Dental Caries in Children and Adolescents During and After Antineoplastic Chemotherapy

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Objective: *To assess caries incidence, intensity, and treatment in children and adolescents under/after antineoplastic treatment.* ***Study design:*** *Patients with permanent and mixed dentition were divided into three groups of 60 patients each (5-18 years): CH – under chemotherapy; PCH – after chemotherapy; CG – generally healthy subjects. Caries incidence, intensity (DMFT/dmft, DMFS/dmfs), and mean numbers of teeth/surfaces with white spot lesions–WSL (D_{1+2}/d_{1+2}) were assessed following the ICDAS-II criteria. Statistical analysis: Mann-Whitney U test, significance at p≤0.05).* ***Results:*** *Caries incidence was significantly higher in PCH and CH (88.33% and 90%) than in CG (66.66%). Caries intensity was higher in both mixed and permanent dentition in patients under and after chemotherapy. The DMFS/DMFT correlation was the highest in PCH. Treatment indexes for primary and permanent teeth treatment were significantly lower in PCH and CH than CG.* ***Conclusion****: Antineoplastic chemotherapy is associated with caries development and its high incidence during/after treatment. As dental hygiene was poor in patients under and after antineoplastic treatment, dental checkups need to be more frequent and thorough.*

Key words: *neoplasm, chemotherapy, children, dental caries*

INTRODUCTION

Literature suggests an increased predisposition to dental caries in patients undergoing antineoplastic chemotherapy[1-5]. During therapy, the pH decreases and salivary buffer abilities are reduced due to disturbed activity of the salivary glands and to vomiting potentially following the administration of chemotherapy drugs[6]. It has been demonstrated that the risk of vomiting was increased in young patients and due to the administration of medication including a high emetogenic potential, i.e., cisplatin, cyclophosphamide, dacarbazine and procarbazine[7]. The mouth's self-cleansing action is also weakened due to neurological disorders, decreased muscle power (asthenia), and xerostomia. The risk of neurological disorders is high when using vincristine[8]. This agent, causing neuropathies of the cranial nerves, may cause pain in the mandible, masseter muscles, temporomandibular joint, and impair mastication. Antineoplastic drug neurotoxicity may also increase dental sensitivity to thermal stimuli and dysgeusia, additionally impairing food consumption.

Hypoalimentation is a serious problem in neoplastic patients. It leads to a decreased resistance of the body, to a lower activity of the salivary glands, and to disturbed mechanisms inhibiting gluconeogenesis from amino acids, mainly those in skeletal muscles. This results in a continuous loss of proteins and body mass as well as of muscular strength, including that of masticatory muscles. Hypoalimentation is chiefly due to the neoplastic process increasing the calorie requirement and mucositis or *mucosal barrier injury* (MBI). MBI is caused by a direct cytotoxic effect of antineoplastic medication acting on oral epithelial cells and further segments of the gastrointestinal tract. A high toxicity against the epithelial cells is demonstrated by agents affecting DNA synthesis, such as 5-fluorouracil, methotrexate, etoposide, and irinotecan[7,9,10].

Patients treated with antineoplastic chemotherapy were found to have a low salivary flow rate, pH, and buffer ability of the saliva, a decreased concentration of immunoglobulins (IgA, IgG), lactoperoxidase, lysozyme, lactoferrin, as well as of fluoride and phosphate ions[5,7,11,12]. Such changes in the quantity and quality of the saliva pose difficulties in neutralizing

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bacterial acids and enamel remineralisation. Unfortunately, hygiene may be very poor in children undergoing antineoplastic chemotherapy. It may contribute to concomitant pain in *Mucositis,* neurological disorders impeding proper hygiene routines, or emotional/psychic disturbances. Dietary faults may also result from efforts made to balance the energy requirements in a child with a decreased appetite.

Dental caries is considered to be a complication of early stage chemotherapy[2,12,13,14] . However, caries risk also remained high after the completion of anticancer therapy[1,7,13,15-17]. A clinical follow-up examination performed in 96 patients, who underwent chemotherapy in childhood, showed a lower salivary flow rate and a higher amount of cariogenic bacteria, such as mutant streptococci and lactobacilli, an increased DMFT, and more frequent enamel mineralization disturbances than in controls[18]. Studies of Polish children and adolescents showed not only a high DMFT but also acute carious disease in post-chemotherapy subjects, affecting multiple dental surfaces and causing pulpal complications or odontogenic infections[1]. These could have been caused simultaneously by a persistent high risk of dental caries (caused by saliva abnormalities and increased enamel susceptibility to acid erosion) and irregularities linked to the protective function of the pulp. Developmental abnormalities are a complication of chemotherapy in children and adolescents[18,19]. Animal and tissue culture studies established that some antineoplastic drugs, particularly vincristine (VCR) and vinblastine (VBL), temporarily impair the odontoblast process function; actinomycin D and adriamycin cause the death of pre-odontoblasts in rat teeth, and doxorubicin reduces the number of live pulp cells and fibroblasts in human teeth[20-22]. Make *et al* observed the changes in old odontoblasts and the formation of irregular dentin with a low mineralization degree medial to the formative disturbances line after administration of VBL[23]. With regard to enamel susceptibility to acid erosion, chemotherapy has an important impact on amelogenesis. Animal studies established that VBL and VCR affected ameloblast morphology and functions. Microtubules in both secretory and maturation stages of amelogenesis were disrupted after VBL administration[24]. VBL also caused a decreased activity of (Ca2+, Mg2+) adenosine triphosphatase in both ruffle-ended ameloblasts and membrane-associated calcium[25].

When the high risk of and the predisposition to extensive caries, affecting subsequent dental surfaces, remain high in post-chemotherapy subjects, dental procedures need to be adjusted. Most of the studies were conducted on groups of children treated with similar chemotherapy regimens and the same type of neoplasm. Thus, it is crucial to conduct a comparative study allowing for verification of the hypothesis in patients treated with similar multi-drug chemotherapy regimens and various types of neoplasms.

The present study is to assess the incidence of dental caries, its intensity and treatment in children and adolescents undergoing antineoplastic therapy, and those shortly after the completion of such a treatment.

MATERIALS AND METHOD

The clinical follow-up examination included 180 patients aged 5 to 18 years, recruited among the patients of the Dental Clinic at the Children's Memorial Health Institute, who participated in the study, i.e.:

- 60 patients who undergoing chemotherapy for at least three months–the CH group;
- 60 patients who completed chemotherapy at least one year earlier–the PCH group; and
- 60 generally healthy patients – the control group (CG)

Each group included 30 children with mixed dentition and 30 children with permanent dentition.

Children qualified to the CG met the age, location (Mazovia province), and socioeconomic criteria. Exclusion criteria included chronic diseases and chronic drug intake.

The patients under and after antineoplastic chemotherapy were selected among those referred to the dentists by their oncologists. All subjects with neoplasms undergoing treatment at the Children's Memorial Health Institute were provided dental care, including tutorials and preventive and oral treatment. Patients with past or present histories of systemic diseases other than neoplasms, undergoing chronic treatments other than antineoplastic therapies or radiation therapy in the head and the neck region, were excluded.

PCH patients and their parents/legal guardians were initially informed that oral and dental health was crucial.

Multidrug therapy, adapted to each neoplasm type and including vincristine, cyclophosphamide, adriamycin, etoposide, cisplatin, ifosfamide, actomycin, and methotrexate, was used in patients with neoplasms and was frequently tailor-made. Chemotherapy was most often used to treat medulloblastoma (12.5%), nephroblastoma (Wilms'tumour,10.8%), Burkitt's lymphoma (10.8%), neuroblastoma (8.3%), rhabdomyosarcoma (RMS, 6.6%), Ewing's sarcoma (5.8%), and less frequently: chondrosarcoma, hepatoblastoma, glioblastoma, ependimoma, and osteosarcoma.

The study was approved by the Children's Memorial Health Institute's Commission on the 12th of May, 2010 (permit 95/KBE/2010).

Physical examinations were performed at a dental clinic by two dentists; Cohen's kappa coefficient was at 0.75 after calibration.

ICDAS-II classification (International Caries Detection and Assessment System) was used to assess caries incidence and intensity[26], instead of DMF, as WSL were also assessed.

1. no opacity changes after prolonged drying (>5 sec);

2. white opacity, slightly visible on wet surfaces and distinctly visible after drying;

1a. dark opacity, slightly visible on wet surfaces and distinctly visible after drying;

3. white opacity, distinctly visible on wet surfaces;

2a. dark opacity, distinctly visible on wet surfaces;

4. localised enamel breakdown within opaque or discoloured enamel without visible dentine or its shadow,
5. underlying dentine shadow with/without localised enamel breakdown;
6. distinct cavity with visible dentine;
7. extensive cavity with visible dentine.

Lesions with codes 1 and 2 were qualified as white spot (d_{1+2}/ D_{1+2}), and those with codes 3 and higher, as carious lesions (d/D). Those with smooth surfaces were divided into white spot lesions (WSL) and developmental opacities. Lesions at plaque deposit sites and gingival margins were qualified as WSL. The number of teeth and tooth surfaces with WSL was assessed (d_{1+2}t, d_{1+2}s and D_{1+2}t, D_{1+2}s). Caries incidence (dmft/DMFt >0) and its intensity was assessed with DMFt/ dmft (for teeth) and DMFs/dmfs (for tooth surfaces) which are respectively the sums of:

- DT/dt – teeth with carious lesions (ICDAS II code≥3), MT/mt–teeth lost due to caries, and FT/ft – filled teeth;
- DS/ds surfaces with carious lesions, Ms/ms – surfaces of teeth lost due to caries, FS/fs – surfaces of filled teeth.

Non-capital letters (d, m, f) indicate primary teeth, capital letters (D, M, F) – permanent teeth.

Indexes represented the number of filled teeth and the sum of filled teeth and those with carious lesions. Mean indexes were calculated for all groups.

Results were then statistically analysed and the non-parametric Mann-Whitney U test was performed. This choice was dictated by the results of a preliminary analysis performed with the Shapiro-Wilk test to assess the compatibility of numeric values distribution with real distribution (statistical significance p≤0.05).

RESULTS

The mean age of patients undergoing chemotherapy was 11.24±4.22 years (total treatment duration was 0.8±0.3 years), that of post-chemotherapy patients was 11.81±3.87 years (time after treatment completion was 4.9±3.4 years; treatment duration 1.3±0.5 years), and that in controls was 12.25 ±3.61 years.

Caries incidence in all oncologic patients, i.e. under and after antineoplastic treatment (PCH+CH) was assessed at 89.16%; 88.33% in the post-chemotherapy group, and 90% in the chemotherapy group. Caries incidence in CH and PCH groups was statistically significantly higher than in CG (66.66%) (p respectively: PCH vs CG–0.004, CH vs CG 0.002).

The mean numbers of permanent teeth and surfaces with WSL and carious lesions, independently of tooth type, were statistically higher in chemotherapy and post-chemotherapy patients than in controls. DMFT and DMFS were higher in both oncological groups; statistical significance, however, was only established between those in CH and CG. The mean numbers of filled teeth and tooth surfaces with WSL were also higher in CH patients than in controls (Table 1). The mean DMFT and DMFS component in PCH and CH groups was the number of filled teeth/surfaces, and in the CG the number of carious teeth/surfaces.

Table 1. Caries intensity in permanent teeth in patients under and after antineoplastic treatment and in controls; Mann-Whitney U test

Parameters	PCH	CG	CH
D_{1+2}T	2.75±3.289	0.711±0.891	2.21±1.762
	P=0.0000*		*P=0.0000**
DT	5.1±5.091	1.559±2.53	5.8±5.446
	P=0.0000*		*P=0.0000**
MT	0.15±0.15	0.398±0.851	0.25±0.976
	P=0.2357		*P=0.3319*
FT	3.2±3.78	3.389±3.518	2.75±3.667
	P= 0.1652		*P= 0.0187**
DMFT	8.3±7.181	5.271±4.861	8.78±6.952
	P=0.0551		*P=0.0153**
D_{1+2t}S	3.0±5.313	0.847±1.03	2.21±1.906
	P=0.0000*		*P=0.0000**
DS	8.21±13.49	2.338±5.415	8.13±7.738
	P=0.0000*		*P=0.0000**
MS	0.71±1.941	0.813±1.916	0.81±2.383
	P= 0.2481		*P=0.3372*
FS	4.066±5.17	4.694±5.793	3.7±5.216
	P=0.1232		*P=0.0248**
DMFS	13.11±16.585	7.627±9.192	12.52±10.445
	P=0.0618		*P=0.0121**
DMFS/DMFT ratio	1.58	1.45	1.42
	P= 0.2232		P=0.0524

*statistically significant differences at p<0.05

Considering the differences in the numbers of permanent teeth in patients with mixed and permanent dentition, the caries level in permanent teeth was assessed in both subgroups (Table 2). Oncological patients in subgroups with permanent and mixed dentition had significantly higher mean numbers of tooth surfaces with WSL compared to controls. Oncologic subgroups also had higher DMFT and DMFS. However, the differences between oncological patients and CG were statistically significant only in subgroups with permanent dentition.

Table 3 shows caries level in primary teeth in patients with mixed dentition. For primary teeth, dmft, d_{1+2}t and d_{1+2}s were statistically significantly higher in CH than in CG. Both oncologic subgroups presented significantly higher dmft and dmfs than those in CG.

Table 4 shows caries treatment indexes in patients under and after antineoplastic treatment and in controls. Mean treatment indexes for permanent and primary teeth in PCH and CH were statistically significantly lower than in generally healthy patients.

Table 2. Caries intensity in permanent teeth in patients with mixed dentition in patients under and after antineoplastic treatment and in controls; Mann-Whitney U test

Parameters	PCH	CG	CH
Permanent dentition			
$D_{1+2}T$	3.60±4.09	1.33±1.07	3.27±1.80
	P=0.0004*	P=0.0000*	
DMFT	12.40±7.36	8.37±4.03	14.13±5.67
	P=0.0234*	P=0.0000*	
$D_{1+2}tS$	4.20±7,14	1.00±1,08	3.37±1.96
	P=0,0002*	P=0,0000*	
DMFS	20.20±20.43	11.43±7.13	20.57±8.50
	P= 0.0374*	P= 0.0727	
Mixed dentition			
$D_{1+2}T$	1.90±2.04	0.73±1.26	1.67±0,95
	P=0.0044*	P=0.0182*	
$D_{1+2}tS$	1.80±2.11	0.67±1.27	1.07±0.98
	P=0.1090	P=0.0259*	
DMFS	6.03±6.93	3.20±2,52	4.46±4.40
	P= 0.1971	P=0.3784	

***statistically significant differences at p<0.05**

Table 3. Caries intensity in primary teeth in patients with mixed dentition, under and after antineoplastic treatment and in controls; Mann-Whitney U test

Parameters	PCH	CG	CH
$d_{1+2}t$	0.40±1.07	0.20±0.61	1.30±1.91
	P=0,6142		P=0,0051*
dt	4.67±3.78	2.07±2.70	6.13±4.05
	P=0,0054*		P=0,0000*
mt	0.70±1.12	0.47±0.82	0.77±1.28
	P=0,5773		P=0.4063
ft	1.20±2.06	3.10±2.75	1.33±2.17
	P= 0,0012*		P= 0,0032*
dmft	6.33±4.46	5.57±3.28	8.00±4.63
	P=0.4991		P=0.0336*
$d_{1+2t}s$	0.63±1.79	0.13 ±0.51	1.30 ±1.91
	P=0,3414		P=0,0019*
ds	8.87±10.11	3.87±5.47	10.50±7.06
	P=0.0289*		P=0.0002*
ms	2.87±4,68	4.83±4.24	3.40±5,56
	P= 0,706		P=0.4752
fs	1.40±2.55	3.87±5.47	2.70±4.436
	P=0.0004*		*P=0.0129**
dmfs	13.23±11.22	10.93±7.93	15.73±9.98
	P=0.5785		P=0.0570
dmfs/dmft ratio	2.09	1.96	1.97
	P=0.7692		P=0.5212

***statistically significant differences at p<0.05**

Table 4. Caries treatment index for permanent and primary teeth under and after antineoplastic treatment and for controls (Mann-Whitney U test)

Treatment index	PCH		CH		CG		P	
	mean	SD	mean	SD	mean	SD		
Permanent teeth	0.33	0.32	0.24	0.29	0.51	0.39	PCH vs. CG	**0.0096***
							CH vs. CG	**0.0003***
Primary teeth	0.08	0.20	0.09	0.22	0.29	0.41	PCH vs. CG	**0.0043***
							CH vs.CG	**0.0036***

*statistically significant difference; p<0.05.

DISCUSSION

In the present study, the highest dmfs/dmft and DMFS / DMFT ratios reflected a high dynamic range of carious spread to subsequent tooth surfaces in post-chemotherapy patients. Other studies also established there was a predisposition of chemotherapy and post-chemotherapy patients to caries, as it was confirmed in the present study[4,15,17,18,27]. Caries incidence in patients with neoplasms was also reported to be higher than in the general population. Olczak-Kowalczyk *et al* assessed caries incidence in children after chemotherapy at 97.06%[4]; Asvar *et al* [18] – at 82% (18); Ponce-Torres *et al* [28] – at 81.6%; and Kung *et al* [29] – 42%.

Many studies also assessed dental caries incidence in oncologic patients. Asvar *et al* [18] , Cubucku *et al* [15], Dens[16], and Lauritinno *et al* [14] reported statistically significantly higher DMFTs in PCH than in CG. Patients had ended chemotherapeutic treatment between one year and 4.1 years prior to the study. However Olczak-Kowalczyk *et al* [1,4], Asplanian *et al* [30], Oguz *et al* [31] , Hutton *et al* [32] and Nasman *et al* [33] did not establish any statistically significant difference in caries intensity in CH when comparing to CG. Hedge *et al* [12] assessed caries intensity until two weeks after treatment completion and found that DMFT was higher in the treatment than in the control group, however the difference was not statistically significant. Pajari *et al* [34] assessed DMFT only in children with neoplasms. Dodan *et al* [13] found that DMFT was statistically significantly higher in the treatment group, but the study included children both under and after antineoplastic treatment. Dens *et al*[16], contrary to the results of the present study where the D component had been found to be the highest in DMFT, established that the F component was the highest in DMFT. Similarly Fleming and Kinirons confirmed that the F component was the highest in children after antineoplastic treatment [35] .

For Olczak-Kowalczyk [4], the number of carious teeth (DT/dt) was the main DMFT component. Asvar[18] and Cubukçu[27] presented similar results, establishing that children receiving antineoplastic treatments presented statistically significantly higher DMFT than controls, where D was also the main DMFT component.

In the present study, caries intensity was higher in both permanent (PCH DMFT=8.3±7.181 and CH-8.78±6.952) and primary teeth (dmft PCH- 6.33±4.46 and CH- 8.00±4.63), when comparing to controls (DMFT=5.271±4.861 and dmft=5.57±3.28). Fleming and Kinirons noted that children in remission examined after the completion of treatment for acute lymphoblastic leukaemia showed a higher incidence of dental caries than controls. However, there were no differences in dmft, even though the number of primary teeth was lower in children in leukaemia remission than in controls[35].

In the Olczak-Kowalczyk study [4], dmft and DMFT in 34 children after a course of chemotherapy were similar to those in the present study, and amounted to 7.4 and 14.1, respectively. Similarly, in the present PCH and CH groups, carious teeth (DT/dt) were the main DMFT component; DMFS and the number of teeth/surfaces with WSL were statistically significantly higher in present chemotherapy patients when compared to controls, confirming a high risk of caries in chemotherapy patients. Similarly, Cubukçu and Güneş noted a higher WSL incidence in children undergoing chemotherapeutic therapies for leukemia[27].

Statistically significantly higher mean numbers of teeth/surfaces with WSL and carious lesions in post-chemotherapy patients revealed that the risk of caries remained high for a long period of time after antineoplastic treatment completion. In the present study, the mean number of teeth with WSL was statistically significantly higher in CH and PCH than in CG. Although Kinirons *et al* did not establish any statistically significant differences in caries intensity nor in the number of teeth with WSL in 54 children aged 3-19 years in remission of acute lymphoblastic leukaemia, when compared to their incidence in children under chemotherapy, they noted that the children who had completed antineoplastic treatments years earlier had more opacities in permanent teeth than when under treatment. However, the number of opacities in primary teeth did not increase[36].

The highest DMFT/DMFS ratio in the post-chemotherapy group is especially prominent, reflecting the dynamics of caries in its spread over subsequent tooth surfaces. Pajari *et al* also confirmed a high risk of dental caries after antineoplastic treatment completion with an increase in DMFT/DMFS, from 2.3/2.7 just after treatment completion to 2.7/3.3 about 3.1 years after treatment completion (however, those results were not statistically analysed)[2]. The DMFT/DMFS ratio in their first and second afore-mentioned studies was lower than the one in the present study. In the present study, poor dental care was significantly higher in patients under and after chemotherapy than in generally healthy children. Nemeth *et al* reported that high caries incidence in patients under antineoplastic therapy was linked to poor dental care[17]. The impact of poor hygiene on dental caries incidence was also confirmed by the Olczak-Kowalczyk study, assessing dental treatment needs linked to caries in children without dental checkups after antineoplastic therapy completion. In that study, the main DMFT component amounting to 12.84 was the number of carious teeth (DT=8.42) and 4.04% of all examined permanent teeth needed to be extracted[1]. It is worth noting that a comparable oral condition, reported by Fleming and Kinirons in generally healthy children and in those in remission of acute lymphoblastic leukaemia, was linked to similarly frequent dental check ups in both groups and to a more frequent than in controls fluoride use for prevention in children under antineoplastic treatment[35].

CONCLUSIONS

Antineoplastic chemotherapy is associated with caries development and its high incidence during/after treatment. Poor dental hygiene suggested that dental checkups needed to be more frequent and thorough in patients under and after antineoplastic treatment.

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