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LATE EFFECTS

Long-term Effects of Chemotherapy on Dental Status of Children Cancer Survivors

Orsolya Nemeth,[1,2] Peter Hermann,[2] Peter Kivovics,[2] and Miklos Garami[1]

[1]2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary; [2]Department of Prosthodontics, Faculty of Dentistry, Semmelweis University, Budapest, Hungary

Background: The aim of this study was to investigate the long-term effects of chemotherapy on the dental and gingival health and dental disturbance parameters of children cancer survivors. *Procedure*: Thirty-eight children (mean age 12.2 ± 0.5 years) who underwent chemotherapy at 4.29 ± 1.71 years of age formed the study group. Forty age- and gender-matched healthy children with a similar socioeconomic background served as controls. Subjects' caries status (number of decayed, missing, or filled permanent teeth [DMF-T]) was recorded according to World Health Organization criteria. Subjects' periodontal status was recorded according to the community periodontal index system. Radiographic dental examination was used to analyze dental malformations. *Results:* DMF-T, D-T (number of decayed permanent teeth), and F-T (number of filled permanent teeth) were significantly higher in the study group compared to the controls (4.61 ± 3.71, 3.97 ± 4.45, respectively, and 0.58 ± 0.14 vs. 2.21 ± 1.01, 0.84 ± 1.82, and 1.18 ±1.07, respectively. The most frequent dental disturbances were root malformation (52.6%) and agenesis (47.4%). *Conclusions*: According to our examination dental status of long-term survivors is worse than in controls. Hence proper oral hygiene for children cancer survivors (CCS) is critical. In order to meet the need for dental care in CCS health authorities are encouraged to revitalize the dental services Long-term follow-up of CCS is necessary to monitor their dental growth and oral health.

Keywords chemotherapy, children cancer survivors, dental disturbances, dental status, long term effects

INTRODUCTION

The availability and adoption of modern therapeutic protocols for childhood cancer has continuously reduced the mortality rate of childhood malignancies in most countries over the past decades. The survival rates of childhood cancer differ depending on diagnosis and patient location, with the poorest survival rates (approximately 60%) observed for acute myelogenous leukemia and primitive neuroectodermal tumor in developing countries such as in Africa and Asia, while the best survival rate for retinoblastoma and Hodgkin disease in developing countries is over 90% [1]. Every 715th young people is a 5-year-posttreatment survivor of childhood cancer; however, treatment can have important immediate and several long-term degenerative and developmental side effects on the maxillofacial structures [2]. The animal studies have shown that antineoplastic agents induce changes in hard and soft tissue [3]. Several

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Address correspondence to Orsolya Nemeth, Department of Prosthodontics, Faculty of Dentistry, Semmelweis University, Szentkiralyi u. 47. Budapest 1088, Hungary. E-mail: drnemethorsolya@gmail.com

chemotherapeutic agents, in particular vincristine can cause increased prominence of incremental lines in dentin due to a temporary disturbance of microtubular function in the odontoblasts [4].

Conflicting results have been reported on the caries profile of children treated for malignant disease. An increased rate of dental caries has been reported in some studies where more mild opacities were observed in patients receiving combination chemotherapy for malignant disease compared to controls [5–7]. A representative follow-up study of Wogelius et al. reported that children treated with anticancer therapy between 5 and 6 years of age had an increased prevalence of severe caries by age 12 [8,9].

The current study includes data on the cariological status, oral hygiene, periodontal status, and frequency of altered dental development in 12-year-old, long-term childhood cancer survivors in Hungary.

METHODS

Patients

Forty-three 12-year-old children were examined, who had been receiving cytotoxic drugs between the ages of 31 month and 6 years, during the period of permanent tooth development. All of them were long-term survivors of their malignancies. Patients were treated according to international protocols (Table 1). None of these children had radiotherapy or stem cell transplantation. The patient did not take any medication at the time of oral examination. Three children did not wish to participate and two had gotten a secondary neoplasm, so they were excluded from the investigation, in this way the data of the remaining 38 were analyzed (Table 1).

Forty age- (22 female and 18 male) and gender-matched healthy children with mean age of 12.5 $\pm$ 0.4 from the same socioeconomic background as the patients served as controls. The control group was admitted for optional check up in a school in Budapest (Fazekas Mihály Gimnázium, Budapest, Hungary). None of the control participants were medicated.

The study protocol was approved by the local ethics committee for human studies, and before the start of the study, relatives of all participants signed an informed consent form.

TABLE 1 Patient's Characteristic in Study Group

Study group	
Number of patients	Female 16 Male 22
Age at study	12.2 $\pm$ 0.5 years
Age at diagnosis	4.29 $\pm$ 1.71 years
Time after chemotherapy	6.9 $\pm$ 2 years
Protocols of chemotherapy	
BFM-95	18 patients
NBL-2	5 patients
CWS 96	4 patients
SIOP 93	4 patients
BFM-98	3 patients
COSS-96	2 patients
DAL-HD 90	2 patients
Radiotherapy	no
BMT	no
Hormone therapy	no
Dental prophylactic treatment (iontophoresis)	no

Cariological Status

Participants were examined clinically according to the methodology and criteria of World Health Organization (WHO), using artificial light, dental mirror, dental probe, and standard community periodontal index of treatment needs (CPITN) periodontal probe. This examination focused on dental status and presence of dental caries. [DMF-T number; number of decayed (D-T), missing (M-T), and filled permanent teeth (F-T).]

The prevalence proportion rate (%) of dental caries is the proportion of children who are exposed to the caries.

The Dental Care Level restorative index (RI) is an indicator of dental care, reflecting the degree of treated carious lesions. It is calculated for the permanent dentition using the following formula: RI = F/DF × 100, where F = filled and DF = decayed and filled teeth.

Periodontal Status and Oral Hygiene

The community periodontal index (CPI) system was used to measure periodontal status; however, the registrations were restricted to score 0 = healthy, 1 = gingival bleeding, and 2 = bleeding and calculus. The CPI scores were computed according to WHO recommendations [10]. The mouth is divided into sextants defined by tooth numbers: 18–14 (right maxillary third molar to right maxillary first premolar), 13–23 (right maxillary canine to left maxillary canine), 24–28 (left maxillary third molar to left maxillary first premolar), 38–34(right mandibular third molar to right mandibular first premolar), 33–43 (right mandibular canine to left mandibular canine), and 44–48 (left mandibular third molar to left mandibular first premolar). The affected sextants were recorded although.

The OHI-S (Simplified Oral hygiene Index) was recorded according to Greene and Vermillion [11]. The OHI-S has two components, the Debris Index and the Calculus Index. These indexes are based on numerical determinations representing the amount of debris or calculus found on the preselected tooth surfaces (the six surfaces examined for the OHI-S are selected from four posterior and two anterior teeth).

Dental Disturbances

The radiographic dental examination included assessment of root malformations (short, blunted, tapered, and V-shaped), microdontia, and agenesis. These dental disturbances were recorded as described by Dahllof et al. [12].

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS, Inc., Chicago, IL, USA) was used in the statistical analysis of all data. The paired Student's *t* test was employed for analysis of the DMF-T number, the Pearson χ^2 test was used for analyzing the CPI scores and the Wilcoxon rank test was used for analyzing OHI-S.

RESULTS

Cariological Status

Table 2 shows D-T, M-T, F-T, and DMF-T number. The DMF-T number ($P = .001$, 95% confidence interval (CI) of difference = −3.784 to −1.005), D-T number ($P < .001$, 95% CI of difference = −4.451 to −1.812) was found significantly higher in the study group than in the control group. But the F-T number ($P = .013$, 95% CI of difference = 0.137–1.073) was significantly lower in the study group.

The prevalence proportion rate (%) of dental caries in the study group was 81.6% and 77.5% in the control group.

TABLE 2 Means, CI of the Difference of D-T Decayed Permanent Teeth, M-T Missing Permanent teeth, F-T Filled Permanent Teeth of Childhood Cancer Survivors and in the Control Group (paired Student's *t* test)

	Mean	95% CI	
DMF-T*			
Study group	4.61	−3.78	−1.01
Control group	2.21		
D-T*			
Study group	3.97	−4.45	−1.81
Control group	0.84		
M-T			
Study group	0.05	−0.02	0.29
Control group	0.18		
F-T**			
Study group	0.58	0.14	1.07
Control group	1.18		

*$P \leq .001$, **$P = .013$.

The RI of permanent teeth in the study group was 12.8%, and 58.2% in the control group.

Periodontal Status and Oral Hygiene

Table 3 shows the CPI. A reading of 2.11 ± 0.32 sextants per subject was deemed healthy, 2.61 ± 0.25 sextants were affected with mild or moderate gingivitis, and 1.28 ± 0.21 sextants were affected with severe gingivitis in the study group.

Analysis of the patients' periodontal health showed the presence of soft deposits in 81.5% of the cases examined. OHI-S found significantly higher values in the study group than in the control group (Table 3).

Dental Disturbances

Table 4 shows the distribution of disturbances in dental development that were diagnosed on panoramic radiographs of 1217 teeth (44 deciduous and 1173 permanent teeth) in the study group, and 1051 teeth (16 deciduous and 1035 permanent teeth) in the control group.

DISCUSSION

The DMF-T number, D-T number was significantly higher and F-T number was significantly lower in the study group than in the control group. This means that there was

TABLE 3 Distribution (%) of 12-year-old Childhood Cancer Survivors and Control Group by Maximum CPI Score (Pearson χ^2 test), Simplified Oral Hygiene Index Scores, Debris Index, and Calculus Index Scores in the Study and Control Group (Wilcoxon test)

	Study group	Control group
CPI		
Healthy	52.6	52.5
Bleeding	42.1	40
Bleeding and calculus	5.3	7.5
OHI-S*	1.53 ± 0.77	0.99 ± 0.78
Debris index*	1.47 ± 0.71	0.93 ± 0.78
Calculus index	0.05 ± 0.32	0.08 ± 0.27

*$P \leq .001$.

TABLE 4 Scores of Dental Disturbance Parameters Studied in the Study Group and in the Control Group (n.d.: No Data Because of Radiation Charging of Panoramic Radiograph)

	Study group				Control group			
Parameters	Patient	$n = 38$	Teeth	$n = 1173$	Patient	$n = 40$	Teeth	$n = 1035$
Agenesis*	47.4%	($n = 18$)	3.75%	($n = 44$)	5%	($n = 2$)	0.6%	($n = 6$)
Without third molars	10.5%	($n = 4$)	0.4%	($n = 5$)	n.d.		n.d.	
Microdontia	31.6%	($n = 12$)	3.4%	($n = 40$)	0%	($n = 0$)	0%	($n = 0$)
Macrodontia	2.6%	($n = 1$)	0.08%	($n = 1$)	2.5%	($n = 1$)	0.2%	($n = 2$)
Unerrupted teeth	15.8%	($n = 6$)	2.2%	($n = 26$)	n.d.		n.d.	
Root malformation	52.6%	($n = 20$)	7.9%	($n = 93$)	n.d.		n.d.	

more untreated dental decay. This is in accordance with many studies [7,13,14]. Kaste et al. reported 29% excessive caries in the childhood cancer survivors [15], resulting in a lower RI value (12.8%). However, there was no significantly difference in caries prevalence between study and control group, and the results were the same as those of Avsar et al. [14]. The rise in DMFT in the study group seems not to be a direct result of anticancer therapy nor oral hygiene, but a consequence of nonprofessional dental care during and after chemotherapy. The debris index and the simplified oral hygiene index scores are signs of poor oral hygiene. We found similar results with recent studies [13,16,17].

Nunn et al. found no difference in dental caries between treated children and their siblings, perhaps because the oral hygiene depends on their parents in this age, though significantly more dental anomalies were detected radiographically in the chemotherapy-treated group [18]. In some studies, the study group consisted of children with a great age difference and the patients were in the mixed dentition [8,19]. The age of 12 years is especially important, as the global monitoring age for caries for international comparisons and monitoring of disease trends [10].

Before anticancer therapy, the children did not visit the dentist for routine fillings of their permanent teeth. We found that none of the children treated with chemotherapy received any additional fluoride prophylaxis apart from brushing with fluoride toothpaste during induction therapy, but not at all after chemotherapy. Childhood cancer survivors are considered equal to healthy children when their therapy is finished. However, they should be placed in a high-risk dental health group because of their therapy. The nutrition of these children changed with cancer, and they often craved sugar-containing soft drinks and pasty foods to moisten their mouths. Their nutrition contained too much fat, carbohydrate, and almost no dietary fiber or protein. Additionally, this routine continued after therapy. Without a healthy lifestyle, oral counseling by a pedodontist, and specific dental protocols and guidelines, child cancer survivors will not be receiving effective care.

Chemotherapeutic agents cyclophosphamide and doxorubicin are known to interfere with dental development after cessation of treatment in rats [20,21]. Medication with the antracyclines and platina agents disturb dentin matrix secretion and collagen fibril formation and cause short, thin, tapered roots [22–24]. That chemotherapy alone can cause permanent dental retardation has been shown by many studies [12,13,16,18,25–27].

We found that the most frequent dental disturbances (52.6%) are root malformations, because coronal size and shape is determined before birth [28]. All teeth with root malformations were erupted in normal positions without evidence of periodontal disease. This is also the reason several studies such as ours have not reported statistically significant differences in hypoplasia, micodontia, and macrodontia between children treated only by chemotherapy and their control [13–15].

We suggest that childhood cancer survivors be considered a high-risk dental group. They should be subjected to follow-up examinations, with specific attention to disturbances of dental and facial development as well as caries and periodontitis prevention and closer cooperation between the dentist and the pediatric oncologist. A rational and flexible budget of cancer treatment should contain funds for preventive dentistry. Hospice care for children should provide for dental care and diet counseling for families with childhood cancer survivors.

It became clear that, for children cancer survivors (CCS) significant differences were observed regarding caries experience and dental care between CCS and healthy controls. The level of untreated dental decay in the CCS population is considerably high, which was reflected by a significant lower dental attendance. CCS should be

expected to run a potential high caries risk taking into account the chemotherapy-associated biological and behavioral alterations.

Declaration of Interest

All authors certify that all of them have contributed to, and read the paper and have given permission for their name to be included as a coauthor. The manuscript has not been published and will not be submitted simultaneously or published in any other paper. Authors state to their own responsibility that there is no conflict of interest with any kind of financial organization or company regarding the material discussed in the manuscript.

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