

MINI-REVIEW

Preventive Protocols and Oral Management in Childhood Leukemia - the Pediatric Specialist's Role

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Abstract

The leukemias are the most common form of childhood malignancy. The pediatric dental professional plays a major role in the prevention, stabilization and treatment of the oral and dental problems that can compromise the child's health and quality of life before, during and after the cancer treatment. This manuscript highlights the incidence of oral complications in leukemic children receiving oncology treatment and the systematic preventive protocol followed during different phases of medical treatment.

Key words: Childhood cancer - acute lymphoid leukemia - chemotherapy - oral mucositis

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Introduction

Leukemia is essentially 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 (Neyzi and Ertugrul, 1990; Sepet et al, 1998). In India, childhood leukemia constitutes 2.3% of the cancer patients. Each year 6000 children in India develop acute lymphoblastic leukemia (Nasim et al., 2007). 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 (Genc et al., 1998). Acute leukemia is the most common childhood malignancy, with the acute lymphoblastic type accounting for the majority of cases (Moore and Hobson, 1990). The cause of leukemia is unknown although certain leucogenic factors are postulated, including ionizing radiation, genetic and immunological factors, viruses and exposure to benzene derivatives and ethyl carbonates (Williams and Lee, 1991).

Diagnosis is made by an examination of a stained blood film and supported by bone marrow biopsy (Williams and Lee, 1991). Advances in the treatment regimens, including multi-agent chemotherapy and radiation therapy, have greatly increased the chances of survival (Runge and Edwards, 2000). 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 (Ylgenly et al., 2001). The type of chemotherapeutic agents, the dosage, and the frequency of drug administration are important therapy related

factors, which affect the development of stomatotoxicity (Peterson and Sonis, 1982; Carl, 1986).

Medical Treatment

Once diagnosed of leukemia, the treatment is carried in distinct phases. The purpose is to induce a remission and maintain this with appropriate supportive care such as the management of anemia, bleeding and infection (Williams and Lee, 1991). Treatment also involves the eradication of malignant cells from extra-medullary sites, such as the central nervous system, and the testes in boys (Williams and Lee, 1991).

The treatment of acute lymphoid leukemia (ALL) is based on clinical risk and is usually divided into four phases (Da Fonseca, 2004; Subramaniam et al., 2008):

1. Remission induction – It consists of 3 or 4 drugs, eg; Vincristine (1.4mg/m² I.V days 1,8,15,22,29), Daunorubicin (30mg/I.V, days 1,8,15), intrathecal Methotrexate (12mg, days 1,8,15,22) and L-asparaginase (6000U/m² IM ALT_X10,2-20); with a 95% success rate. It generally lasts for 28 days. Achievement of remission is a known pre-requisite for prolonged survival.

2. CNS preventive therapy/prophylaxis – CNS can act as a sanctuary site for leukemic infiltrates because systemically administered chemotherapeutic drugs are not able to cross the blood-brain barrier. Cranial irradiation (200Rads/Dose) and/or weekly intrathecal injection of a chemotherapeutic agent, usually methotrexate (12mg, days 1,8,15), are used. Other drugs include 6-Mercaptopurine (75mg/m² days 1-7) and Cyclophosphamide (750mg/m² I.V, days 1 and 15). This pre-symptomatic treatment can be done in each phase as well. A repetition of the induction therapeutic phase for another 4 weeks follows.

3. Consolidation or intensification – In an attempt to

kill any remaining leukemic cells, it is designed to minimize the development of drug cross-resistance through intensified treatment. It lasts for 4 weeks. The drugs in this phase include: 6-Mercaptopurine (75mg/m² days 1 and 1-7 & 15-21), Cyclophosphamide (750mg/m² I.V, days 1 and 15), Cytarabine (70mg/m² SCX6, days 1-3 & 15-17).

4. Maintenance – A continuous administration of methotrexate and 6-mercaptopurine to suppress the leukemic growth is performed. The optimal length of this phase may last approximately up to 2.5 to 3 years. Vincristine (1.4mg/m² I.V days 1), methotrexate (15mg/m² once a week), Predniolone (40mg/m², days 1-7), L-asparaginase (6000U/m² IM days 1,3,5,7), Daunorubicin (30mg/I.V, day 1) are the drugs administered here.

This drug regimen is followed according to the 'Multi Centre protocol' (MCP) 841 [Standard drug regimen for ALL children used in various centers in India, designed in collaboration with National Cancer Institute (USA)]. Introduction of a standard protocol and improvement in supportive care led to an increase in the event-free survival (EFS) from less than 20% to 45-50% in 4 years (The International Network for cancer treatment and Research, 2007).

Acute myeloblastic leukemia is managed differently. The commonly used drugs are daunorubicin, cytarabine, and thioguanine. As stated previously, the results are much poorer for these children. Cranial irradiation and intrathecal therapy are given vigorously and bone marrow transplantation is given where possible during the first remission (Kung, 1985).

Oral Complications in Leukemia

Oral and dental infections may complicate the oncology treatment as well as delay it, leading to morbidity and an inferior quality of life for the child. Early and radical dental intervention reduces the frequency of problems, minimizing the risk for oral and associated systemic complications (Greenberg et al., 1982; Wahlin, 1989; Toth et al., 1991; Schubert et al., 1998). Therefore, the dental consultation on a newly diagnosed patient should be done at once so that enough time is available for care to be completed before the cancer therapy starts. Every patient should be dealt with on an individual basis, and appropriate consultations with physicians and other dental specialists should be sought before dental care is instituted (Schubert et al., 1998).

The pediatric dentist should gather information about the underlying disease, time of the diagnosis, modalities of treatment the patient has received since the diagnosis (chemotherapy, radiation therapy, surgeries, etc.), and complications, including relapses. Hospitalizations, emergency room visits, infections (both oral and systemic), current hematological status, allergies, medications, and a review of systems (heart, lungs, kidneys, etc.) should be noted (Da Fonseca, 2004).

The problems that children get initially because of the disease can be related to the effect of leukemic cell infiltration, thrombocytopenia, normal white cell leucopenia and anemia (Tubewrgen, 1987). These may be

reflected by oral changes exhibited by children (White, 1970; Thoma and Goldmann, 1978). Dental involvement may come unexpectedly following treatment complications caused by the unwary dentist (Resch, 1940; Tagaki et al., 1978) or else may be observed by the diligent dentist (Curtis, 1971).

The most common oral problems caused by chemotherapy are the inflammation of the mucous membrane of the mouth, ie. Mucositis characterized by redness, loss of the epithelial barrier and ulceration. Oral mucositis may appear from 4-7 days after the initiation of chemotherapy. It affects the soft oral mucosa which includes soft palate, oropharynx, buccal and labial mucosa, floor of the mouth and the underside (ventral) and lateral surfaces of the tongue. Complete resolution of mucositis occurs seven to fourteen days after its onset.

The neutrophils are the body's first line of defense. Therefore, the incidence and severity of infection are inversely related to their number. Fungal infections (Candida) of the oral mucosa are common and can cause burning sensation, distortion of taste and problems with swallowing. Viral infections especially the re-activation of herpes simplex virus type I (HSV-1) is serious because they can cause pain and problems with hydration and nutrition (Acute Lymphoblastic Leukemia in children, 2009).

Prolonged bleeding in childhood malignancy may be caused by chemotherapy induced myelosuppression, certain medications and disorders of clotting and platelets related to the baseline disease. Decrease in the number of platelets (thrombocytopenia) leads to spontaneous oral bleeding, that is when the platelet count goes below 20,000/cu.mm.

Ameloblasts and odontoblasts can be damaged by chemotherapy agents if these cells are in a susceptible phase of their cell cycle (Mitotic or Synthesis stage). This can result in teeth which have short, thin, tapered root or hypomineralized or hypomature enamel. Radiation therapy also can lead to some complications. Direct radiation of the jaw, face and head produces the most serious side effects in children which includes incomplete development of the jaws, arrested tooth development which can cause small teeth, atrophy of the overlying soft tissue; enamel malformation and incomplete calcification of teeth (Acute Lymphoblastic Leukemia in children, 2009). Radiation therapy directed at salivary glands can lead to oral dryness caused by damage to the salivary glands.

Children undergoing an allogenic bone marrow transplant (BMT) often develop Graft-versus-Host-Disease (GVHD) and oral cavity may be the first or only site showing GVHD. An increasing level of xerostomia and/or generalized stomatitis which appear hundred or more days after the BMT are indicators of chronic GVHD. The younger the child, the greater is the risk for craniofacial and developmental abnormalities (Acute Lymphoblastic Leukemia in children, 2009).

Management of Oral Complications of Leukemia Treatment in Children

Up to 90% of children undergoing leukemia treatment may suffer oral complications. Elimination of pre-existing

dental problems, as well as good oral hygiene during leukemia therapy can reduce the occurrence and severity of oral complications.

1) Oral Management before leukemic treatment

At least one month prior to leukemic treatment, all the children should be evaluated by a pediatric dentist to assess the oral health status and identify drug potential oral problems. Treatment planning should be done to reduce the oral complications during and after the cancer therapy. A panoramic radiograph should be attempted in all children who can cooperate before cancer treatment. Oral hygiene and dental rehabilitation should be aggressive as possible before cancer treatment is started, especially when bone marrow transplantation is planned. Dental treatment should only be provided after consultation with the child's oncologist.

When there is time prior to the initiation of cancer therapy, dental scaling and prophylaxis should be done, defective restorations repaired and teeth with sharp edges polished. Preventive therapies like topical fluoride therapy and pit and fissure sealant therapy may be promptly considered. Although there have been no studies till date that address the safety of performing pulp therapy in primary teeth prior to the initiation of chemotherapy and/or radiotherapy, it is prudent to provide a more radical treatment in the form of extraction to minimize the risk of oral and systemic complications ((Da Fonseca, 2004).

Teeth that have been already pulpally treated and are clinically and radiographically sound presents no threats. Symptomatic nonvital permanent should receive root canal therapy at least 1 week before initiation of cancer therapy. If that is not possible, extraction is indicated. Endodontic treatment of permanent teeth with asymptomatic periapical involvement can be delayed if the patient is neutropenic (Semba et al., 1994; Little et al., 2002).

Fixed orthodontic appliances and space maintainers should be removed if the patient has poor oral hygiene or the treatment protocol carries a risk for the development of moderate to severe mucositis (Runge and Edwards, 2000).

Partially erupted molars can become a source of infection due to pericoronitis, so the overlying gingival tissue should be excised if the dentist believes it is a potential risk (Schubert et al., 1986). Loose primary teeth should be left to exfoliate naturally and the patient counseled not to play with them to avoid bacteremia. If the patient cannot comply with this recommendation, the teeth should then be removed. Impacted teeth, root tips, partially erupted third molars, teeth with periodontal pockets >5mm, teeth with acute infections, and non restorable teeth should be removed ideally 3 weeks before cancer therapy starts to allow adequate healing (Sonis et al., 1995; Little et al., 2002).

2) Oral management during leukemic treatment

Routine oral care is important to reduce the incidence and severity of oral sequelae of the treatment protocol, therefore aggressive oral hygiene should be done throughout the entire oncology treatment, regardless of the child's hematological status (Wahlin, 1989; Epstein

1990; Bavier, 1990; Toth et al., 1991; Borowski et al., 1994; Sonis et al., 1995; Ransier et al., 1995; Schubert et al., 1998; Epstein and Schubert, 1999; Little et al., 2002; NCI Cancer information, 2003).

Although the nursing staff have the initial responsibility for the oral care of the ill child under their care (Albright, 1984), frequently because of the lack of time, staff, or basic knowledge, the provisions of oral care does not match the standard set by the nursing authorities (Hart and Ramussen, 1982) and many treatment centers value the services of the dental staff member, who is responsible for oral care of their patients while they are in hospital (Niehaus, 1987). The child should rinse with cold sterile water, or cold normal saline as often as possible, to keep the oral tissues clean and wet and thus help with the removal of thick saliva, remove debris, and decrease the risk of opportunistic infections. A lip moisturizer, either water or lanolin can be applied using a cotton tip applicator several times in a day. Preventive measures using topical fluoride therapy and pit and fissure sealants have to be administered when recommended.

The care takers may indulge the child with frequent unhealthy snacks. The patients may also be prescribed daily nutritional supplements rich in carbohydrate to maintain or gain weight such as Pediasure. Furthermore, many oral pediatric medications contain high amounts of sucrose (eg. Nystatin) predisposing the individual to an increased risk of dental caries.. Despite the fact that nystatin is often prescribed, it cannot be recommended for prophylaxis and prevention of Candida infections in immunodepressed patients because of its effect similar to that of a placebo on fungal colonization and inferior to fluconazole, in the prevention of invasive fungal infections and colonization (Schubert et al., 1998; Gotzche and Johansen, 2002). It is important to make care takers and the medical team aware of this risk factor so that medications are used in a manner that minimizes the caries risk. Children should not be allowed to fall asleep immediately after rinsing with nystatin or a clotrimazole troche that is not sugar free.

A regular soft toothbrush or an electric brush used at least twice daily is the most efficient means to reduce the risk of significant bleeding and infection in the gingiva (Greenberg et al., 1982; Bavier, 1990; Toth et al., 1991; Ransier et al., 1995; Schubert et al., 1998). Sponges, foam brushes, and supersoft brushes cannot provide effective mechanical cleansing due to their softness; therefore, they should be used only in cases of severe mucositis when the patient cannot tolerate a regular brush (Bavier, 1990; Ransier et al., 1995; NCI Cancer information, 2003). Brushes should be air dried between uses and toothpaste without heavy flavoring agents should be considered because they can irritate the tissues (NCI Cancer information, 2003). During neutropenic periods, the use of toothpicks and water irrigating devices should be avoided because they may break the integrity of the tissues, creating ports of entry for microorganism colonization and bleeding (Da Fonseca, 2004). Ultrasonic brushes and dental floss can be used if the patient is properly trained (Da Fonseca, 2004).

Vomiting is often seen as a side effect of the cancer

therapy; so young patients should rinse and spit with water or any bland solutions after episodes of emesis. This will prevent stomach acids from decalcifying the teeth and irritating the oral tissues (Massler, 2000). A good dietary management program should encourage the intake of bland, non-acidic foods with high moisture content. Intake of ice creams, mashed potatoes, icy drinks, and popsicles can be entertained.

A variety of chemical substances has been used for the prevention and treatment of chemotherapy-induced oral complications, such as chlorhexidine (McGaw et al., 1985; Ferretti et al., 1987; Epstein et al., 1992; Dodd et al., 1996; Levy-Polack et al., 1998), vitamin E (Wadleigh et al., 1992), itraconazole (Foot et al., 1999), fluconazole (Epstein et al., 1999), oral sucralfate suspension (Shenet et al., 1988), and low energy helium-neon laser (Cowen et al., 1997). However, conflicting results with respect to the prophylactic use of chlorhexidine in patients with leukemia or those who have a bone marrow transplant has been presented (McGaw et al., 1985; Ferretti et al., 1987; Epstein et al., 1992; Dodd et al., 1996; Levy-Polack et al., 1998), the reason being, they contain alcohol, desiccate the oral tissue, and have an unpleasant taste (Acute Lymphoblastic Leukemia in Children, 2009). Thus, non-alcoholic mouth rinses could be best preferred. Hydrogen peroxide rinses are also avoided as they may delay wound healing and cause further dryness of mucosa.

The child should brush with a soft tooth brush after every meal under the supervision of hospital staff to ensure its safety. Brushing is discontinued when the platelet counts fall below 20,000 per cubic mm, or when the absolute neutrophils count is less than 500 per cubic mm. Fungal infections, such as candida, are treated aggressively using Flucanazole (Diflucan) (Massler, 2000).

For the young child above 6 years, living in a non-fluoridated area, daily fluoride supplements should be considered. However, some physicians consider that the addition of yet another tablet to the daily collection of drugs already given is not justifiable and refuse to countenance such measures. In such circumstances, the use of daily topical fluoride gels has been used, and is particularly helpful in the xerostomic child and those at high risk for caries.

3) Emergency dental care during leukemia treatment

All emergency dental procedures should be performed following consultation with the pediatric oncologist. Appropriate timing for the dental procedures is critical as the risk of infection is greatest 7 to 10 days following induction therapy when the neutrophils count drops drastically. Only if the absolute neutrophils count exceeds 1000 per cubic mm, and platelet counts are appreciable, any dental treatment is performed. A prophylactic antibiotic coverage should be provided according to the norms of the American Heart association and consultation with the child's oncologist (Massler, 2000; Acute Lymphoblastic Leukemia in children, 2009).

4) Oral management after completion of leukemia treatment

Periodic recall visits in every 3 months for the first

year and every 6 months thereafter should be strictly followed. Children who received bone marrow transplant may not be able to undergo any dental procedures for another 1 year due to profound impairment of the immune function (Massler, 2000). Latest blood pictures are taken on every visit. The dentist should inform the parents/caretakers regarding the possible long term side effects of chemotherapy on the teeth, oral mucosa and craniofacial complex.

Conclusion

The key to success in maintaining a healthy oral cavity during cancer therapy is patient compliance. A pediatric dentist should educate the care takers and the child about the importance of oral care, to minimize discomfort and maximize the chances for a successful treatment outcome. The deleterious effects involved in indulging children have unhealthy food and the potential carcinogenicity of pediatric medicaments and nutritional supplements should be emphasized. Finally, a program on dental health education should be initiated and periodically maintained while carefully monitoring the progress of each leukemic child.

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