungal therapy is fundamental to prevent mucositis because its delay is associated with increased mortality due to candidemia.[138] Soft toothbrush is an effective method to reduce the risk of bleeding, gingivitis.[139] Chronic periodontal infection should be treated chlorhexidine mouth wash.[29,140] Sodium bicarbonate mouth wash or saline are used to dilutes mucous secretion which moistens oral mucosa, increases oral pH and inhibition colonization of *Candida albicans.*[141]

Oral pediatric medications contain sucrose which makes patients susceptible to dental infections. Dental caries or mucositis are prevented with fluoride supplements and neutral fluoride rinses or gels. Chlorhexidine mouth wash is effective to suppress virulent micro-organisms.[142] If needed, the operation area must be sterile and no bony edges margin remains there before closure of the wounds.[143] A tooth can be extracted when platelet count 50,000/mm^3, but a minimum 100,000/mm^3 is required for the extraction of an impacted tooth.[144] The local hemostatic must be applied to stop further bleeding. A fixed orthodontic appliances act as mechanical irritants thus potentiates secondary infections.[145]

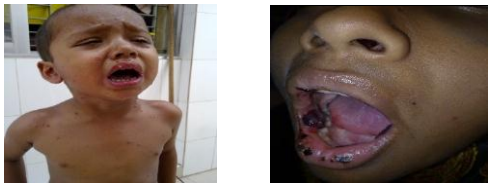
Before Chemotherapy

Identification, removal, elimination of infective sources, local irritants or dormant lesion; a reminder to maintain oral hygiene; and know about acute, late complications.[146] Consultation with a dentist about the present condition and make a schedule of treatment. The patient should have a medical history, hematological test, oral examination including x-ray, and protocol of treatment. In medical history; disease type, stage, prognosis, treatment; surgery or chemotherapy, medications; allergies, hematological status; complete blood count, coagulation status, immune status, and presence of catheter are ensured. The American Heart Association (AHA) recommends antibiotic prophylaxis only during placement of devices to prevent infections.[147-48] The dentist should examine the oral cavity: removal of periapical lesions if any and periodontal health status, checking for any dental aids and removal of infected prostheses and x-ray peri-apical and panoramic view should be done if required. Before chemotherapy, prophylactic chlorhexidine mouth wash should be started and removal of tartar is being ensured.[19] The non-viable teeth, artificial dentures, or any dental plug should be extracted.

During Chemotherapy

The children should maintain oral hygiene; and should avoid secondary infections; awareness for infection free oral cavity. The most frequent oral complication during chemotherapy is mucositis. The children are associated with neutropenia.[146,149] Ensure the treatment of mucositis, oral ulcer, oral thrush, xerostomia. They should perform oral hygiene with chlorhexidine rinses and fluoridation. Analgesics (paracetamol) are given for relief of pain. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be prescribed. Antibiotics should be adjusted based on the renal function test. No elective dental treatment is indicated but emergency oro-dental care is given when required.[147]

Importance of Mucositis: Oral mucositis is painful affects dietary intake and quality of life.[150] It develops within two weeks of chemotherapy,[151-52] erythema of oral mucosa leads to erosion, ulceration, and excoriation. (Figure 3 A,B).



(A) (B)

Figure 3: Extensive mucositis, tooth infection both upper and lower jaw. (A, B)

Mucositis is found in the non-keratinized area in oral cavity.[153] The severity of mucositis is related to the dose of chemotherapy.[154] It causes severe pain and weight loss (≥5%) compared to normal,[155] compromises the outcome of therapy.[156] Good oral hygiene practice decreases mucositis.[51] The dose of chemotherapeutic agents should be adjusted meticulously.

Assessment of Oral Mucositis.[157] World Health Organization (WHO) established assessment scales for oral mucositis. Grade I and grade II oral mucositis requires a soft brush using fluoride gel toothpaste and rinse with salt and bicarbonate solution. Grade III oral mucositis requires salt and bicarbonate solution wash 3-4 times a day. Grade IV oral mucositis requires to wash the oral cavity with salt and bicarbonate solution 3-4 times a day. WHO,[11] National Institute of Health and National Cancer Institute:[158] reported oral assessment guidelines: Grade 0: asymptomatic or mild: no maneuver is required, Grade 1: moderate pain, no difficulties with oral intake; modified diet is advised, Grade 2: severe pain, difficulties with oral intake, Grade 3: life-threatening

condition, an urgent maneuver is required, Grade 4: patient is expired.

The health care providers require early assessments to identify oral complications. They should teach the patients how to perform oral assessments correctly so that they can report any change in the oral cavity. Pre-chemotherapy dental evaluation, mouth-care, antibiotics, and analgesic decreases oral discomfort and complications.[159] Mucositis more or less found in every patient with chemotherapy which can be controlled but severe mucositis must be handled properly.

Oral Care Plan[157] First step to prevent mucositis is the maintenance of oral hygiene. Incidence and severity of mucositis decrease pain that have followed the ideal method of tooth brushing and mouth wash with 0.9% saline rinse.[160] Soft toothbrushes with normal saline gurgling prevent colonization. Oral hygiene practice should be started 24 hours before 10 days following chemotherapy. Oral lesions decrease in severity and duration with regular with chlorhexidine mouth wash.[161] Bottles of mouthwash with chlorhexidine decrease infections and other complications.

Prevention of Oral Mucositis[152] Various agents are used for the prevention of oral mucositis. Multinational Association for Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) has developed clinical guidelines: (1) control of pain (2) nutritional supplement (3) decontamination of oral cavity (4) palliation of dry mouth (5) bleeding management and drug for mucositis.

Control of Pain[152] Mucositis seriously affects nutritional intake, oral care, and quality of life because of pain. Mouth rinses with saline, ice chips, and topical mouth wash with 2% viscous lidocaine relieve pain. A stepwise approach of oral wash (saline solution, sodium bicarbonate), topical lidocaine, benzocaine, diphenhydramine mouthwashes, lidocaine, and combinations of aluminum hydroxide; magnesium hydroxide, simethicone, and mucosal surface protectants sucralfate solutions are recommended. If no improvement with these drugs systemic analgesics are advocated.[162]

Nutritional Support[152] Nutritional intake in leukemic children is severely affected with oral mucositis. It alters taste sensation during chemotherapy. [157] A nasogastric tube is required who are susceptible to extensive mucositis. These children are increased risks of infection, electrolyte abnormalities, and cholestatic liver disease.[163] Parenteral nutrition should be given who fail to maintain adequate oral nutrition. Nutritional improvement is vital for a good outcome.

Decontamination[157] Microbial colonization in oral mucosa exacerbates the severity of oral mucositis in leukemic children. Decontamination will reduce the severity of mucositis. Severe mucositis is three times more common to develop septicemia than without mucositis.[11,157] Chlorhexidine is an effective antimicrobial agent and topical prophylactic against oral mucositis and candidiasis. It is a local anesthetic, anti-inflammatory agent against the antimicrobial activity. Benzydamine is found with more mucositis (48%) than chlorhexidine (26%). Chlorhexidine cause decreased evidence of pain, difficulty in eating, chewing and swallowing.[164] Chlorhexidine mouthwash is preventive against contamination of oral infection and keeps the oral cavity healthy in immunocompromised children.

Prevention of Dry Mouth[152] Children are often developing sudden or permanent dry mouth, decreased salivation which potentiates inflammation of oral tissues increases the risk of local infection, and makes mastication difficult. They are advised to take a small amount of water to reduce dryness, rinse with baking soda to clean, lubricate oral tissues. Chewing gum and cholinergic drugs are added to stimulate salivation. Frequent taking of a small amount of fluid is encouraged.

Local Bleeding[152] Fibrin glue or gelatin gauge can be used to control local intra-oral bleeding. In some situations, Tranexamic acid can be given locally to control bleeding.

After Chemotherapy

ALL children should maintain good oral hygiene to the prevention of infection. The children with xerostomia, trismus, mucositis should be follow-up every 6 months' interval. Moderate to severe mucositis should follow-up for any change in oral mucosa for five years (risk of relapse is reduced when a patient is no longer on chemotherapy).[147,165] Pediatric Hemato-Oncologist and dentists should consult on the immune status of the child and they should inform about the importance of oral hygiene, mouthwashes with chlorhexidine, and elective dental treatment.[147] The parents are advised to ensure improved nutritional support of their child throughout therapy.

Recent Update

Zinc Supplement: Zinc is a micronutrient that is found with a deficient state of the disease. It causes epithelial and mucous membrane stabilization and should be given from the beginning of treatment. The specific role of zinc concerning taste perception is unknown, but this is a recognized cofactor of alkaline phosphatase, the most abundant enzyme within the taste bud membrane. This may play a pivotal role in the confirmation of proteins which involved in the regulation of pores of taste bud microvilli.[166-67] Role of zinc gluconate in the management of abnormal test sensation in non-cancer patient improve the general gustatory function and general mood scores in patients with dysgeusia.[76] Zinc supplement therapy thus prevent altered taste sensation and should be practiced in ALL during chemotherapy.

Cryotherapy:[154] Application of ice chips in the mouth causes poor entry of drugs to oral mucous membranes due to vasoconstriction and poor blood flow. Ice reduces the severity of oral mucositis.[168-70] Management of oral mucositis with 2% lidocaine rinses along with 0.12-0.2% chlorhexidine is an ideal alternative.[162] A regular spray containing collagen precursor amino acids with sodium hyaluronate found the immediate and excellent result to relieve pain and rapid healing of the mucous membrane.[171] Chlorhexidine mouth wash should be practiced from the initial day throughout the maintenance period.

***Growth* Factors:**[152] Growth factors stimulate epithelial cell proliferation. It significantly decreases the incidence of oral mucositis in ALL receiving high-dose chemotherapy.[172] Intravenous Human Fibroblast Growth Factor-20 recently in a clinical trial is administered intravenously for treatment and prevention of oral mucositis.[173] Though intravenous growth factors not usually practiced; but could be given during high dose methotrexate therapy in leukemic children.

Anti-inflammatory Drugs:[152] Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cytokine (TNF-α). In general, NSAIDs are known to have anti-inflammatory properties, including suppression of the cyclooxygenase pathway and inhibition of the production of pro-inflammatory prostaglandins. Benzydamine hydrochloride has been shown to inhibit inflammatory cytokine production, such as TNF-α and IL-1β. Benzydamine hydrochloride mouth wash reduces the severity of oral mucositis in children receiving chemotherapy.[174]

Antioxidants: N-acetyl cysteine can stimulate glutathione synthesis and scavenge free radicals. N-acetyl cysteine inhibits the activation of NF-κB, leading to an increase in an inflammatory response. N-acetyl cysteine significantly reduces the incidence of severe oral mucositis in the immunocompromised patient.[175]

Glutamine:[157] During chemotherapy glutamine stores decreases which results from the development of oral mucositis.[176] Glutamine supplement decreases the duration of mucositis and pain.[177] Glutamine can be practiced in children to prevent mucositis in leukemic children.

Sucralfate:[157] The basic principle for the protective action of sucralfate is an enhancement of natural defensive mechanisms thus stimulating mucus secretion, bicarbonate, prostaglandin release, and mucosal cell renewal.[178] The children who received sucralfate suspension developed 58% bacterial colonization compared to 92% who not received sucralfate. About 58% of children received this suspension complains of no oral pain compared to 25% receiving placebo.[179] Sucralfate suspension should be given from the beginning of chemotherapy preventing infections and pain.

Palifermin:[157] About 88% of patients receiving placebo are found in grade II or higher mucositis, compared to only 44% of palifermin treated children (44%). This stimulates proliferation, differentiation, and migration of epithelial cells throughout the gastrointestinal tract thus prevents mucositis.[180] Palifermin prevents mucositis and speeds the healing of severe sores in the mouth.

Low Dose Laser Therapy:[152] Low dose laser therapy stimulates healing of wounds in oral mucositis of leukemic children,[169] through the acceleration of mitochondrial ATP, growth factors release, excessive fibroblasts production, detoxification of free radicals, excess microcirculation. It significantly reduces the incidence and duration of grades 3 and 4 oral mucositis. Low dose laser therapy decreases chance of secondary infection thus rapidly progress to healthy nutrition.[181]

Mucosal Barrier: Mucosal coating agents are effective to provide a temporary physical barrier. Water-soluble lubricating agents moisten mucosa if the patient developed dry mouth. Amifostine, Topical Vitamin E, Topical Beta-carotene, Prostaglandin E Lozenge, Glutamine, Granulocyte Colony Stimulating Factor have been proposed a mucosal barrier to prevent oral mucositis:[182] Regular intake of a small amount of water washes out food debris and keeps the mouth moist; provide a temporary mucosal barrier to prevent infection in leukemic children.

CONCLUSION

The key to success in maintaining a healthy oral cavity during cancer therapy is patient compliance. Mucositis, gum bleeding, oral ulceration, cavities, oral pain, dysgeusia, and dry mouth are common during chemotherapy in ALL. Chlorhexidine mouth wash and toothpaste containing fluoride gel is an effective tool. Zinc has epithelial and mucous membrane stabilization, taste perception, and regulation of pores in taste bud microvilli. Children should rinse mouth and lubricate with baking soda. Chewing gum and cholinergic drugs control pain and stimulate saliva secretion. Benzydamine hydrochloride mouth wash, N-acetyl cysteine, Sucralfate prevent dental caries, pain, xerostomia, and mucositis. Ice chips cause poor entry of drugs to oral mucosa, vasoconstriction, poor blood flow, and reduces the severity of mucositis. Low dose laser therapy is instrumental to decrease the chance of secondary infections. Intravenous Human fibroblast growth factor-20 can be administered intravenously to prevent oral mucositis. Palifermin stimulates the proliferation and differentiation of epithelial cells. Amifostine, Topical Vitamin E, Topical Beta-carotene, Prostaglandin E Lozenge, Glutamine, Granulocyte Colony Stimulating Factor provide as oral lubricating agents. The participation of pediatric dentists, nutritionists, and counselors in the hematology and oncology team is of

irrefutable importance in reducing complications before, during, and, after treatment in ALL.

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Ethicial Issue
The confidentiality and responsibility of patients have followed the method of the World Medical Association Declaration of Helsinki, 2000.

Conflict of Interests
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REFERENCES

1. Hayati H, Kebriaeezadeh A, Ehsani MA, Nikfar S, Sari AA, Troski M, Tigabu BM. Treatment costs for pediatrics acute lymphoblastic leukemia; comparing clinical expenditures in developed and developing countries: A review article. Int J Pediatr, 2016; 4(12): 4033-41.
2. Van Cutsem E, Cunningham D, Maroun J, Cervantes A, Glimelius B. Raltitrexed: Current clinical status and future directions. Ann Oncol, 2002; 13(4): 513-22.
3. Bao PP, Zheng Y, Wang CF, Gu K, Jin F, Lu W. Time trends and characteristics of childhood cancer among children age 0-14 in Shanghai. Pediatr Blood Cancer, 2009; 53(1): 13-6.
4. Maanan MA. Pediatric Oncology Bangladesh-The long safari. Bangladesh J Child Health, 2003; 27: 34-35.
5. Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, Conter V, Otten J, Ohara J, Versluys AB, Escherich. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med, 2012; 366(15): 1371-81.
6. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia, N. Eng J Med, 2006; 354: 166-78.
7. Islam A, Akhter A, Eden T. Cost of treatment for children with acute lymphoblastic leukemia in Bangladesh. J Cancer Policy, 2015; 6: 37-43.
8. Veerman AJP. Acute lymphoblastic leukemia in children: Experiences in West and East. Bangladesh J Child Health, 2003; 27: 16-17.
9. IIgenli T, Oren H, Uysal K. The acute effects of chemotherapy on the oral cavity. Prevention and management. Turkish J Cancer, 2001; 31(3): 93-105.
10. Deliverska EG, Krasteva A. Oral signs of leukemia and dental management- literature data and case report. J IMAB, 2013; 19(4): 388-91.
11. World Health Organization. Handbook for Reporting Results of Cancer Treatment, World Health Organization, Geneva, Switzerland, 1997.
12. Farber S, Diamond LK, Mercer RD, Sylvester RF, Jr. Wolff JA. Temporary remissions in acute leukemia in children produced by the folic acid antagonist, 4-aminopropyl-glutamic acid (aminopterin). N Eng J Med, 1948; 238: 787-93.
13. George SL, Aur RJA, Mauer AM, Simone JV. A reappraisal of the results of stopping therapy in childhood leukemia. N Eng J Med, 1979; 300(6): 269-73.
14. Evans AE, Gilbert ES, Zandstra R. The increasing incidence of central nervous system leukemia in children (Children's Cancer Study Group A). Cancer, 1970; 26(2): 404-09.
15. Margolin JF, Steuber CP, and Poplack DG. Acute lymphoblastic leukemia. in *Principles and Practice of Pediatric Oncology*, P. A. Pizzo and D. G. Poplack, Eds., Lippincott Williams & Wilkins, Philadelphia, PA, USA, 4th edition, 2002; 489-544.
16. Hou GL, Huang JS, Tsai CC. Analysis of oral manifestations of leukemia: a retrospective study. Oral Diseases, 1997; 3(1): 31-38.
17. Rahim MR, Saleh AA. Miah MRA, Anwar S, Rahman MM. The pattern of dermatophyte in Bangabandhu Sheikh Mujib Medical University. Bangladesh J Med Microbiol, 2012; 6(2): 11-14.
18. Rehman MH, Hadiuzzaman M, Bhuiyan MKJ, Nahida I, Parvin AN, Mumu SA, Chowudhary IJ. Prevalence of superficial fungal infections in the rural areas of Bangladesh. Iran J Dermatol, 2011; 14(3): 86-91.
19. Barberıa E, Hernandez C, Miralles V, Maroto M. Paediatric patients receiving oncology therapy: a review of the literature and oral management guidelines. Euro J Paed Dent, 2008; 9(4): 188-94.
20. Oral Complications of Chemotherapy and Head/Neck Radiation (PDQ), Bethesda, MD, USA, http://cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/Health Professional, 2016.
21. Little JW, Falace D, Miller C, Rhodus NL. Dental management of the medically compromised patient, Mosby, St. Louis, Mo, USA, 7th edition, 2017.
22. Mathur VP, Dhillon JK, Kalra G. Oral health in children with leukemia. Indian J Palliat Care, 2012; 18(1): 12-18.
23. Emidio TCS, Maeda YC, Caldo-Teixeria AS, Puppin-Rontani RM. Oral manifestations of leukemia and antineoplastic treatment-A literature review (part II). Braz J Health, 2010; 1(2): 136-49.
24. Burke VP, Startzell JM. The leukemias. Oral Maxillofacial Surg Clin N Am, 2008; 20(4): 597-608.
25. Aronovich S, Connolly TW. Pericoronitis as an initial manifestation of Acute Lymphoblastic Leukaemia: A Case Report. J Oral Maxillofac Surg, 2008; 66(4): 804-08.

26. Fatahzadeh M, Krakow AM. The manifestation of acute monocytic leukemia in the oral cavity: A case report. Spec Care Dentist, 2008; 28(5): 190-94.
27. Benson RE, Rodd HD, North S, Loescher AR, Farthing PM, Payne M. Leukaemic infiltration of the mandible in a young girl. Int J Paediatr Dent, 2007; 17(2): 145-50.
28. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahahi M, Baltimore RS, Newburger JW, Strom BL, Tani LY,Gerber M, Bonow RO, Pollasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT. Prevention of infective endocaeditis.The Council on Scientific Affairs of the American Dental Association has approved the guideline as it relates to dentistry. In addition, this guideline has been endorsed by the American Academy of Pediatrics, Infectious Diseases Society of America, the International Society of Chemotherapy for Infection and Cancer, and the Pediatric Infectious Diseases Society. Circulation, 2007; 116(15): 1736-54.
29. Schubert MM, Epstein JB, Peterson DE. Oral complications of cancer therapy in: Pharmacology and Therapeutics for Dentistry, Yagiela JA, Dowd FJ and Neidle EA, Eds, Mosby-Year Book, St. Louis, Mo, USA, 5th edition, 2004; 797-813.
30. Franch AM, Esteve CG, Perez MGS. Oral manifestations and dental management of the patient with leukocyte alterations. J Clin Exp Dent, 2011; 3(1): 53-59.
31. Dean AK, Ferguson JW, Marvan ES. Acute leukaemia presenting as oral ulceration to a dental emergency service. Austr Dent J., 2003; 48(3): 195-97.
32. Guzeldemir E, Toygar HU, Kocer NE, Kizilkilic E. The periodontal management of a patient with acute myelomonocytic leukemia. Nobel Med, 2012; 8: 110-13.
33. Chapple ILC, Saxby MS, Murray JA. Gingival hemorrhage, myelodysplastic syndromes, and acute myeloid leukemia. A case report. J Periodontol, 1999; 70(10): 1247-53.
34. Greenberg MS, Glick M, Ship JA. (Editors.) Burket's Oral Medicine. 11 th edition. Hamilton. BC Decker Inc., 2008; 400-03.
35. Cooper CL, Loewen R, Shore T. Gingival hyperplasia complicating acute myelomonocytic leukemia. J Can Dent Assoc, 2000; 66(2): 78-79.
36. Khera P, Zirwas MJ, English JC. Diffuse gingival enlargement. J Am Acad Dermatol, 2005; 52(3): 491-99.
37. Anil S, Smaranayake LP, Nair RG, Beena VT. Gingival enlargement as a diagnostic indicator in leukaemia. Case report. Aust Dent J., 1996; 41(4): 235-37.
38. Bergmann OJ, Philipsen HP, Ellegaard J. Isolated gingival relapse in acute myeloid leukaemia. Euro J Hematol, 1988; 40(5): 473-76.
39. Hou GL, Tsai CC. Primary gingival enlargement as a diagnostic indicator in acute myelomonocytic leukemia: A case report. J Periodontol, 1988; 59(12): 852-55.
40. Long RG, Hlousek L, Doyle JL. Oral manifestations of systemic diseases. Mt Sinai J Med, 1998; 65(5-6): 309-15.
41. American Academy of Periodontology. Parameter on periodontitis associated with systemic conditions. J Periodontol, 2000; 71: 876-79.
42. Sheehy EC, Beighton D, Roberts GJ. The oral microbiota of children undergoing liver transplantation. Oral Microbiol Immunol, 2000; 15(3): 203-10.
43. McKenna SJ. Leukemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2000; 89: 137-39.
44. Azher U, Shiggaon N. Oral health status of children with acute lymphoblastic leukemia undergoing chemotherapy. Indian J Dent Res., 2013; 24(4): 523.
45. Nasim V, Shetty YR, Hegde A. Dental health status in children with acute lymphoblastic leukemia. J Clin Pediatr Dent, 2007; 31(3): 210-13.
46. Hegde AM, Joshi S, Rai K, Shetty S. Evaluation of oral hygiene status, salivary characteristics and dental caries experiences in acute lymphoblastic leukemic (ALL) children. J Clin Pediatr Dent, 2011; 35(3): 319-23.
47. Wu J, Fantasia JE, Kaplan R. Oral manifestations of acute myelomonocytic leukemia: a case report and review of the classification of leukemias. J Periodontol, 2002; 73(6): 664-68.
48. Martini V, Schiavone P, Bonacina R, Mariani U, Rambaldi A. NK leukemia: a rare case of oral manifestations representing the initial sign. Ann Stomatol, 2013; 4(2): 28.
49. Pai A, Prasad S, Dyasanoor S. Acute leukemias: a dentist's perspective. Minerva Stomatol, 2012; 61(5): 233-38.
50. Silva BA, Siqueira C, Castro P, Araújo SS, Volpato LE. Oral manifestations leading to the diagnosis of acute lymphoblastic leukemia in a young girl. J Indian Soc Pedod Prev Dent., 2012; 30(2): 166-68.
51. Pels E. Oral hygiene status and selected saliva biomarkers in children with acute lymphoblastic leukemia during anticancer therapy. J Leuk, 2013; 1(115): 1-4.
52. William MC, Lee GT. Childhood leukemia and dental considerations. J Clin Pediatr Dent, 1991; 15(3): 160-64.
53. Levy-Polack MP, Sebelli P, Polack NL. The incidence of oral complications and the application of a preventive protocol in children with acute leukemia. Spec Care Dentist, 1998; 18(5): 189-93.
54. Sepulveda E, Brethauer U, Rojas J, Fernandez E, Le Fort P. Oral ulcers in children under chemotherapy: Clinical characteristic and their relation with Herpes Simplex Virus type1 and Candida albicans. Med Oral Pathol Oral Cir Buccal, 2005; 10(1): 1-8.

55. Da Fonseca MA. Dental care of the pediatric cancer patient. Pediatric Dent, 2004; 26(1): 53-57.
56. Alberth M, Majoros L, Kovalecz G, Borbas E, Szegedi I, Marton I, Kiss C. Significance of oral Candida infections in children with cancer. Pathol Oncol Res., 2006; 12(4): 237-41.
57. Pels E. Oral mucositis in children suffering from acute lymphoblastic leukemia. Contemp Oncol (Pozn), 2012; 16(1): 12-15.
58. Borbasi S, Cameron K, Quested B, Olver I, To B, Evans D. More than a sore mouth: Patients' experience of oral mucositis. Oncol Nurs Forum, 2002; 29(7): 1051-57.
59. Parulekar W, Mackenzie R, Bjarnason G, Jordan RCK. Scoring oral mucositis. Oral Oncol, 1998; 34(1): 63-71.
60. Dreizen S, McCredie KB, Keating MJ. Chemotherapy-induced oral mucositis in adult leukemia. Postgrad Med. 1981; 69(2): 103-12.
61. Wingard JR: Importance of Candida species other than C. albicans as pathogens in oncology patients. Clin Infect Dis., 1995; 20(1): 115-25.
62. Osma CI, Villaron LG, Miguel JFS, Caballero MD, Vazquez L, de Castro S. Iron metabolism and fungal infections in patients with hematological malignancies. J Clin Pathol, 1995; 48(3): 223-25.
63. Subramaniam P, Babu KL, Nagarathna J. Oral manifestations in acute lymphoblastic leukemic children under chemotherapy. J Clin Pediatr Dent., 2008; 32(4): 319-24.
64. Javed F, Klingspor L, Sundin U, Altamash M, Klinge B, Engström PE. Periodontal conditions, oral Candida albicans and salivary proteins in type 2 diabetic subjects with emphasis on gender. BMC Oral Health, 2009; 9(1): 1-8.
65. Scully C. Oral and Maxillofacial Medicine: The Basis of Diagnosis and Treatment. 4 th ed. London: Elsevier Science Limited, 2004; 252-68.
66. Ponce-Torres E, Ruíz-Rodriguez MS, Alejo-Gonzalez F, Hernandez-Sierra JF, Pozos-Guillen AJ. Oral manifestations in pediatric patients receiving chemotherapy for acute lymphoblastic leukemia. J Clin Pediatr Dent., 2010; 34(3): 275-79.
67. Greenberg MS, Glick M, Skip JA. Burket's Oral Medicine. 11 th ed. Hamilton: BC Decker Inc., 2008; 79-84.
68. Mazaheri R, Jabbarifar E, Gasemi E, Akkafzadeh E, Poursaeid E. Oral health status, salivary pH status, and *Streptococcus mutans* counts in dental plaques and saliva of children with acute lymphoblastic leukemia. Dent Res J., 2017; 14(3): 188-94.
69. Weckx LL, Hidal LB, Marcucci G. Oral manifestations of leukemia. Ear Nose Throat J., 1990; 69(5): 341-42, 345-46.
70. Milins B, Martin MV, Williams MC. Raised salivary endotoxin concentration as a predictor of infection in pediatric leukemia patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1999; 88(1): 50-55.
71. Sixou JL, de Medeiros-Batista O, Bonnaure-Mallet M. Modifications of the microflora of the oral cavity arising during immunosuppressive chemotherapy. Eur J Cancer B Oral Oncol., 1996; 32(5): 306-10.
72. Richet HM, Andremont A, Tancrede C, Pico JL, Jarvis WR. Risk factors for candidemia in patients with acute lymphocytic leukemia. Rev Infect Dis., 1991; 13(2): 211-15.
73. Myoken Y, Sugata T, Kyo T, Fujihara M, Kohara T, Katsu M, Tamura M, Mikami Y. Invasive *Aspergillus* stomatitis in patients with acute leukemia: Report of 12 Cases. Clin Infect Dis., 2001; 33(12): 1975-80.
74. Pajari U, Ollila P, Lanning M. Incidence of dental caries in children with acute lymphoblastic leukemia is related to the therapy used. J Dent Child., 1995; 62(5): 349-52.
75. Welbury RR, Craft AW, Murray JJ, Kernahan J. Dental health of survivors of malignant disease. Arch Dis Child, 1984; 59(12): 1186-87.
76. Halyard MY. Taste and smell alterations in cancer patients-real problems with few solutions. J Support Oncol, 2009: 7(2): 68-69.
77. Steinbach S, Hummel T, Bohner C, Berktold S, Hundt W, Kriner M, Heinrich P, Sommer H, Hanusch C, Prechtl A, Schmidt B, Bauerfeind I, Seck K, Jacobs VR, Schmalfeldt B, Harbeck N. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol, 2009; 27(11): 1899-1905.
78. Javed F, Romanos GE. Impact of diabetes mellitus and glycemic control on the osseointegration of dental implants: A systematic literature review. J Periodontol, 2009; 80(11): 1719-30.
79. Hong JH, Omur-Ozbek P, Stanek BT, Dietrich AM, Duncan SE, Lee YW, Lesser G. Taste and odor abnormalities in cancer patients. J Support Oncol, 2009; 7(2): 58-65.
80. Li-Wei O, Pel-Ching C, Aileen T, Tang-Her J, Shiao-Yu L. Salivary microbial counts and buffer capacity in children with acute lymphoblastic leukemia. Pediatr Dent, 2010; 32(3): 218-22.
81. Sreebny LM. Xerostimia: Diagnosis, management and clinical complications. Saliva and Oral health. Br Dent Assoc, 1996; 14: 43-66.
82. Larmas M. Saliva and dental caries: diagnostic tests for normal dental practice. Int Dent J., 1992; 42(4): 199-208.
83. Sepet E, Aytepe Z, Ozerkan AG, Yalman N, Guven Y, Anak S, Devecioglu O, Agaoglu L, Gedikoglu G. Acute lymphoblastic leukemia: dental health of children in maintenance therapy. J Clin Pediatr Dent., 1998; 22(3): 257-60.
84. Pajari U, Poikonen K, Larmas M, Lanning M. Salivary immunoglobulins, lysozyme, pH, and microbial counts in children receiving anti-

neoplastic therapy. Euro J Oral Sci., 1989; 97(2): 171-77.
85. Uderzo C, Fraschini D, A Balduzzi A, Galimberti S, Arrigo C, Biagi E, Pignanelli M, Nicolini B, Rovelli A. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. Bone marrow transplant., 1997; 20(10): 865-69.
86. Epstein JB, Schubert MM. Managing pain in mucositis. Semin Oncol Nurs., 2004; 20(1): 30-37.
87. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB. Perspectives on cancer therapy-induced mucosal injury. Cancer, 2004; 100(9): 1995-2025.
88. Herrstedt J. Prevention and management of mucositis in patients with cancer. Int J Antimicrob Agents, 2000; 16(2): 161-63.
89. Karolewska E, Konopka T, Pupek M, Chaber R. Mucositis in children with Leukemia and salivary defense factors. Dent Med Probl, 2007; 44: 30-36.
90. Karolewska E, Konopka T. Preventive-therapeutic dental care protocol in children with leukemia. Czas Stomatol, 2006; 59(4): 245-52.
91. Al-Mashhadane FA. Oral Health Status among children receiving chemotherapy. Al-Rafidain Dent J., 2006; 7(1): 96-100.
92. Pels E, Mielnik-Blaszczak M. Oral hygiene in children suffering from acute lymphoblastic leukemia living in rural and urban regions. Ann Agri Env Med., 2012; 19(3): 529-33.
93. Pels E, Mielnik-Błaszczak M. State of oral hygiene and levels of selected salivary parameters in children with acute lymphoblastic Leukemia. Pol J Environ Stud., 2007; 16(2): 114-17.
94. Dominique D, Frans V. Oral complications of leukemia. Quintessence Int., 1988; 19(8): 575-83.
95. Runge ME, Edwards DL. Orthopedic treatment for an adolescent with a history of acute lymphoblastic leukemia. Pediatr Dent., 2000; 22(6): 494-98.
96. da Costo Lino MDM, de Carvalho FB, de Oliveira LR, Magalhaes EB, Pinheiro ALB, Ramalho LM. Laser phototherapy as a treatment for radiotherapy-induced oral mucositis. Braz Dent J., 2011; 22(2): 162-65.
97. de Lima AG, Antequera R, de Melo Peres MPS, Snitocosky IML, Federico MHH, Villar RC. Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. Braz Dent J., 2010: 21(3); 186-92.
98. Sonis ST. Mucositis: the impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol, 2009: 45(12); 1015-20.
99. Anirudhan D, Bakhshi S, Xess I, Broor S, Arya LS. Etiology and outcome of oral mucosal lesions in children on chemotherapy for acute lymphoblastic leukemia. Indian Pediatr, 2008: 45(1): 47-51.
100. Kumar S, Balan A, Sankar A, Bose T. Radiation-induced oral mucositis. Indian J Palliat Care, 2009; 15(2): 95-102.
101. Sonis ST. New thoughts on the initiation of mucositis. Oral Dis, 2010; 16(7): 597-600.
102. Dens F, Boute P, Otten J, Vinckier F, Declerk D. Dental caries, gingival health, and oral hygiene of long term survivors of pediatric malignant diseases. Arch Dis Child, 1995; 72(2): 129-32.
103. Maciel JCC, de Castro jr CG, Jr. Brunetto AL, Di Leone LP, da Silveira HED. Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. Pediatric Blood Cancer, 2009; 53(3): 361-65.
104. Cubukcu CE, Gunes AM. Caries experience of leukemic children during intensive course of chemotherapy. J Clin Pediatr Dent, 2007; 32(2): 155-58.
105. Kinirons MJ, Fleming P, Boyd D. Dental caries experience of children in remission from acute lymphoblastic leukemia in relation to the duration of treatment and the period of time in remission. Int J Pediatr Dent, 1995; 5(3): 169-72.
106. Epstein JB, Vickars L, Spinelli J, Reece D. Efficacy of chlorhexidine and nystatin rinses in the prevention of oral complications in leukemia and bone marrow transplantation. Oral Surg Oral Med Oral Pathol, 1992; 73(6): 682-89.
107. Kusumakumary P, Sankaranarayanan R, Padmakumary G, Cherian V, Rajeev KS, Krishnan NM. Childhood cancer in Kerala, India. Lancet, 1991; 338(8764): 455-56.
108. Carl W, Schaaff NG. Dental care for the cancer patient. J Surg Oncol, 1974; 6(4): 293-310.
109. Pui CH, Campana D, Evans WE. Childhood acute lymphoblastic leukemia-Current status and future perspectives. Lancet Oncol, 2001; 2(10): 597-607.
110. Maguire A, Welbury RR. Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development. Dent Update, 1996; 23(5): 188-94.
111. Goho C. Chemoradiation therapy: Effect on dental development. Pediatr Dent, 1993; 15(1): 6-12.
112. Vahlsing HL, Kim SK, Feringa ER. Cyclophosphamide-induced abnormalities in the incisors of the rat. J Dent Res., 1977; 56(7): 809-16.
113. Stene T. Effect of vincristine on odontoblasts in rat incisor. Euro J Oral Sci., 1978; 86(5): 346-56.
114. Goodman ED, Fuks AB. The effects of anti-leukemic therapy on the developing dentition: case report. Pediatr Dent, 1985; 7: 318-21.
115. Dahllof G, Rozell B, Forsberg CM, Borgström B. Histologic changes in dental morphology induced by high dose chemotherapy and total body irradiation. Oral Surg Oral Med Oral Pathol, 1994; 77(1): 56-60.
116. Minicucci EM, Lopes LF, Crocci AJ. Dental abnormalities in children after chemotherapy

treatment for acute lymphoid leukemia. Leuk Res., 2003; 27(1): 45-50.
117. Maciel JC, de Castro CG Jr, Brunetto AL, Di Leone LP, da Silveira HED. Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. Pediatric Blood Cancer, 2009; 53(3): 361-65.
118. Khojastepour L, Zareifar S, Ebrahimi M. Dental anomalies and dental age assessment in treated children with acute lymphoblastic leukemia. Iran J Ped Hematol Oncol, 2014; 4(4): 172-77.
119. Alpaslan G, Alpaslan C, Gogen H, Oguz A, Cetiner S, Karadeniz C. Disturbances in oral and dental structures in patients with pediatric lymphoma after chemotherapy A preliminary report. Oral Surg, Oral Med, Oral Pathol, Oral Radiol, Endodon, 1999; 87(3): 317-21.
120. National Instutes of Health. National Cancer Institute. Oral Complications of Chemotherapy and Head/Neck Radiation (PDQ) [Online], 2008.
121. Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radia Oncol Biol Phys, 2002; 52(3): 739-47.
122. Rankin K, Jones D, Redding S. Oral health in cancer therapy: a guide for health care professionals, Second edition. Dallas: Texas Cancer Council, 2003.
123. Vasconcelos NPS, Caran EMM, Lee ML, Lopes NNF, Weiler RME. Dental maturity assessment in children with acute lymphoblastic leukemia after cancer therapy. Forensic Sci Int., 2009; 184(1-3): 10-14.
124. Brook AH. Dental abnormalities of number, form and size: their prevalence in British school children. J Int Assoc Dent Child., 1974; 5: 37-53.
125. Xavier AM, Hegde AM. Preventive protocols and oral management in childhood leukemia-the pediatric specialist's role. Asian Pac J Cancer Prev, 2010; 11(1): 39-43.
126. Jaffe N, Toth BB, Hoar RE, Ried HL, Sullivan MP, McNeese MD. Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: Effects of treatment with chemotherapy and radiation to the head and neck. Pediatrics, 1984; 73(6): 816-23.
127. Rosenberg SW, Kolodney H, Wong GY, Murphy ML. Altered dental root development in long-term survivors of pediatric acute lymphoblastic leukemia. A review of 17 cases. Cancer, 1987; 59(9): 1640-48.
128. Mataki S. Comparison of the effect of colchicine and vinblastine on the inhibition of dentinogenesis in rat incisors. Arch Oral Biol., 1981; 26(12): 955-61.
129. Kaste SC, Hopkins KP, Jones D, Crom D, Greenwald CA, Santana VM. Dental abnormalities in children treated for acute lymphoblastic leukemia. Leukemia, 1997; 11(6): 792-96.
130. Pajari U, Lanning M, Larmas M. Prevalence and location of enamel opacities in children after anti-neoplastic therapy. Community Dent Oral Epidemiol, 1988; 16(4): 222-26.
131. Dahllof G, Barr M, Bolme P, Modeer T, Lonnqvist B, Ringden O, Heimdahl A. Disturbances in dental development after total body irradiation in bone marrow transplant recipients. Oral Surg Oral Med Oral Pathol, 1988; 65(1): 41-44.
132. Pajari U, Lanning M. Developmental defects of teeth in survivors of childhood ALL are related to the therapy and age at diagnosis. Med Pediatr Oncol, 1995; 24(5): 310-14.
133. Al-Ghani BA, Hasan NM, Hassan JM. Enamel hypoplasia in patients with acute lymphoblastic leukemia. J Baghdad Coll Dent., 2005; 17(3): 53-56.
134. Lopes NNF, Petrilli AS, Caran EMM, França CM, Chilvarquer I, Lederman H. Dental abnormalities in children submitted to antineoplastic therapy. J Dent Child, 2006; 73(3): 140-45.
135. Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. Cancer, 1990; 66(12): 2645-52.
136. Biermann JS, Golladay GJ, Greenfield ML, Baker LH. Evaluation of cancer information on the internet. Cancer, 1999: 86(3): 381-90.
137. Devi KS, Allenidekania A. The relationship of oral care practice at home with mucositis incidence in children with acute lymphoblastic leukemia. Compr Child Adolesc Nurs, 2019; 42(1): 56-64.
138. Taur Y, Cohen N, Dubnow S, Paskovaty A, Seo SK. Effect of antifungal therapy timing on mortality in cancer patients with candidemia. Antimicrob Agents Chemother, 2010; 54(1): 184-90.
139. Ransier A, Epstein JB, Lunn R, Spinelli J. A combined analysis of a toothbrush, foam brush and chlorhexidine soaked foam brush in maintaining oral hygiene. Cancer Nursing, 1995; 18(5): 393-96.
140. Lawson K. Oral-dental concerns of the pediatric oncology patient. Issues in Comprehensive Pediatric Nursing, 1989; 12(2-3): 199-206.
141. Semba SE, Mealey BL, Hallmon WW. Dentistry and the cancer patient: part 2-oral health management of the chemotherapy patient. Compendium, 1994; 15(11): 1378-87.
142. Gjermo P. Chlorhexidine and related compounds. J Dental Res., 1989; 68: 1602-08.
143. Schubert MM, Sullivan KM, Truelove EL. Head and neck complications of bone marrow transplantation. In: Head and Neck Management of the Cancer Patient, Peterson DE, Elias EG and Sonis ST, Eds. Martinus Nijhoff, Boston, Mass, USA, 1986; 401-27.
144. Hudspeth M, Symons H. Oral and dental considerations in a pediatric leukemic patient. In: Hematology, The Harriet Lane Handbook, Gunn

VL and Nechyba C, Eds. Mosby, Philadelphia, Pa, USA, 16th edition, 2002; 283-306.
145. Dahllof G, Johnson A, Ulmner M, Huggare J. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. Am J Orthodon Dentofac Ortho, 2001; 120(5): 459-65.
146. No authors listed. Guideline on dental management of pediatric patients receiving chemotherapy, hematopoietic cell transplantation and/or radiation. Pediatr Dent, 2012; 34: 280.
147. Lopez BC, Estave CG, Perez MGS. Dental treatment considerations in the chemotherapy patient. J Clin Exp Dent, 2011; 3(1): 31-42.
148. Baddour LM, Bettmann MA, Bolger AF, Epstein AE, Ferrieri P, Gerber MA, Gewitz MH, Jacobs AK, Levison ME, Newburger JW, Pallasch TJ, Wilson WR, Baltimore RS, Falace DA, Shulman ST, Tani LY, Taubert KA. Nonvalvular cardiovascular device-related infections. Circulation, 2003; 108(16): 2015-31.
149. Williams MC, Martin MV. A longitudinal study of the effects on the oral mucosa of treatment for acute childhood leukaemia. Int J Paediatr Dent, 1992; 2(2): 73-79.
150. Duncan GG, Epstein JB, Tu D, Sayed SE, Bezjak A, Ottaway J, Pater J. Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis. J Sci Spec Head Neck, 2005; 27(5): 421-28.
151. Barasch A, Peterson DE. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. Oral Oncol, 2003; 39(2): 91-100.
152. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent Clin North Am, 2008; 52(1): 61-77.
153. Lalla RV, Peterson DE. Oral mucositis. Dent Clin North Am, 2005; 49(1): 167-84.
154. Epstein JB, Gorsky M, Guglietta A, Le N, Sonis ST. The correlation between epidermal growth factor levels in saliva and the severity of oral mucositis during oropharyngeal radiation therapy. Cancer, 2000; 89(11): 2258-65.
155. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Rad Oncol Biol Phys, 2007; 68(4): 1110-20.
156. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, Komaroff E, Nalysnyk L, Zilberberg MD. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiol and Oncol, 2003; 66(3): 253-62.
157. Miller MM, Donald DV, Hagemann TM. Prevention and treatment of oral mucositis in children with cancer. J Pediatr Pharmacol Therap, 2012; 17(4): 340-50.
158. Common Terminology Criteria for Adverse Events, version 4.0. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Cancer Therapy Evaluation Program.
159. Madeya ML. Oral complications from cancer therapy: Part 2-Nursing implications for assessment and treatment. Oncol Nurs Forum, 1996; 23(5): 808-19.
160. Cheng KKF, Molassiotis A, Chang AM, Wai WC, Cheung SS. Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. Euro J Cancer, 2001; 37(16): 2056-63.
161. Debrito Costa EMM, Fernandes MZ, Quinder LB, deSouza LB, Pinto LP. Evaluation of an oral preventive protocol in children with acute lymphoblastic leukemia. Pesqui Odontol Bras, 2003; 17(2): 147-50.
162. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA, McGuire DB, Hutchins RD, Peterson DE. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer, 2007; 109(5): 820-31.
163. ASPEN Board of Directors. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenteral Enteral Nutr, 2002; 26: 1SA-138SA.
164. Cheng KKF, Chang AM. Palliation of oral mucositis symptoms in pediatric patients treated with cancer chemotherapy. Cancer Nurs, 2003; 26(6): 476-84.
165. Sheller B, Williams B. Orthodontic management of patients with hematologic malignancies. Am J Orthodon Dentofac Ortho, 1996; 109(6): 575-80.
166. Ohrn KE, Wahlin YB, Sjoden PO. Oral status during radiotherapy and chemotherapy: a descriptive study of patient experiences and the occurrence of oral complications. Support Care Cancer, 2001; 9(4): 247-57.
167. Ripamonti C, Fulfaro F. Taste alterations in cancer patients. J Pain Symptom Manage, 1998; 16(6): 349-51.
168. Aisa Y, Mori T, Kudo M, Yashima T, Kondo S, Yokoyama A, Ikeda Y, Okamoto S. Oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. Supp Care Cancer, 2005; 13(4): 266-69.
169. Mahood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Thernrauj TM, Sorensen M, Gainey DK, Mailliard JA, Gusa NL. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol, 1991; 9(3): 449-52.
170. Worthington HV, Eden OB, Clarkson JE, Eden OBT. Interventions for preventing oral candidiasis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews, 2004; 1(1): IDCD001972.

171. Colella G, Cannavale R, Vicidomini A, Rinaldi G, Compilato D, Campisi G. Efficacy of a spray compound containing a pool of collagen precursor synthetic aminoacids (L-proline, L-leucine, L-lysine and glycine) combined with sodium hyaluronate to manage chemo/radiotherapy-induced oral mucositis: preliminary data of an open clinical trial. Int J Immunopathol Pharmacol, 2010; 23(1): 143-51.
172. von Bultzingslowen I, Brennan MT, Spijkervet FKL, Logan R, Stringer A, Ruber-Durlacher JE, Keefe D. Growth factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. Supp Care Cancer, 2006; 14(6): 519-27.
173. Lalla RV, Velafermin CG. Current Opinion in Investigational Drugs (London, England, 2000; 2005; 6: 1179-85.
174. Epstein JB, Silverman Jr S, Paggiarino DA, Crockett S, Schubert MM, Senzer NN, Lockhart PB, Gallagher MJ, Peterson DE, Leveque FG. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer, 2001; 92(4): 875-85.
175. Moslehi A, Taghizadeh-Ghehi M, Gholami K, Hadjibabaie M, Jahangard-Rafsanjani Z, Sarayani A, Javadi M, Esfadbod M, Ghavamzadeh A. N-acetyl cysteine for prevention of oral mucositis in hematopoietic SCT: A double-blind, randomized, placebo-controlled trial. Bone Marrow Transplant, 2014; 49(6): 818-23.
176. Storey B. The role of oral glutamine in pediatric bone marrow transplant. J Pediatr Oncol Nurs, 2007; 24(1): 41-45.
177. Skubitz KM, Anderson PM. Oral glutamine to prevent chemotherapy induced stomatitis: a pilot study. J Lab Clin Med, 1996; 127(2): 223-28.
178. Tarnawski A, Hollander D, Gergely H. The mechanism of protective, therapeutic and prophylactic actions of sucralfate. Scand J Gastrol. (Supple), 1987; 140: 7-13.
179. Shenep JL, Kalwinsky DK, Hutson PR. George SL, Dodge RK, Blakenship RNKR, Thorton RND. Efficacy of oral sucralfate suspension in prevention and treatment of chemotherapy-induced mucositis. J Pediatr, 1988; 113(4): 758-63.
180. Vadhan-Raj S, Trent J, Patel S, Zhou X, Johnson MM, Araujo D, Ludwig JA, O'Roark S, Gillenwater AM, Bueso-Ramos C, El-Naggar AK, Benjamin RS. Single-dose palifermin prevents severe oral mucositis during multicycle chemotherapy in patients with cancer: a randomized trial. Annals of Int Med, 2010; 153(6): 358-67.
181. Gholamreza ED, Amirhossein E, Leila AF, Reza SS, Farzad MB, Mohsen F, Nasrin Z. Low-level laser therapy in management of chemotherapy-induced oral mucositis: prophylaxis or treatment? J Lasers Med Sci., 2011; 2(1): 12-17.
182. Kostler WJ, Hejna M, Wenzel C, Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: Options for prevention and treatment. CA Cancer J Clin, 2001; 5(5): 290-315.