

Aim of the study: To determine reasons for the increase in caries among children/adolescents treated for neoplasms.

Material and methods: Health promoting behaviour, oral hygiene (PLI), gingiva (GI), dentition (DMFt/DMFs), number of teeth with white spot lesions (WSL), and enamel defects (ED) were assessed in three groups of 60 patients each. The three groups were as follows: under chemotherapy (CH), after chemotherapy (PCH), and generally healthy (CG). Medical files supplied information on neoplasm type, chemotherapeutic type and dose, age at treatment start, chemotherapy duration, and complications. Statistical analysis was performed with Mann-Whitney *U* test and Spearman's rho test.

Results: The age at which chemotherapy was started/its duration was 5.9 ±4.0/1.3 ±0.5 years in PCH and 9.12 ±4.44/0.8 ±0.3 years in CH; PCH completed treatment 4.9 ±3.4 years ago. Chemotherapy most often included vincristine (VCR), etoposide (VP-16), adriamycin (ADM), cyclophosphamide (CTX), cisplatin (CDDP), and ifosfamide (IF). Mucositis occurrence was 28.33% in PCH and 45.00% in CH; vomiting occurrence was 43.33% and 50.00%, respectively. Nutrition and prophylaxis mistakes occurred more often in CH/PCH than in CG; PLI, GI, caries incidence and severity, and the number of teeth with WSL were higher. Correlation between caries incidence and chemotherapeutic type and dose, age at treatment start and treatment duration, mucositis, emesis, PLI, GI, ED, no fluoride prophylaxis, and nutritional mistakes was established. Ifosfamide and mucositis treatment played a major role in chemotherapy; after chemotherapy – ED and CTX, ADM, IF, and VP-16.

Conclusions: Caries in permanent teeth in children/adolescents undergoing chemotherapy result from nutritional mistakes, poor prophylaxis, and indirectly from chemotherapy complications (first mucositis and emesis, and later developmental ED).

Key words: caries, chemotherapy, mucositis, developmental ED, eating habits, oral hygiene.

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Factors influencing caries incidence in permanent teeth in children/adolescents under and after anti-neoplastic treatment

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Introduction

The use of chemotherapeutics presents a risk of side effects. Oral chemotherapy complications might result directly from drug impact on dental and periodontal tissues, mucosa, and salivary glands, or indirectly from general complications, such as malnutrition or metabolic/neurological disorders. Mucositis, fungal infections, salivary secretion disorders, and neuropathies are examples of early oral complications, and dental developmental disorders are examples of late complications [1–15]. Caries is considered to be an early complication; however, clinical observations suggest its risk remains high even many years after chemotherapy completion [8, 14].

The study objective: assess the impact of anti-neoplastic chemotherapy on caries incidence in permanent teeth, and establish the reasons for caries increase in children/adolescents under/after chemotherapy.

Material and methods

Patients

The study included 180 patients of the Children's Memorial Hospital, divided into three groups: CH – 60 patients undergoing chemotherapy (patients of the Department of Oncology at least three months from onset of chemotherapy); PCH – 60 patients after chemotherapy (patients of the Department of Oncology at least one year after chemotherapy completion); and CG – 60 generally healthy patients (patients of the Department of Paediatric Dentistry of the Children's Memorial Hospital). Patients/their parents/their legal guardians gave written consent. Children undergoing radiation therapy in the head and neck region or with chronic diseases other than neoplasms were excluded. The study included as many oncology patients as were available during the period 2009–2013.

Methods

The study was approved by the Children's Memorial Hospital Commission for Bioethics on May 12, 2010 (permit 95/KBE/2010). The study included retrospective analysis of medical files and physical dental examination.

Patient medical files were analysed retrospectively for information on: neoplasm type, age at treatment start, treatment duration, type and accumulated dose of administered drugs, and mucositis occurrence and severity. Mucositis severity was scored from the notes with CTCAE v4.0, as follows: I – redness; II – single ulcerations, pseudomembranes; III – clustered ulcerations, pseudomembranes, provoked bleedings; and IV – extensive tissue necrosis, spontaneous bleeding [1].

Medical history was obtained by talking to patients and their parents/legal guardians about eating habits (cariogenic snack intake), oral hygiene, and prevention with fluoride.

Dental examination, performed at a dental practice, assessed oral hygiene, gingiva, dentition, and potential visible decrease in salivary secretion. This was performed by physicians employed at the Department of Paediatric Dentistry of the Children's Memorial Hospital under supervision of authors of the study.

The plaque index (PLI) assessed oral hygiene, and the Silness-Löe (2, 3) index (GI) assessed gingival tissues. Plaque on buccal and lingual surfaces of teeth 16 (55), 12, 24 (64), 36 (75), 32, and 44 (84) were recorded (deciduous teeth were assessed only if no permanent anatomical teeth were present in children with mixed dentition) as follows: 0 – no plaque; 1 – no visible plaque, only seen on probing; 2 – plaque seen with the naked eye, forming a thin layer at gingival margin; and 3 – plaque visible in the gingival crevice, abundant at gingival margin and on tooth surface. The PLI was the sum of all mean scores for all assessed surfaces.

Gingiva around teeth 16 (55), 12, 24 (64), 36 (75), 32, and 44 (84) were assessed as follows: 0 – no visible inflammation; 1 – mild inflammation and redness, no bleeding on probing; 2 – moderate inflammation, redness, oedema, glazing, and bleeding on probing; and 3 – severe inflammation, marked redness and hypertrophy, ulceration, and a tendency for spontaneous bleeding. The GI was the sum of mean scores for all assessed surfaces.

Cariou lesions, fillings, teeth missing due to caries/developmental defects – enamel opacities and hypoplasia

were assessed. Carious lesions assessment followed ICDAS – II, where codes 1 and 2 qualified as WSL (white/dark opacity, poorly visible on humid/dried surfaces), and codes 3 and higher qualified as carious lesions (3 – localised enamel breakdown within opaque/pigmented enamel with no visible dentine/underlying dentine shadow; 4 – visible dentine with/without localised enamel loss; 5 – distinct cavity with visible dentine; and 6 – extensive cavity with visible dentine) [4]. Enamel opacities and hypoplasia were scored using modified DDE-Index as follows: 0 – normal enamel; 1 – demarcated opacity; 2 – diffuse opacity; 3 – hypoplasia; 4 – other defects, combine defects; 5 – demarcated and diffuse opacities; 6 – demarcated opacity and hypoplasia; 7 – diffuse opacity and hypoplasia.

Saliva flow was assessed as follows: resting flow rate normal – drops of saliva appearing on labial mucosa within 30–60 seconds of observation; resting flow rate low – drops of saliva appearing on labial mucosa after 60 seconds of observation, and stimulated flow rate (after chewing wax) normal > 5.0 ml/5 min; low: 3.5–5 ml/5 min.

Caries occurrence and DMFT, the sum of carious teeth (Dt), teeth lost to caries (Mt), and filled teeth (Ft), were assessed. Teeth lost to caries were distinguished from lack of tooth germs on the basis of medical/dental history and radiological examination; moreover, all extractions due to caries were performed in the Department of Paediatric Dentistry.

Statistical analysis

The Shapiro-Wilk test was performed in all groups to assess the compatibility of numeric values distribution

Table 1. The most common neoplasms, age at treatment start/completion, treatment duration, and drugs used in respective groups

Parameters	PCH		CH	
	mean ± SD			
Age at treatment start in years	5.9 ±4.0		9.12 ±4.44	
Treatment duration in years	1.3 ±0.5		0.8 ±0.3	
Time since treatment completion in years	4.9 ±3.4		0	
Anti-neoplastic drug	n/%	mean dose ± SD (mg/m ²)	n/%	mean dose ± SD (mg/m ²)
VCR	53/88	10.46 ±8.0	46/76.6	9.2 ±12.16
ACTD	18/30	3.06 ±8.54	12/20	2.654 ±4.621907
CTX	41/68.3	5287.18 ±12233.51	33/55	2841.83 ±3821.813
DTIC	17/28.3	1649.14 ±2757.64	14/32.6	906.08 ±2650.754
MTX	13/21.6	3795.90 ±8195.43	5/8.3	3230.875 ±16245.27
VP-16	39/65	1434.58 ±1712.87	47/78.3	1298.083 ±1114.76
CDDP	26/43.3	255.9167 ±402.0743	40/66.6	349.0667 ±363.6871
IF	25/41.6	12511.67 ±21032.63	38/63.3	14187.5 ±18862.85
CBDCA	11/18.3	1478.7 ±7148.41	28/46.6	1156.333 ±1482.473
ADM	40/66.5	167.41 ±152.43	37/61.6	145.91 ±166.1281
5-FU	3/5	83.333 ±457.954	1/1.6	53.333 ±409.661
VBL	8/13.3	15.33 ±56.238	3/5	5.95 ±24.05301
VM-26	7/11.6	155.6667 ±446.7638	8/13.3	114.8333 ±396.5707
Ara-C	8/13.3	1592.857 ±5498.391	3/5	871.6667 ±4533.03

with real distribution. Results were statistically analysed with the Mann-Whitney *U* test (comparison of variables in particular groups) and Spearman's rho test to establish the impact of chemotherapy on oral health. Difference significance was at $p \leq 0.05$.

Results

Mean patient age in all groups was similar: 11.24 \pm 4.22 years in CH, 11.81 \pm 3.87 in PCH, and 12.22 \pm 3.63 in controls. Table 1 presents age at treatment start/completion, chemotherapy duration, and used drugs. Various specific treatment schedules were used, requiring individual adjustments. Most often, chemotherapy was used to treat the following: medulloblastoma (12.5%), nephroblastoma (10.8%), Burkitt's lymphoma (10.8%), neuroblastoma (8.3%),

rhabdomyosarcoma (6.6%), Ewing's sarcoma (5.8%), and, less often, chondrosarcoma, hepatoblastoma, glioblastoma, ependymoma, and osteosarcoma.

Mucositis during chemotherapy occurred in 38.33% of patients (I – 10.0%, II – 21.7%, III – 6.6%), including 28.33% in PCH, and 45.00% in CH. Vomiting occurred in 43.33% of PCH and in 55.00% of CH (Table 1).

All patients reported brushing their teeth with fluoride toothpaste twice a day. No child had taken/was taking endogenous fluoride supplements. Systematic professional fluoride preventive routines (2–4 times/year) were most often carried out in controls. Patients under chemotherapy presented the most cariogenic eating habits (Table 2).

No patient presented decreased salivary flow. Mean PLI and GI in CH and PCH were significantly higher than in

Table 2. Health habits, oral hygiene, gingiva, and caries severity in examined groups

	PCH	CH	CG	<i>p</i>	
	<i>n</i> / <i>%</i>				
Fluoride prevention (varnishes/gels)	26/43.33	18/30.00	43/71.66	PCH vs. GK	0.0002*
				CH vs. GK	0.0000*
Snacks with sucrose (sweets and drinks)					
> 3/day	17/28.3	29/48.3	16/26.6	PCH vs. GK	0.841
				CH vs. GK	0.014*
Number of snacks/day	mean \pm SD				
	1.6 \pm 0.75	1.75 \pm 0.43	1.4 \pm 0.58	PCH vs. GK	0.169
				CH vs. GK	0.011*
Oral and gingival hygiene and dentition					
PLI	1.4 \pm 0.812	1.83 \pm 0.5	0.771 \pm 0.771	PCH vs. GK	0.011*
				CH vs. GK	0.01*
GI	0.48 \pm 0.722	0.699 \pm 0.816	0.269 \pm 0.668	PCH vs. GK	0.022*
				CH vs. GK	0.011*
Enamel defects					
Opacities	6.316 \pm 6.10	3.75 \pm 5.06	1.866 \pm 2.64	PCH vs. GK	0.000
				CH vs. GK	0.006
Hypoplasia	1.516 \pm 3.61	0.4 \pm 1.240	0.15 \pm 0.55	PCH vs. GK	0.003
				CH vs. GK	0.241
Combination of lesions (opacities and hypoplasia)	0.533 \pm 1.83	0.166 \pm 0.71	0.083 \pm 0.38	PCH vs. GK	0.06
				CH vs. GK	0.477
Caries in permanent teeth					
Number of teeth with WSL	2.75 \pm 3.289	2.21 \pm 1.762	0.711 \pm 0.891	PCH vs. GK	0.0000*
				CH vs. GK	0.0000*
Dt	5.1 \pm 5.091	5.8 \pm 5.446	1.559 \pm 2.53	PCH vs. GK	0.0000*
				CH vs. GK	0.0000*
Mt	0.15 \pm 0.15	0.25 \pm 0.976	0.398 \pm 0.851	PCH vs. GK	0.2357
				CH vs. GK	0.3319
Ft	3.2 \pm 3.78	2.75 \pm 3.667	3.389 \pm 3.518	PCH vs. GK	0.1652
				CH vs. GK	0.0187*
DMFt	8.3 \pm 7.181	8.78 \pm 6.952	5.271 \pm 4.861	PCH vs. GK	0.0551^y
				CH vs. GK	0.0153*

*Statistically significant differences; $p < 0.05$; *y* – at significance limit

controls (Table 2). Developmental ED occurred in 83.3% of PCH, 80.0% of CH, and 40.0% of controls. Mean numbers of teeth with developmental ED were highest in PCH (Table 2).

Caries occurred more often in CH (90.0%) and PCH (88.3%) than in controls (66.6%). In these groups, mean numbers of teeth with WSL and caries were statistically significantly higher. Despite visibly higher DMFTs in both oncologic groups, statistical significance was only proven for CH (for PCH p was at significance limit) (Table 2).

Spearman's rho was measured for all patients, assessing correlations between caries incidence and anti-neoplastic treatment, developmental ED, mucositis (II and III), gingivitis, and no professional preventive fluoride application (Table 3). The number of teeth with caries/WSL increased with age at treatment start, its duration, time elapsed since completion, number of cariogenic snacks, and PLI. Cyclophosphamide (CTX), adriamycin (ADM), ifosphamide (IF), etoposide (VP-16), cisplatin (CDDP), and IRI presented positive correlations with both DMFT and Dt. Vincristine (VCR), ACTD, VM-26, and IRI use also resulted in Dt increase. The number of teeth with WSL was correlated with VCR, carboplatin (CBDCA), CTX, ADM, IF, VP-16, and

CDDP. Doses of cytostatics also appeared to be crucial. An increase in doses resulted in higher caries incidence, mostly caused by an increase in Dt.

Spearman's rho assessing chemotherapy factors solely in PCH confirmed a correlation between DMFT, Dt, the number of teeth with WSL, the age at which treatment started, and the number of teeth with opacities. Dt was correlated with ADM and VP-16 treatments, and the number of teeth with WSL with the number of teeth with a combination of developmental ED (Table 4). However, mucositis and vomiting under chemotherapy were not significant. A similar analysis in CH revealed a correlation between DMFT and Dt, and IF use and mucositis. Mucositis was positively correlated with the number of teeth with WSL (Table 4). No correlation with developmental ED was established (Tables 3, 4).

Discussion

Many researchers state that children after chemotherapy are predisposed to caries [14, 20–22]; in Poland, 97.06% presented caries (Olczak-Kowalczyk *et al.*). The Avşar *et al.*

Table 3. Statistically significant Spearman's rho assessing correlations between caries severity and chemotherapy, eating habits, oral hygiene, and gingiva in all patients

Parameters	DMFT	Dt	Number of teeth with WSL
Age when CH was started	0.1154	0.2148*	0.2397*
Treatment duration	0.0797	0.1998*	0.2054*
Time since completion	0.0912	0.1952*	0.1800*
VCR/dose	0.1421/0.1398	0.3418*/0.2956*	0.2897*/0.2838*
CBDCA	0.0541/0.0457	0.1504*/0.1385	0.1818*/0.1608*
ACTD	0.0215/0.0239	0.1727*/0.1795*	0.1076/0.1099
CTX	0.1982*/0.2241*	0.4041*/0.3956*	0.2528*/0.2634*
ADM	0.1687*/0.1937*	0.3905*/0.3983*	0.1833*/0.2398*
DTIC	0.0810/0.0885	0.1607*/0.1705*	0.0717/0.0795
IF	0.2342*/0.2681*	0.3672*/0.3936*	0.2750*/0.2924*
VP-16	0.2612*/0.2326*	0.4143*/0.3669*	0.2979*/0.2758*
CDDP	0.1997*/0.1753*	0.2990*/0.2678*	0.3347*/0.3076*
VBL	0.0961/0.0949	0.1517*/0.1511	0.1210/0.1204
VM-26	0.0974/0.0938	0.2008*/0.2000*	0.0879/0.0909
IRI	0.1785*/0.1790*	0.1793*/0.1789*	0.1288/0.1283
Vomiting	0.1138	0.2187*	0.1980*
Mucositis	0.1061	0.2886*	0.2372*
2°	0.1591*	0.2554*	0.2508*
3°	0.0894	0.1500*	0.1065
Cariogenic snack number	0.0928	0.1764*	0.1804*
Varnish/gel	-0.1649*	-0.2394*	-0.1120
GI	0.2418*	0.3294*	0.2767*
PLI	0.0403	0.1827*	0.2477*
Number of teeth with opacities	0.388*	0.383*	0.342*
Number of teeth with hypoplasia	0.1592*	0.1587*	0.2358*
Number of teeth with a combination of ED	0.1267	0.1203	0.1903*

*Statistically significant difference; $p < 0.05$

Table 4. Statistically significant Spearman's rho assessing correlations between caries severity and chemotherapy in PCH and CH

Parameters	DMFt	Dt	Number of teeth with WSL
PCH group			
Age at start	0.3987*	0.2847*	0.3652*
ADM/dose	0.1562/0.1965	0.2579*/0.2478	0.0113/0.1657
VP-16	0.2469	0.2452*	0.1073
Number of teeth with opacities	0.4928*	0.4996*	0.3753*
Number of teeth with lesion combination (opacities and hypoplasia)	0.2297	0.1869	0.3012*
CH group			
IF/dose	0.2398/ 0.3060*	0.2120/ 0.2591*	0.1342/0.1484
Mucositis	0.1754	0.3862*	0.2484
2	0.2808*	0.4169*	0.3072*

and Ponce-Torres *et al.* studies encountered only 18% of caries-free children after chemotherapy [20, 24].

Researchers noted a higher caries incidence in oncological patients [19–24]. The Cubukçu *et al.* study presented a statistically significantly higher DMFt in children after chemotherapy (3.9 ± 0.7) than in controls (1.8 ± 0.1) [25]. The Avşar *et al.* study presented similar DMFt results: for children under chemotherapy – 7.756 ± 4.9 , and for controls – 4.21 ± 3.76 . In Poland, caries severity in children after chemotherapy was also significantly higher than in healthy children (DMFt = 2.1 ± 0.6 vs. DMFt = 1.6 ± 0.2) [4]. The number of carious teeth (Dt/dt) was the highest DMFt component. In contrast, Alpaslan *et al.* [26] and Nasman *et al.* [27] did not observe any statistically significant differences in caries incidence between the group after chemotherapy and controls [26, 27].

Few researchers assessed caries incidence during/shortly after chemotherapy completion. According to Hedge *et al.*, mean DMFts in children after chemotherapy, examined at latest two weeks after treatment completion, were not statistically different from those in controls [28]. In the present study, caries severity was lowest in controls, and the difference between DMFt in CH and controls was statistically significant.

Dens *et al.* established teeth with fillings were the highest DMFt component [24]. According to the present observations and the Olczak-Kowalczyk *et al.* study, teeth with carious lesions were the highest DMFt component [14]. Some researchers believe highly severe caries in patients under chemotherapy is not a direct result of the treatment itself, but of inappropriate dental care. None of the children examined by Nemeth *et al.* underwent a dental check-up before starting chemotherapy, and none had professional fluoride prophylaxis [22]. The present CH and PCH groups presented more serious dental negligence than healthy children.

Many local and systemic factors, also treatment-associated, have an impact on dental health. Supplying the substrate necessary for the bacterial metabolism to function, i.e. carbohydrates, is unquestionably responsible for caries development [29, 30]. Medical history often revealed nutritional mistakes in all groups. However, they were sta-

tistically significantly most often made in CH, probably because of the necessity to compensate higher metabolic requirements manifesting in oncological diseases, coupled with malaise and concomitant taste disorders. Hong *et al.* [31] and Lauritano and Petrucci [32] also mention a higher number of cariogenic snacks eaten by children during chemotherapy compared to healthy children. Regular exogenous fluoride use is known to be an important factor in caries prevention [32–35]. Its absence results in severe caries, as confirmed by the present statistical analysis. Unfortunately, among the 180 patients, only 87 underwent professional preventive routines, and these were most often part of controls. According to Nasman *et al.*, in 1994 no child undergoing chemotherapy underwent preventive fluoride routines [26]. On the other hand, Clarkson and Eden [36] reported 25 out of 60 examined patients under chemotherapy underwent professional preventive fluoride routines. However these studies were carried out years ago. Currently, common dental guidelines for post- and under-chemotherapy patients state that daily brushing with fluoride toothpaste should be accompanied by a regular enhanced fluoride preventive routine [39, 40].

Caries-risk under chemotherapeutics also results from disadvantageous local oral environment (altered salivary gland secretion and saliva properties, and vomiting), and also from mucositis. Patients in the present study did not present any visible decrease in salivary flow/consistency. Chemotherapy is often accompanied by vomiting, which promotes enamel demineralisation, and caries and dental tissue erosion [14, 42–44]. Although vomiting in CH patients was limited to when the drug was administered, there existed a correlation between its occurrence and the incidence of caries and local enamel lesions (cariou spots). In the present study, mucositis also had an impact on caries incidence. Gohl *et al.* [42] also established a correlation between mucositis and caries and actinomycin D administration. The correlation between mucositis, poor oral hygiene, and caries was also confirmed by Cheng *et al.* [45].

Publications confirm the impact of mucositis on oral health [38, 46, 47]. The PLI was also correlated with the number of carious teeth. GI, as confirmed by statistical

analysis, was also considered an important indicator of oral health and caries risk. In 2010, Dahloff *et al.* and Foncica *et al.* confirmed a positive correlation between GI and caries incidence [48, 49].

In the presented study, the average GI was two-times higher in PCH, and three-times higher in CH, than in controls. In CH this may mean that general health, related to chemotherapeutic treatment and early oral complications, had an impact. Unfortunately, a high GI and PLI, also in PCH, reflected a poor preventive routine.

According to Nunn *et al.*, the impact of chemotherapy on dental tissues also depends on chemotherapeutic type, dose, and treatment duration. The longer the chemotherapy, the higher the risk of caries [50]. Pajari *et al.* assessed caries incidence according to time elapsed since chemotherapy completion and, over a period of three years, noted an increase in DMFt/DMFs [37]. However, Cubukçu *et al.* did not establish any substantial differences between caries incidence in children before (DMFt = 3.1 ± 0.6) and after (DMFt = 3.8 ± 0.5) chemotherapy, which they imply proves that chemotherapy does not promote caries [24]. In the present study, chemotherapy duration had an impact on the number of carious teeth, although no correlation with DMFt and DMFs was established. It was also influenced by age at treatment start and time elapsed since treatment completion. Avşar *et al.*, Cubukçu *et al.*, and Olczak-Kowalczyk *et al.* came to similar conclusions [14, 20, 25].

There are no publications on the impact of respective chemotherapeutics on caries incidence. The analysis of the Spearman's rho coefficients established that it was related to certain treatments. Under chemotherapy, it could be related to early complications, and after chemotherapy, to odontogenesis disorders, leading to structure or dental tissue mineralisation abnormalities. Poorer enamel mineralisation increases the risk of demineralisation, and abnormally structured dentine formed under certain treatments predisposes to fast caries spread. The present assessment also revealed a positive correlation between caries incidence and enamel developmental abnormalities (opacities and hypoplasia). Many researchers consider enamel underdevelopment a crucial caries factor and a reason for its higher severity [52, 56].

Despite a lot of research concerning the impact of chemotherapy on caries intensity, it is still debatable whether chemotherapy itself has such a significant influence on caries, or if lack of dental care, dietary habits, and hygienic negligence are more crucial in the development of caries in patients undergoing antineoplastic treatment.

In conclusion, cariogenic diet and poor prophylaxis, especially poor oral hygiene and topical fluoride application, and, indirectly, chemotherapeutic use followed by its early complications (mucositis and emesis), and distant post-chemotherapy complications (such as enamel developmental abnormalities) can result in higher intensity of caries in permanent teeth in children/adolescents under chemotherapy.

The authors declare no conflict of interest.

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