Late oral effects of chemotherapy in children cancer survivors

Ph. D. theses

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1. INTRODUCTION

The availability and adoption of modern therapeutic protocols for childhood cancer have continuously reduced the mortality rate of childhood malignancies in most countries over the past decades. There are several publications on the long-term effects of different childhood cancer therapies. The adverse effects of irradiation has long been known, high dose chemotherapy can cause similar oral late effects, such as dental abnormality, microdontia, agenesis, delayed tooth eruption, and root malformation.

Very few studies have been published on the long-term salivary effects of high dose chemotherapy in adolescence. Children being treated for cancer are actively growing, creating unique problems in the long-term development of both the orofacial hard and soft tissue. Complications during and after chemotherapy depend on the type of malignancy, age at diagnosis and the drugs used during the therapy. There are many protocols to prevent acute oral toxicity and infections like mucositis, candidiasis or hyposalivation. As far as it is known, the increased caries risk is correlated with the decreased saliva flow rate and the adverse side-effect of the treatment can be hyposalivation and concomitant changes of oral microflora. The decreased salivary gland function can be either a short-term effect or detected after several years, too.

The aim of this study was to investigate the long-term effects of chemotherapy on the salivary function, the cariological status, and the buffer capacity of the saliva in children.

2. OBJECTIVES

Very few studies have been published on the long-term effects of high dose chemotherapy in adolescence. Complications after chemotherapy depend on the type of malignancy, age at diagnosis and the drugs used during the therapy.

1. The aim of this study was to investigate the long-term effects of chemotherapy on the oral hygiene status, periodontal status of 5 years post-treatment survivors. This data compared with data of 12 years old Hungarian healthy population.

2. The aim of this study was to investigate the long-term effects of chemotherapy on dental disturbance parameters of children cancer survivors.

3. The aim of this study was to investigate the long-term effects of chemotherapy on quantitative and qualitative salivary gland function. (Unstimulated and stimulated saliva flow rate, buffering capacity, microbiological culture)

4. The aim of this study was to investigate the long-term effects of chemotherapy on minor salivary gland function.

5. The aim of this study was to investigate the long-term effects of chemotherapy on caries status (DMFT number of decayed, missing and filled permanent teeth).

6. The aim of this study was to investigate the long-term effects of chemotherapy on the oral health of 12 years old children cancer survivors with focus on craniofacial growth.

3. MATERIAL AND METHODS

All measurements were carried out in the Department of Prosthodontics at Semmelweis University, Faculty of Dentistry, Budapest, Hungary by one examiner (O Nemeth).

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

Patients

Forty-three 12 years old children were examined, who had been receiving cytotoxic drugs between the ages of 1 month and 7 years, during the period of permanent tooth development. All of them were long-term survivors of their malignancies. None of these children had radiotherapy or stem cell transplantation (SCT). Patients were treated according to international protocols.

The patients did not receive any special dental prophylactic treatment (fluoride, iontophoresis) during and after cancer treatment and they were not taking any other medications known to impact salivary function. The patient did not take any medication at the time of oral examination. Three children did not wish to participate and two had got a secondary neoplasm. The remaining 38 were examined. (Table 1)

Thirty-eight (female 22, male 16), age ($12,2 \pm 0,5$ years) and gender-matched healthy children with similar socioeconomic background served as controls. The control group admitted for the optional check up in a school in Budapest. None of the control participants were on any medications.

Dental examination

Participants were examined clinically according to the methodology and criteria of the WHO (1997). (Oral health surveys. Basic methods, 4th edition. World Health Organization: Geneva, pp. 41–46) The DMF-T scores (number of decayed, missing and filled teeth) was determined with a dental mirror, explorer probe and supplemented with panoramic radiographs.

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 The OHI-S (Simplified Oral hygiene Index) was recorded according to Greene and Vermillion. 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, V-shaped), microdontia, and agenesis. These dental disturbances were recorded as described by Dahllof et al.

Measurement of the unstimulated and stimulated whole saliva flow rate (USF and SSF)

The flow rate of USF was determined in every person according to the method described by Sreebny et al between 8.30-11.00 a.m. after the oncologic control examination. USF was collected into preweighed vessels for 5 minutes with the patient seated in an upright position.

Patients were asked to refrain from eating and drinking 2 hours prior to the test session, to avoid swallowing and to make as few movements as possible during the procedure (Sreebny et al, 1992 a,b). Measuring vessels were weighed before and after each collection using an electronic scale (Sartorius BA 110 S. Sartorius, Germany). USF flow rate was expressed in ml min^{-1} (which is nearly equivalent to g min^{-1}). A saliva flow rate of 0.1 ml min^{-1} or less was considered as an objective sign of salivary hypofunction (hyposalivation).

The flow rate of stimulated whole saliva was also determined in every child according to the method described by Sreebny et al.

Participants were asked to chew a piece of paraffin wax (weighing 7±0,1 g) in their mouth for 30 seconds to soften it, then to swallow the accumulated saliva. Now the participants were asked to chew the piece of wax in their usual manner of chewing for 2 minutes, and then, to expectorate the accumulated saliva into a sterile calibrated container. The procedure was repeated twice more and the volume of saliva could be read off the vessel and flow rate was expressed as ml min^{-1}

The flow rate of the palatal saliva (PS)

The flow rate of the minor salivary glands of the palate was determined in every child with the Periotron 8000® device (Oraflow® Inc., P.O. Box 219 Plainview, New York 11803, USA) according to the Periotron method after calibration with different volumes of distilled water.

The PS flow rate was measured with 8-mm-diameter filter paper discs placed bilaterally in the region of the maxillary first or second molars, 15 mm palatally from the gingival margin. Saliva collection occurred over 30 seconds. The readings were highly reproducible. Flow rates were recorded in μl min^{-1} cm^{-2}, from the regression formula y=0.0303-1,212. (y: the volume of μl; x: the displayed Periotron digits)

Buffering capacity of saliva

The buffer capacity of saliva was determined from stimulated saliva samples, by paper colorometric test (CRT® buffer Ivoclar Vivadent AG., Schaan, Lichtenstein). The colour of the test field showed the result after exactly 5 minutes of reaction time. Blue indicates a high (endpoint pH between 5,6 and 7,0), green a medium (endpoint pH between 4,6 and 5,5) and yellow a low buffer capacity of saliva (endpoint pH<4,6).

Cephalometric analysis

In order to classify patients` skeletal type and direction of facial growth, cephalometric analyses were carried out according to Ricketts and Hasund, obtained using SMILE, a computer-based cephalometric software (Smile®, Budapest, Hungary). The cephalometric measurements were compared with standard reference values.

The study was extended to compare patients treated with differential anti-neoplastic agents. To compare the long-term effects of different anti-neoplastic agents, subjects were grouped according to the drug(s) received:

Group A, B (Vincristine)
Vincristine is a mitotic inhibitor. Group B consists of individuals who had received Vincristine, a drug that neither of the subjects in Group A had ever received. Patients in Group A had been treated with other cytostatic drugs.

Group C, D (Vincristine and Doxorubicin)
Doxorubicin is an anthracycline antibiotic, it works by intercalating DNA. Group D consists of individuals who had received Vincristine and Doxorubicin, drugs that neither of the subjects in Group C had ever received. Subjects in Group C were treated with cytostatic agents other than Vincristine and Doxorubicin.

Group E, F (Methotrexate)

Methotrexat acts by inhibiting the metabolism of folic acid. When patients were grouped according to whether (Group E) or not (Group F) they had been administered the cytotoxic drug Methotrexate,

Group G, H (Ifosfamide)

Ifosfamide is a nitrogen mustard alkylating agent. Group H consists of individuals who had received Ifosfamide, drugs that neither of the subjects in Group H. Patients in Group H had been treated with other drugs.

Group I, J (Platina agents)

Platina agent is alkylating agents. When Group J who had been administered any platina agent and in Group I had not been administered any platina agent were analysed.

Standard lateral cephalograms (parameters: 76 kV, 6mA) of the subjects were taken with the mandible in intercuspal position by Gendex Orthoralix 9200. The scanned conventional lateral cephalograms were analysed twice by three dentists experienced in analysis. (Figure 1.) Therefore six series of points were obtained. The described points of landmarks are slightly different in all series caused by the determination. Points which were substantially differing from the five other results were filtered and substituted by their arithmetic mean. After determining the average of the coordinates, the program calculated the values of the Hasund and the Ricketts cephalometric analyses.

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 Mann-Whitney U Test was used to compare the palatal flow rate in the study (n=38) and the control group (n=40), and to show gender differences, paired Student's t-test and ANOVA for USF and SSF and palatal saliva flow rates and the Chi-square, the logistic regression test for the buffer capacity of saliva. The Kolmogorov-Smirnov Test was employed for the analysis of the DMF-T indeces, while the Spearman test was used to find correlation between USF, SSF flow rates and minor saliva flow rates, the DMF-T, and the buffering capacity. P values <0,05 were considered significant. Student`s t-test was used to compare the values of the subjects with the mean values given by Ricketts and Hasund, and to compare the different anti-neoplastic agent groups, ANOVA for comparing the dentists` measurements.

4. RESULTS

Dental examination

Table 1 shows D-T, M-T, F-T and DMF-T index. These mean values were compared with the mean caries experience of 12-year-old Hungarian children. The caries prevalence in the test group was 76,3% and 76,4% in the control group.
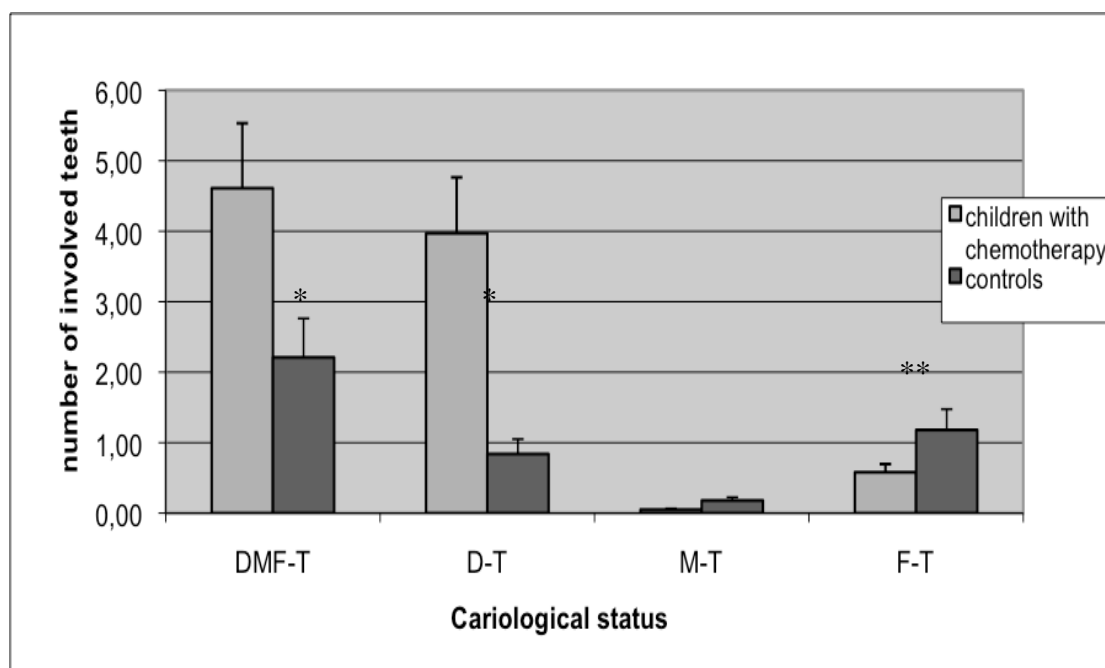
Figure 1.

Cariological status of 12-year old children (n=38) obtaining early childhood chemotherapy, compared to healthy controls. (n=40)

	Vizsgált csoport	Kontroll csoport
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

Unstimulated and stimulated whole saliva flow rates

The USF flow rate was $0,278\pm0,257$ ml min^{-1} in the test group, while in the control group $0,378\pm0,241$ ml min^{-1} was measured. The difference between the two groups was not significant.

The SSF flow rate was $0,849$ ml min^{-1} in the test group. This was significantly lower than in the control group, where it was 1,132 ml/min.

Buffer capacity of saliva

High prevalence (81,6%) of high buffer capacity in the test group was found, while this result was only 40% in the control group. (OR=0,667)

Palatal saliva flow rate

The palatal saliva (PS) flow rate was 1,64 µl min^{-1} cm^{-2} in the test group. This was significantly higher (p<0,05) than in the control group, where it was 0,456 µl min^{-1} cm^{-2}. Ratio of palatal gland salivary secretion to whole stimulated saliva secretion in the study group was significantly higher (p< 0,001) than in the control group.

A significant positive correlation was found between stimulated whole saliva flow rate - palatal saliva flow rate. A negative significant correlation was found between DMFT-buffering capacity, DMFT-unstimulated whole saliva flow rate, DMFT-stimulated whole saliva flow rate and DMFT-palatal saliva flow rate.

Hasund analysis

There was a statistically significant difference in six measurements of the cephalometric values according to Hasund. SNB, SNPg angles were significantly larger than the standard values. However, ANB, H-angle, ML-NL, I-NA were significantly smaller than the standard values.

Ricketts analysis

There was a significant difference in four measurements of cephalometric values according to Ricketts, cranial base (it is defined by Frankfurt horizontal line and the Ba-N line) and facial depth were significantly larger and point A convexity and the mandibular plane were significantly smaller than the standard values. The ratio between the posterior and anterior facial heights was significantly lower than the standard value.

Vincristine

There was no significant difference in any other measurements. While there was a significant difference in five measurements (except SNPg angle) between Group B and the reference value there was no significant difference between Group A and the reference value.

Vincristine and Doxorubicin

There was no significant difference in any other measurements. While there was significant difference in three of the listed measurements (except for lower incisor inclination) between Group D and reference value, there was no significant difference between Group C and reference value.

Methotrexate, Ifosfamid, Platina agents

The statistical analysis of the Group E and Group F showed no significant difference in any variables.

5. CONCLUSIONS

Loss of major salivary gland function could cause more problems in the oral region in adults but the increasing palatal salivary gland secretion can protect their oral health. These findings indicate that salivary gland function in children is affected even after years of completed cancer therapy.

It can be concluded that 12-year old children after more than 5 years of the chemotherapy have a higher caries risk compared to their healthy fellows. Authors believe that the slight damage in the major salivary glands caused in these children by the chemotherapy was not a real reason for this, since it was compensated by the minor salivary gland function and that is the reason why unstimulated whole saliva flow rate was normal and the buffer capacity of the saliva was higher than in the healthy controls. Since saliva functions were compensated attention should be paid to the arrangement of proper dental control and treatment nearby the therapy of the main disease in these children, because they had significantly higher number of carious teeth but significantly less filled teeth than their healthy fellows from the same age-group.

Dental protocols and orthodontic guidelines for childhood cancer survivors should be used to provide the best and the most effective care. We suggest that the correction of facial growth disturbances resulting from cancer therapy during childhood is best left until the age of 18-20 years, when facial growth has ceased. These findings indicate that craniofacial growth in children is affected even after years of completed cancer therapy.

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