The Results of a Preventive Dental Program for Pediatric Patients with Hematologic Malignancies

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Purpose: The aim of this retrospective study was to assess the safety of dental treatment in pediatric patients with acute lymphoblastic leukemia (ALL), and Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), and to report any complications related to dental treatment during a preventive dental program covering a 4-year period.

Materials and Methods: In this study 74 preventive fissure sealants, 69 fillings and 81 extractions along with periodontal treatment that included prophylaxis and/or scaling were performed on 124 patients with a mean age of 7.00 ± 2.3. The patients were monitored for at least three weeks after the treatment for bleeding, pain, local and/or systemic infection, fever, delayed wound healing or any other complication.

Results: Two patients (one ALL and one HL) suffered delayed wound healing after extractions which resulted in the delay of chemotherapy. In three of the patients who were in remission-induction phase of ALL, oral mucositis occurred in the cheek mucosa adjacent to extraction sites and five patients had tooth staining due to the routine use of a chlorhexidine mouthrinse. The healing was uneventful in all other patients.

Conclusions: The findings of this study suggest that with special precautions such as adequate hematological values, timing of the intervention and supportive medical care, dental treatment can be safely performed in pediatric patients with hematological malignancies.

Key words: leukemia, lymphoma, dental treatment, tooth extraction, periodontal therapy

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Leukemia and lymphoma are the most common malignancies of childhood. Impressive advances have been made in the treatment of hematologic malignancies (HM) in the past two decades. While the prognosis of acute lymphoblastic leukemia (ALL) has been considered almost hopeless in the 1960s and 1970s, a probable cure rate of 50% percent has been reported in 1983 (Shafer, 1983). Furthermore in the 1990 s, the overall cure rate for childhood ALL is estimated at about 80% (Crist, 2000). Therefore, the population of adolescents who are in a remission period or completely cured from the disease is rapidly growing over the years.

The dental care for patients with leukemia/lymphoma is extremely important for many reasons. DePaola et al (1986) have reported that morbidity and mortality, which result from oral complications, can significantly be reduced with supportive dental care in these patients. Both dental caries and periodontal diseases are infectious diseases and the retention of a diseased tooth can cause an infec-

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tion, which can subsequently lead to morbidity or even mortality in these patients. It has been reported that 24% of life-threatening infections arise from oral sites in ALL patients (DePaola, 1986). It is therefore crucial to eliminate potential infection sources from oral sites in the prechemotherapy and pretransplant time period.

The safety of dental extractions in hematologic malignancies was evaluated in previous studies. Overholser et al (1982) performed 119 extractions in 28 acute non-lymphoblastic leukemia patients and Williford et al (1989) undertook a series of 142 extractions in 26 ALL patients. These two studies revealed that adequate hematologic values and special surgical techniques have minimized the risk of post-extraction hemorrhage and infection. Both studies concluded that dental extractions could be safely performed in patients with hematologic malignancies in combination with supportive care from cancer centers. More recently, Raut et al (2001) have emphasized that dental extraction intervention provided in the prechemotherapy and pre-bone marrow transplantation (BMT) time frame did not have a negative effect on medical outcome.

The aim of this retrospective study was to assess the safety of dental procedures which included restorative and periodontal treatment and tooth extractions in pediatric leukemia/lymphoma patients, and to report any possible local or systemic complications associated with these treatments during a dental preventive program covering a 4-year period.

MATERIALS AND METHODS

This study was approved by the ethical review board of Çukurova University. Along with a preventive dental care program, 185 patients who had been referred to the Pediatric Hematology/Oncology Department had an intraoral examination. The examination followed the World Health Organization (WHO) guidelines. Of these 185 patients, it was concluded that 124 children, 57 girls and 67 boys with a mean age of 7.0 ± 2.3 (range 3 – 3), needed dental treatment. Besides the need of periodontal prophylaxis for all, there were decayed teeth in 62 children; and abnormal tooth development such as hypodonti, microdonti and enamel hypoplasia, which required restorative treatment, was present in 9. The distribution of the children by sex, age, diagnosis and the stage of the malignancy and the performed type of dental treatment modality are shown in Table 1. All patients received ALL Berlin-Frankfurt-Münster 95 (BFM-95) and lymphoma BFM-95 chemotheraupatic regimens. The drugs used in these regimens are the same for both ALL and lymphoma and involve prednisone, vincristine, daunorubicine, L-asparaginase, mecaptopurine, cyclophosphamide, cytarabine, methotrexate in various protocols and dosages. Twelve ALL patients were cured of the disease and did not receive chemotherapy at the time of dental treatments.

Preventive and Restorative Treatment

Seventy four fissure sealants and 69 fillings were performed on 59 deciduous and 84 permanent teeth. The cooperation of the patients was achieved and no local or general anesthesia was used in any of them. Preventive fissure sealants were done on caries-free permanent molar teeth, which had deep pits and fissures susceptible to caries. Superficial enamel and dentin caries were treated with fillings. No endodontic therapy was performed since the benefits of endodontic therapy for patients receiving chemotherapy is not clear in the literature; instead extraction was chosen to be the type of treatment modality for symptomatic teeth with periapical infection.

Periodontal Treatment

All 124 children received oral hygiene instructions, rubber-cup prophylaxis and scaling. No patient required deep root planning or surgical procedures such as gingivectomy or gingivoplasty. A granulocyte count of at least 1,500/mm^3 and a platelet count of at least 40,000/mm^3 were required for scaling.

Tooth Extractions

Sixty two deciduous and 19 permanent teeth were extracted from 48 patients. Indications for deciduous teeth extraction were: severe caries, pulpal necrosis and physiological root resorption of 50% of the root length. Indications for permanent tooth extraction were: severe caries, pulpal necrosis, cracked teeth, supernumerary teeth and teeth associated with apical lesions. Hemotologic values

Table 1 Distribution of the patients by sex, age, type and stage of the hematologic malignancy and performed type of dental treatment

		Male	Female	Total	Mean age	Fissure sealants	Fillings	Extractions	Periodontal treatment
ALL	Remission-induction	22	26	48	6.6	26	28	36	48
	Intensification	7	8	15	6.3	14	9	14	15
	Maintenance	9	10	19	8.2	16	6	9	19
	Cured	6	5	11	8.3	2	5	3	11
NHL	Remission-induction	5	3	8	6.1	8	9	7	8
	Intensification	–	5	5	7.3	4	3	3	5
	Maintenance	3	4	7	8	–	5	4	7
HL	Remission-induction	5	6	11	6.5	6	4	6	11
TOTALS		57	67	124	7.0 ± 2.3	74	69	81	124

ALL: Acute Lymphoplastic Leukemia
NHL: Non-Hodgkin Lymphoma
HL: Hodgkin Lymphoma

with a granulocyte count of at least 1,500/mm^3 and a platelet count of at least 40,000/mm^3 were considered essential for extractions. Local anesthesia of the extraction region was achieved by 2% lidocain containing 1:100,000 epinephrine. In 14 patients, because of the lack of cooperation, sedation was performed by means of kethamine (0.1 mg/kg). The extractions were performed as atraumatically as possible. After permanent teeth extraction, alveolar plates were firmly compressed to diminish the pre-surgical bucco-lingual width of alveolar processes. No alveolar compress was done after deciduous teeth extraction to prevent any possible hazard to the underlying permanent teeth germ. No sutures or packing materials were used at extraction sites. A sterile gauze roll was placed on the extraction site and the patient was instructed to bite it for 20 minutes. For patients under sedation, bleeding control was done by the dentist by applying pressure on the site with a gauze roll for 20 minutes. Following the extractions, the patients and/or their parents were instructed to avoid violent exercise, stimulants or very hot food and drinks to minimize the risk of post-operative hemorrhage. If multiple extractions were needed in patients, at least one week was allowed to elapse before the next extraction.

All periodontal treatments and extractions were performed under antibiotic coverage. Since most of the patients were administered broad-spectrum antibiotics at the time of the procedures, no additional antibiotics were prescribed. Prophylactic ampicillin-sulbactame (50 mg/kg) was administered 1 hour before treatments to those patients who needed extractions and periodontal therapy but did not receive antibiotics. The antibiotic regimen was continued three times a day at the same dosage for 1 week after treatments for this group.

All treatment modalities (restorative, periodontal and extractions) were performed at least 3 days before the initiation of chemotherapy. In other words, all treatments were done approximately 10 days before the patient's granulocyte count fell below 500/mm^3 as a result of chemotherapy. If this time schedule could not be achieved, dental treatment was delayed until the hematologic values rose to the desired levels. Therefore, the therapy was postponed for 14 patients who needed extractions and for 21 patients who needed periodontal treatment. The longest delay time until the desired hematological values were achieved for these patients was one month. If possible, restorative and periodontal treatment or restorative treatment and extraction

Table 2 The distribution of observed complications

Complication	No. of patients	The type and the stage of the disease
Bleeding	–	–
Platelet Transfusion	–	–
Pain	–	–
Delayed wound healing	2	1–ALL (remission induction) 1–HL (remission induction)
Post-operative infection	–	–
Delay of chemotherapy	2	1–ALL (remission induction) 1–HL (remission induction)
Mucositis	3	3–ALL (remission induction)
Death	–	–
Other (staining of teeth)	5	3–ALL (remission induction) 1–ALL (maintenance) 1–NHL (remission induction)
Total no. of events	12	
No. of patients with multiple events	2	

were performed in the same visit. However, care was taken not to perform periodontal treatment and extractions in the same visit to minimize the risk of bleeding.

Patients and/or their parents were strictly instructed to maintain oral hygiene by means of toothbrushing at least three times a day with a soft toothbrush and by chemical plaque control with twice-daily rinses of 0.2% chlorhexidine gluconate (CHG) mouthrinses regardless of hematological values.

All patients were monitored on a daily basis for at least 3 weeks for symptoms that could be related to dental treatment modalities. Platelet and granulocyte counts were checked daily and the patients were evaluated for bleeding, the need for platelet transfusion, pain, post-operative infection, fever, delayed wound healing, mucositis, hospitalization and death (Raut, 2001). Complications were defined as described by Raut et al (2001): bleeding was defined as persistent bleeding after external pressure; postoperative infection was defined as alveolitis, persistent edema, purulence and systemic fever; delayed wound healing was defined as the extended time of the alveolar plates to reorganize and close after extractions; and mucositis was defined as the inflammation and painful ulceration of the lining of oral mucosa. Chi-square and Fisher's exact tests were performed for the statistical analysis of the comparison of the complication rates between disease groups.

RESULTS

Seventy-four fissure sealants, 69 fillings and 81 extractions besides periodontal treatment were performed on 124 patients in this study. The post-treatment follow-up period was 3 – 8 weeks with a mean of 6 weeks.

The observed complications and their distribution by the type and the stage of disease are shown in Table 2. There were a total of 12 complications and the number of patients with multiple post-treatment events was 2. The overall complication rates between disease groups were not statistically significant ($p = 0.4$), nor there were differences between individual disease types (ALL vs. HL $p = 0.3$; ALL vs. NHL $p = 1.0$ and NHL vs. HL $p = 0.2$).

No local or systemic complications were observed after restorative treatments. However, 9 children reported a mild sensitivity in the restored teeth on the following day of treatment, which had completely subsided after two days. The major complaint of the children was 'tiredness of the jaws' related to the prolonged periods of treatment.

Bleeding was easily controlled by means of pressure gauze after scaling and/or rubber-cup prophylaxis. The bleeding tendency was significantly reduced in all children during the follow-up period after professional and personal oral-hygiene procedures, which included toothbrushing and 0.2% CHG rinse. Children complained about the bitter taste of the mouthrinse. Staining of the teeth was observed in five patients in the third and fourth week related to CHG rinse. Rubber-cup prophylaxis was repeated and CHG rinse was replaced with benzydamine hydrochloride rinse for these patients. No other complications were noted related to periodontal therapy.

No hemorrhagic complications occurred in any patient after extractions. The bleeding ceased after 10 – 15 minutes following deciduous teeth extraction, and after 20 minutes to 1 hour following permanent teeth extraction. No platelet transfusions were required for any patient. Mild pain, during the subsequent 24 hours after extraction, was the major complaint after extractions. However, severe pain, which might require the prescription of analgesics, was not reported by any of the extraction patients and the enteral nutrition did not seem to be affected. There was no pain reported by any of the patients within the postoperative third-day period.

Two patients (one ALL and one HL) suffered delayed wound healing which resulted in the delay of chemotherapy after extractions. However, these two patients did not experience post-operative infection or the alveolitis of extraction sites. All other extraction sites were either completely or partially closed in one week

Three ALL patients who had extractions of the mandibular second deciduous molar and two mandibular permanent first molars, developed mucositis at their cheek mucosa adjacent to the extraction sites in the post-operative tenth day. However, there were no signs of infection in the extraction sockets. The mucositis lesions (1 x 2 cm. in size) extended from the muco-vestibular fold adjacent to the extraction sites to the cheek mucosa. All three patients were in the remission-induction phase of ALL and chemotherapy was started five days after extraction. The mucositis occurred on the fifth day of chemotherapy in which the granulocyte count was 400/mm^3, 750/mm^3, and 800/mm^3 respectively. A mouthrinse containing granulocyte-macrophage colony-stimulating factor (GM-CSF) was prescribed to these patients and the mucositis recovered uneventfully within ten days (post-operative third week).

DISCUSSION

Similar (Sepet, 1998) or higher (Pajari, 1995) prevalences of dental diseases are reported for children with leukemia/lymphoma when compared to systemically healthy children. DePaolo et al (1986) have mentioned that besides preventing oral complications, the self-esteem of the patients with hematologic malignancies greatly improves by correcting facial esthetics with dental care. Another important reason for dental care relates to the improvement of patients' chewing ability to achieve sufficient enteral nutrition. However, there are conflicting opinions in the literature for dental treatment of these patients – especially for surgical procedures such as tooth extraction. Zegarelli et al (1978) have suggested that tooth extractions or any other surgical procedure is usually contraindicated for ALL patients. Little and Falace (1980) have reported that these patients should only receive conservative emergency dental care. Tai et al (1994) have recommended that the prophylactic extraction of partially erupted or impacted third molars may be proposed if there is an increased risk of post-cancer treatment extraction and if the management of third molars interferes with cancer treatment.

Dental caries and periodontal diseases are both infectious in nature and may cause significant morbidity and mortality in these patients during periods of chemotherapy, in which bone marrow is suppressed and the subjects are more susceptible to infection. Postextraction osteomyelitis in a BMT recipient (Barasch, 1993) and sinus polyp-associated soft tissue lesion together with unilateral blindness in a leukemic patient (Acikgoz, 1999) are reported in the literature. Doerr and Marunick (1997) have noted that patients who have solid tumors and whose extractions were performed concurrent with the oncologic resection of these solid tumors had fewer postoperative complications compared to those patients whose extractions performed after the resection. Thus, they recommended that the management of the dentition should be managed prior to ablative and reconstructive procedures. The timing of dental treatment in cancer patients is, therefore, important and should be before chemotherapy, resection and/or BMT to prevent complications arising from oral sites. In this study all treatment modalities were performed at least three days before the chemotherapy regimen and that is approximately ten days before granulo-

cytopenia occurs. No post-operative infection related to dental treatment was noted in our study. This may be explained by the timing of the procedures in which no patient had a granulocyte count of $\leq 1500/mm^3$ and a platelet count of $40,000/mm^3$, and by the use of antibiotics. Dental treatment was postponed if these minimal hematologic values were not present.

Although there were not statistical differences, the risk of complication was higher in patients with acute leukemia than in patients with malignant lymphoma, and in patients receiving remission induction therapy compared to patients with intensification and maintenance therapy. This can be described by the severe granulocytopenia and thrombocytopenia induced by the intensive and multi-agent chemotherapy treatment protocols, which are aimed to achieve a remission for the management of the active stages of the disease. Therefore, special precautions such as intensive follow-up, routine hematological analysis and hospitalization are needed after invasive dental treatments for the patients who are in the active stages of HM. It is not clear whether the mucositis lesions, which developed adjacent to extraction sites in this study, were directly related to the procedure itself. The lesions occurred in patients who were at the remission-induction period of ALL in which intense chemotherapy is applied. High-dose chemotherapy directly affects the rate of cell proliferation in the epithelium, causing atrophy and a break in the mucosa resulting in painful, debilitating mucositis lesions (Epstein, 1999). Personal oral-hygiene procedures, oral microflora, dental appliances, and smoking are considered to be risk factors in the development of mucositis (Dodd, 1999). All cases of mucositis noted in this study occurred in the mucosa adjacent to extraction sites of mandibular molar teeth. One explanation for this finding might be the size of the extraction sockets which were larger when compared to anterior teeth, resulting in a larger space to be reorganized during the process of wound healing. However, the extraction sites were uneventful during the course of mucositis with no signs of infection. During wound healing, local circulation and blood supply must also be adequate in order to provide substrate for the formation of new tissue. Abnormalities that may interfere with blood flow, such as chemotherapy, together with the fact that vascularization and blood supply to the mandible are much less than to the maxilla (Peterson, 1998) might be the explanation of why all cases of mucositis noted in this study were on the mandible. Current approaches in the management of mucositis include oral rinsing with antiseptic containing mouthwashes, maintaining oral hygiene, and using topical analgesics (Epstein, 1999). Successful clinical results, which conform to the findings of this study, have been reported with GM-CSF mouthrinses (Bez, 1999).

No sutures were used after extractions in this study. Instead, alveolar plates were firmly compressed after permanent teeth extractions to reduce the sizes of the extraction sockets, which will be exposed to the oral environment. Overholser et al (1982) have emphasized the necessity of primary wound closure with multiple interrupted sutures after extractions in patients with leukemia. Williford et al (1989) stated that silk or gut sutures must be used after multiple tooth extractions in patients with HM. However, it has been reported that sutures which are placed in gingiva, produce a prolonged tissue response that might be a result of the continual influx of microbial contamination (Selvig, 1998). Furthermore, after intraoral suture removal, bacteremia, which may threaten immunocompromised patients, has also been reported (King, 1988).

In the presented preventive program, the patients and/or their parents were instructed to perform meticulous oral hygiene regardless of hematologic values, and this reduced the plaque levels without concurrent bleeding problems. The bleeding tendency was significantly reduced in all children during the follow-up period after professional and personal oral-hygiene procedures. However, soft toothbrushes with gentle bristles must be used and care should be taken in order not to traumatize the gingival tissues with harsh brushing for pediatric patients with HM. Previous studies have proved that maintaining an excellent oral hygiene reduces the incidence of oral infections and mucositis while not increasing the risk of bacteremia (Borowski, 1994). Although a large volume of studies has been done evaluating the effectiveness of mouthrinses in patients with HM, chlorhexidine glucanate has received most attention in the literature. The antibacterial and antifungal properties of CHG have been reported to be beneficial in both leukemia and BMT patients (Epstein, 1992). However, some local, reversible side effects with long-term use such as staining of the teeth as seen in this study and impairment of taste perception (Molinari, 1992) in addition to the bitter taste of

the rinse which was the major complaint of all patients, may limit the routine prophylactic use of CHG.

In conclusion, the findings of this study suggest that with special precautions such as adequate hematological values, timing of the treatment and supportive medical care, dental treatment can be safely performed in pediatric patients with hematological malignancies

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