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The Oral Health of Long-term Survivors of Acute Lymphoblastic Leukaemia: a Comparison of Three Treatment Modalities

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Sixty-eight children who were diagnosed with acute lymphoblastic leukaemia (ALL) prior to age 5 years and treated with chemotherapy alone, chemotherapy plus 1800 cGy cranial irradiation (RT), or chemotherapy plus 2400 cGy RT were assessed clinically for overall dental health. All patients were at least 60 months in continuous remission. Dental caries were assessed by NIDR diagnostic criteria, oral hygiene was assessed by the modified Oral Hygiene Index, and gingival health was assessed by the modified gingival index of Loe and Silness. There was no significant difference in caries experience between the three groups nor with the normal population. Those patients that received 2400 cGy RT had significantly higher plaque and periodontal index scores than patients in the other treatment groups. The results of this study suggest that: (1) children with ALL treated with any of the described modalities are at no greater risk of developing dental caries than the normal population; and (2) patients receiving 2400 cGy prior to age 5 years are at greater risk of developing periodontal disease than patients treated with other central nervous system prophylaxis regimens examined in this study.

Keywords: acute lymphoblastic leukaemia, cranial irradiation, oral health, dental caries, gingivitis

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INTRODUCTION

THE ADVERSE dental effects of cancer therapy for acute lymphoblastic leukaemia (ALL) patients have been reported in both the medical and dental literature. These effects include tooth agenesis, arrested tooth development, microdontia and enamel dysplasia, as well as alterations to the developing craniofacial skeleton [1]. The severity of these effects on the dentofacial structures was found to be related to the age of the patient at initiation of treatment and the use of cranial radiation.

The significance of these dentofacial changes on long-term dental health has not been well explored. Previous research would suggest that conditions associated with the administration of chemo- and radiotherapy (RT), such as hypoplastic and missing teeth, would make one more susceptible to dental disease [2, 3]. Currently, several different therapeutic regimens are used in the treatment of ALL: chemotherapy with and without varying doses of RT. The purpose of the present study was to compare the effects of three ALL treatment approaches on caries prevalence, and periodontal health in children with ALL in long-term remission.

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MATERIALS AND METHODS

Sixty-four children who were diagnosed with ALL prior to age 5 years and were at least 60 months in continuous remission were studied. All patients received varied combinations of chemotherapeutic agents given by previously described protocols [4–6]. Central nervous system treatment consisted of either: (i) intrathecal methotrexate with and without cytosine arabinoside (IT MTX) ($n = 14$); (ii) IT MTX plus 1800 cGy cranial RT ($n = 33$); or (3) IT MTX plus 2400 cGy cranial RT ($n = 17$). All radiation therapy was given on 4–8 MV linear accelerators, 180 cGy fractions daily to a total of 1800 cGy, or 200 cGy fractions daily to a total of 2400 cGy with opposed lateral fields using a clinically placed lens block. The inferior border of the field was positioned along a line from the inferior orbital ridge to the middle of the second cervical vertebra. All patients received radiotherapy isocentrally.

Dental caries assessment

Detection and scoring of dental caries utilized the diagnostic criteria and methodology developed by the National Institute of Dental Research (NIDR) [7]. All tooth surfaces are scored as decayed, missing, or filled based on a clinical examination utilising a dental explorer, mirror, and light. Teeth with enamel hypoplastic defects were scored in the usual manner in accordance with the NIDR system.

Oral hygiene assessment

Oral hygiene was assessed utilizing the modified Oral Hygiene Index (OHI-S) [8]. Briefly, following the application

of a erythrocin plaque disclosing solution the following tooth surfaces were scored: the facial surface of the first permanent molar on the right and left maxilla; the facial surface of the maxillary right central incisor and mandibular left central incisor; and the lingual surface of the first permanent molar on the right and left sides of the mandible. The plaque score was scored as 0 (no plaque), 1 (greater than 0, but less than $\frac{1}{3}$ surface covered with plaque), 2 ($\frac{1}{3}$ to $\frac{1}{2}$ surface covered with plaque), and 3 (greater than $\frac{1}{2}$ surface covered with plaque). The total plaque score was then determined for each patient.

Gingival assessment

A modification of the gingival index of Loe and Silness [9] was used to assess gingival health. The buccal, mesial, lingual, and distal surfaces of the gingival tissues of the right and left first maxillary molars, the maxillary right central incisor, the mandibular left central incisor, and the right and left first mandibular molars were scored according to the following criteria: 0: normal gingiva; 1: mild inflammation-slight changes in colour, slight edema. No bleeding on probing; 2: moderate inflammation-redness, edema and glazing. Bleeding upon probing; 3: severe inflammation-marked redness and edema. Ulceration. Tendency to bleed spontaneously.

The scores were summed and divided by the total number of teeth examined to determine the gingival index for the individual.

Examiner reliability

All clinical examinations were performed on all patients by a single dentist (the first author). Examiner reliability was determined by re-examining 10 patients for caries and periodontal assessment 4 weeks post-initial examination and comparing charting. A 100% agreement was found on the caries assessment and a 94% agreement on the periodontal index. Oral hygiene was not reassessed.

Statistical analysis of data

The three patient groups were compared with respect to each of the indices examined using two-sided, stratified Wilcoxon rank-sum tests of significance. Caries scores were then compared to the regional findings of The National Survey of Dental Caries in U.S. School Children: 1986–1987 using a one-way test of analysis (ANOVA). Patients were matched for age, sex, and region of the country for this analysis.

RESULTS

Dental caries

The mean caries rate as measured by DMFT/dmft for each of the treatment groups is presented in Table 1. The mean DMFT/dmft for children receiving chemotherapy alone was 2.3 ± 2.5, for children receiving 1800 cGy RT it was 2.7 ± 3.0, and for children receiving 2400 cGy it was 4.2 ± 5.5. There was no significant difference in caries experience between the three groups for either the primary or permanent dentitions.

Oral hygiene

The mean plaque scores as measured by the S-OHI are presented in Table 1. The mean score for those patients receiving chemotherapy alone was 4.9 ± 3.3, for patients receiving 1800 cGy RT it was 6.1 ± 4.1, and for patients who received 2400 cGy RT it was 12.9 ± 3.1. Those patients in the 2400 cGy RT group had significantly higher plaque scores than patients in the other three treatment groups ($P < 0.001$).

Table 1. Comparison of DMFT/dmft, simplified oral hygiene index scores (OHI-S), and gingival index scores in long-term survivors of ALL by type of CNS prophylaxis

Type of CNS prophylaxis (no.)	DMFT/dmft	OHI-S	Gingival index score
Intrathecal methotrexate (14)	$2.3 \pm 2.5/2.9 \pm 2.7$	4.9 ± 3.3	4.7 ± 3.2
IT MTX plus 1800 cGy (33)	$2.7 \pm 3.0/1.9 \pm 1.7$	6.1 ± 4.1	5.0 ± 4.5
IT MTX plus 2400 cGy (17)	$4.2 \pm 5.5/3.9 \pm 2.3$	12.9 ± 3.1*	10.1 ± 4.3†

NIDR mean DMFT for New England Region: 2.31
NIDR mean dmft for New England Region: 3.14
*Significant $P < 0.001$; †significant $P < 0.01$.

Gingival health

The gingival health scores as assessed by the modified Loe and Silness index are presented in Table 1. The mean score for those patients receiving chemotherapy alone was 4.7 ± 3.2, for patients receiving 1800 cGy RT it was 5.0 ± 4.5, and for patients receiving 2400 cGy it was 10.1 ± 4.3. The 2400 cGy group had significantly higher gingivitis scores than the other groups ($P < 0.01$).

DISCUSSION

The results of this study demonstrate that while differences in ALL treatment protocols for CNS prophylaxis do not significantly affect dental caries susceptibility, they do impact on plaque retention and gingival health. Patients who received 2400 cGy of cranial irradiation had significantly higher plaque and gingival scores than the other treatment groups.

These results both confirm and contradict several previous studies. As in this study, the studies by Welbury *et al.*, Maquire *et al.*, and Nunn *et al.* all found leukemia patients to have no greater dental caries experience than the normal population or their siblings [10–12]. However, also as in this study, although no statistically significant differences in caries experience was demonstrated between the ALL patients and the controls, there was a general trend of higher DMFT/dmft scores in the ALL population. This is in contrast to the results of Purdell-Lewis *et al.* and Bertelone *et al.* who found a statistically higher caries rates in the ALL population [13, 14]. This discrepancy made be due to differences in fluoride exposure or the aggressive preventive programme to which parents and patients are exposed at our research institution.

The differences in scores of both oral hygiene and periodontal indices between the groups may be related to several variables. As reported in an earlier study by our group, 95% of patients who have received 2400 cGy prior to age 5 years demonstrate enamel hypoplasia [1]. The irregular enamel surfaces characteristic of these teeth undoubtedly results in a

greater susceptibility to plaque retention, negatively impacting on both the oral hygiene and periodontal indices scores of these patients.

There may have been some unique radiation effects on the salivary glands of those patients in the 2400 cGy group. Portions of the parotid gland were included in the field of all patients who received cranial irradiation. The studies by Valdez, Westcott *et al.*, and Mira *et al.*, have all demonstrated permanent decreased salivary function with radiation levels as low as 2000 cGy [15–17]. While salivary function was not measured as part of this study, these potential adverse changes may be a contributing factor in the differences observed between the study groups. Decreased salivary flow can result in changes in the oral microbiota, lubrication, and self-cleansing, all of which may have contributed to increased plaque accumulation of patients who received 2400 cGy of cranial irradiation.

Another, perhaps less appreciated, variable is the detrimental effect of cranial irradiation on normal mental development. Several recent studies have demonstrated markedly decreased I.Q.s in children receiving 2400 cGy of cranial irradiation [18]. The mean I.Q. for patients in the 2400 cGy group was 85, closely approximating the classification of borderline mental retardation (70–79). The impact of mental retardation on dental health has been well documented in the literature [19, 20]. Poor oral hygiene and periodontal disease appear to be related to the degree of mental retardation [21]. Consequently, the differences in oral hygiene and periodontal health observed in our study groups may be the result of cognitive effects of antileukaemic therapy rather than any intrinsic changes in the oral environment.

CONCLUSIONS

(1) Children with ALL who have received 2400 cGy of cranial irradiation are at no greater risk of developing caries than patients receiving other forms of central nervous system prophylaxis or the normal population.

(2) Patients who have received 2400 cGy of cranial irradiation demonstrate significantly higher plaque scores and periodontal index scores than patients treated with other central nervous system prophylaxis regimens examined in this study.

(3) Patients who have received 1800 cGy of cranial irradiation demonstrate no adverse effects on their dental health.

(4) In light of the dramatic improvements in long-term survival of these patients, it is imperative that aggressive preventive programmes be initiated with this patient population. It is particularly important to emphasize periodontal health considerations and their impact on long-term dental health.

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