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Long-term Dental Anomalies After Pediatric Cancer Treatment in Children

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Introduction

Malignant tumors are the second most common cause of death in children all around the world [1-3]. Various "late side effects", can develop in these patients after cancer treatment. Late side effects are

defined as permanent changes caused by disease, treatment, or both [1-5]. It has been reported that at least one side effect and related health problems are observed in approximately 40% of children receiving cancer treatment [6-9,10,11]. Most of these late side effects are not so serious, however these can cause functional and aesthetic problems later in life which may cause decrease in quality of life [7].

The most common types of pediatric cancers are leukemia, central nervous system tumors and lymphomas [1]. Chemotherapy (CT) and/or radiotherapy (RT) are usually the treatment of choice in these diseases. Most anti-cancer drugs used for cancer treatment block the growth of cancer cells owing to their cytostatic and cytotoxic effects and also enable these cells to be destroyed [1,2]. Previous animal studies have shown dental development disturbances induced by vincristine, vinblastine, doxorubicin and cyclophoshamide [12,13]. RT can also cause disturbances in dental development in children; however, the minimal RT dose necessary to cause changes in dental development is unknown. On the other hand, researchers reported that the dose of 10 Gy RT will cause permanent changes in mature ameloblasts and the dose of 30 Gy is enough to stop the dental development [13,14]. Therefore, the risk of dental anomalies (DA) as a long-term side effect is quite high in children after cancer treatment. [3,5-7]. The frequency and severity of DAs can vary depending on age of diagnosis, type and dose of chemotherapeutic agent used, RT total and fraction dose, and volume of oral cavity involved in the RT field [3,15,18].

It is known that DA is more common among children who have received cancer treatment at an earlier age which is usually before the age of 5 years [3,6-8]. On the other hand, age 4-5 years is considered critical for tooth development [7]. For this reason, it is emphasized that it is very important to investigate the possible DAs in pediatric patients who have received cancer treatment before the age of 5 years [6,7].

There is limited data for the long term effects of cancer therapy on dental growth in pediatric patients in Turkey. The aim of this study is to determine the frequency of DAs in pediatric patients who were treated for cancer, and to compare these patients with their siblings with regard to the frequency of DAs.

Materials and Methods

Study population

Patients

The pediatric patients who were diagnosed with cancer and treated in the Departments of Pediatric Hematology-Oncology and Radiation Oncology at Dokuz Eylül and Ege Universities and Outpatient Clinic of Hematology-Oncology at Behçet Uz Children's Hospital between January 2000 and December 2010 were invited to the study. The first signs of root development in permanent teeth are generally observed on panoramic radiographs beginning approximately at the age of 3 to 7.5 years [6,9]. For that reason, patients with an age over 8 years were included into the study and the dental examinations were made between 5 to 8 years after cancer therapy. The patient population is divided into two groups according to critical age for dental growth and previously published data: Group A: 9 months and 4 years; Group B: 5 and 7 years [7,8]. Leukemia, lymphoma, and LCH were accepted as lymphoproliferative diseases (LT), and the remaining cancers were classified as solid cancers (ST). Patients were treated according to appropriate international CT protocols depending on their cancer diagnoses [19].

Controls

Among 85 siblings of 93 treated patients, 72 siblings (8 to 16 years) who are otherwise healthy were included in the control group.

This study was approved by the ethics review committee of

Gazi University, Faculty of Medicine, Ankara, Turkey.

This study was approved by Dokuz Eylul University, Ethics Committee (571-GOA, 2012/16-22). All participants and their parents were given verbal information about the study and written informed consents were obtained from the parents.

Clinical and radiographic examination for the diagnosis of DA

Intraoral examinations of all patients and controls were performed in dental clinical environment. All teeth and their surfaces were examined by one pediatric dentist (GK). Panoramic radiographs (Castellini X-Pan 85 2D) were taken just after intraoral examination in the same session. The panoramic radiographs were analyzed to determine the number of present permanent teeth and the changes in the size of the tooth crown or the root structure.

The teeth with short roots and V-shaped roots were evaluated as root malformations (RM). The Hölttä's Defect Index was used for the assessment of root length as previously described [9,18]. The teeth for which the ratio between the root and crown length was below 1.6 were evaluated as short-rooted teeth. If a tooth is in half-size of other teeth in the same group, this condition is accepted as microdontia [1,7,18]. The absence of tooth or tooth germ in intraoral examination and in the panoramic radiograph without a history of extraction was evaluated as hypodontia. While assessing hypodontia, classification was performed as absence of a single tooth, absence of 2-5 teeth, and absence of 6 and more teeth (oligodontia) [7]. The presence of white/cream and colored opacities or hypoplasia on the enamel >2mm was considered as enamel defect (ED). The condition of having supernumerary teeth in the dental arch was classified as hyperdontia.

Dental findings of all patients and controls in the study were shared with their families. All patients are later followed up for the treatment of DAs in our clinics.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS for Windows), version 15.0 (SPSS, Inc., Chicago, IL, USA) was used in statistical analyses. Differences in clinical variables were evaluated using the Chi-square test or Fisher Exact test for qualitative variables. A p-value of < 0.05 was considered statistically significant.

Results

A total of 93 children treated for cancer were included into the study. The mean age was 9.54±1.25 (range 8-13years) and 48 (51.6%) were male. The mean age at cancer treatment was 3.75±2.01 years (range 9 months and 7 years). The distribution of, cancer types are presented in Table 1. The mean age of the control group was 10.60±2.40 (range 8-16) years.

Seventy-eight children (83.9%) had at least one DA. ED was detected in 90 teeth of 22 patients (23.7%) in the treatment group and in 20 teeth of 7 patients (9.7%) in the control group (p=0.009).

Group A consisted of 59 patients and group B consisted of 34 patients. The total number of DA was not different between the groups, however the rates of microdontia and hypodontia were higher in Group A than in Group B (p=0.041 and p=0.045, respectively) (Table 2). However, the rates of RM and ED were similar in both groups.

No statistically significant difference was detected in patients in terms of gender and frequency of DAs (microdontia, hypodontia, hyperdontia, ED, and RM) (p>0.05) (Table 3).

The frequency of DAs was 80.6% in ST, 85.5% in LT, 81.0% in CT, and 88.6% in CT+RT group. There was no significant difference in terms of tumor type and method of treatment (p=0.790 and p=0.397, respectively). However, RM was observed to be more common in patients receiving CT+RT than in those receiving only CT (p=0.006). When patients receiving CT+RT to the head-neck region were analyzed (n=24), the rate of RM significantly increased (p=0.001). According to the dose of RT (<20 Gy/≥20 Gy) in 24 patients receiving RT to the head-neck region, only the rate of RM was observed to significantly increase in parallel with dose (p=0.013) (Table 4).

Totally 413 teeth of the patients and 20 teeth of the controls were affected by DAs. The number of teeth with DAs is quite high in patients undergoing cancer treatment (Table 5). While the numbers of teeth with microdontia and hypodontia were higher in Group A, the numbers of teeth with ED and RM were close in Group A and B.

Microdontia was more frequently found among second incisors, first and second premolars, and second molars in Group A compared to Group B. Hypodontia was often found among second incisors, first and second premolars, and second molars in Group A. RMs were almost equally distributed among all classes of teeth in Group A and B, but they were more often found in the lateral or central incisors and first molars in Group A while in the first and second premolars in Group B. ED rate was detected similar in both groups. Hyperdontia was observed in the right-left mandibular first and second premolars of only one patient in Group A.

Discussion

Patients receiving cancer treatment in childhood are prone to development of DAs [3,7,8,17,20]. In our study, the overall rate of DAs was found to be 83.9%. There is a wide variation of the rate of DA in the literature. Despite the presence of studies reporting rates similar results to ours (82.9%-89.1%) [3,6,21], some others reported much lower rates (29%-62.3%) [7,20]. These differences are attributed to treatment age, CT protocols that are applied, and of the presence of RT to the head and neck [9,22].

In our study, the rates of occurrence of DAs in Group A and Group B were similar. This result can be explained by the fact that dental development between 1 and 7 years is very active. In the studies conducted on rats and hamsters, it has been biochemically and histologically demonstrated that chemotherapeutic agents affect developing teeth much more than developed teeth [10,23-25].

Maguire et al. [28] reported the absence of a statistically significant difference in the rate of DA between leukemia and ST. Similar results were also found in our study. We found no significant differences between the patients receiving CT and those receiving CT+RT in terms of DAs, except for RM. Maciel et al. [26] reported that, in patients with acute lymphoblastic leukemia, the mean number of teeth with DA

was higher in the group undergoing conventional CT+RT of the whole cranium than in the group undergoing only conventional CT, but the difference was not statistically significant. In our study, when the frequency of DA was analyzed considering the dose of RT (<20 Gy/≥20 Gy) in patients receiving RT to the head-neck region, the rate of RM was significantly increased with dose. Similarly, Kaste et al. [15] reported a dose-dependent risk of having at least one DA among 9308 pediatric cancer survivors; exposure of jaw to RT doses exceeding 20 Gy contributed to a 4 to10-fold higher risk of developing Das [15].

Several studies have reported a prevalence of microdontia ranging from 7% to 78% in childhood cancer survivors [6,17,18,21,27-29]. In our study, the rate of occurrence of microdontia was 64.5%. The rate of microdontia was previously reported 0.5% in healthy Turkish children [30]. Höltta et al. [18] found this rate as 75% in children younger than 3 years, 60% in those between the ages of 3 and 5 years, and 13% in those older than 5 years. Wilberg et al. [27] reported the rate 54.0% in children with leukemia at the age of ≤5 years. Proc et al. [7] stated that microdontia was mostly observed in the first and second premolars in pediatric patients whose treatments were started at the age of ≤ 30 months. In our study, the rate of occurrence of microdontia was higher in Group A and first and second premolars were observed to be affected more frequently.

Anti-cancer treatment applied in patients causes hypodontia and its prevalence varies between 6% and 44% [8,9,20,31]. Pedersen et al. [1] reported a strong relationship between microdontia and hypodontia. In our study, the rate of occurrence of hypodontia was 23.7%. Nishimura et al. [17] found the rates of hypodontia and microdontia to be higher in children at the age of ≤4 years. In our study, the rates of microdontia and hypodontia were significantly higher in children younger than 5 years old. While hypodontia is mostly observed in lateral incisors, second premolars, and third molars in healthy individuals [32,33], it is more frequent in second premolars and second molars in patients receiving cancer treatment [7]. The reason for hypodontia to occur in some tooth groups more commonly is that the time of calcification differs for the different kinds of teeth [7,34].

In small children, application of CT and/or RT during odontogenesis can delay the development of Hertwig's epithelial root sheath. For this reason, higher rate of RM are reported for these patients [3,22]. Researchers have found the rate of occurrence of RM between 11.5% and 16.1% which is more frequently encountered in patients older than 4 years [7,9,35]. RMs were significantly more common among first and second premolars and first and second molars. The development of tooth roots begins approximately at the ages of 3 and 4 years and finishes at the age of 16 years [36]. Although the rate of RM was higher in Group B (32.4%) than in Group A (22.0%), there was no statistically significant difference. Similarly, Maciel et al. [26] found no significant difference between patients older than 5 years and patients ≤ 5 years old in terms of RMs. In our study, RMs were mostly in central, lateral, and first molars in Group A and in first and second premolars in Group B. Our findings are consistent with the developmental periods of tooth roots [36].

EDs are the most common defects in general population. They are the result of ameloblastic damage as far as it concerns their reproductive and secretory function, their membrane permeability, and calcium exchange across the membrane. Studies have reported that children in long-term remission of a malignant disease display a high incidence of EDs [3,8]. It is mentioned that chemotherapeutic agents such as vincristine, vinblastine, and cyclophosphamide affect odontogenesis much more [8,10]. In our study, the rate of ED was higher in the patients (23.7%) than in their siblings (9.7%) and the difference was statistically significant. Similarly, the frequency of ED was higher in patients undergoing cancer treatment compared to their siblings in some studies [28,31,37].

Hyperdontia was encountered in two teeth of a patient receiving treatment for retinoblastoma. Maciel et al. [26] stated that they found hyperdontia in their study, but its incidence was quite low and there was no difference between the study group and control group.

Our study has several limitations. First, the number of patients is relatively small and our results cannot be generalizable to all pediatric cancer patients. However, we have included patients from 3 centers. Second, we did not have detail information about patient's routine oral and dental care which might have an impact on DAs. The strength of the present study is the time period between cancer therapy and dental evaluation. We think that this duration is enough for confirmation of the development of DA after cancer therapy especially in patients aged less than 5 years. Another important point is we have included patients' siblings as a control group into the study in order to compare possible genetic effect.

Conclusion

Pediatric patients undergoing cancer treatment at early ages constitute a high-risk group in term of dental complications. Therefore, parents of the pediatric patients undergoing cancer treatment should be informed by pediatric oncologists-hematologists and radiation oncologists about dental abnormalities that can develop in the future. Moreover, pediatric dentists should be integral members in the management of all children receiving cancer therapy. We think that periodic dental control and protective measures, at least twice a year, are essential and should be performed both during and after cancer therapy in pediatric patients.

Conflicts of Interest

The authors of this paper have no conflicts of interest.

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Table 1: Patient and control group characteristics

	Patient group	Controls
n	93	72
Male gender	48 (51.6)	38(52.8)
Mean age (years)	9.54±1.25	10.60±2.40
Mean age at cancer treatment	3.75±2.01 years	-
Types of cancer		-
LT		
Leukemia	43(46.2)	
Lymphoma	18 (19.3)	
LCH	1 (1.1)	
ST		
Neuroblastoma	8(8.6)	
Renal tumor	8(8.6)	
STS	6 (6.5)	
GCT	3 (3.2)	
Hepatic tumor	3(3.2)	
CNS tumor	2(2.2)	
Retinoblastoma	1 (1.1)	
Total DA	78(83.9)	7(9.7)*
Types of DA		
Hypodontia	21 (22.6)	-
Microdontia	60 (64.5)	-
Root malformations	24 (25.8)	-
Enamel defect	22 (23.7)	7 (9.7)
Hyperdontia	1 (1.1)	-

*p=0.009

ST: Solid tumor, LT: Lymphoproliferative tumor, STS: Soft tissue sarcoma GCT: Germ cell tumor,

CNS: Central Nervous System, LCH: Langerhans cell histiocytosis

Table 2. Comparison of patient groups according to age of treatment

	Group A	Group B	P value
n	59 (63.4)	34 (36.6)	
Type of tumor			
LT	34(36.6)	28(30.1)	
ST	25(26.9)	6(6.4)	
Type of treatment			
CT	43(46.2)	15(16.2)	
CT+RT	16(17.2)	19(20.4)	
Total DA	50(84.7)	28(82.4)	0.762
Types of DA			
Hypodontia	42(71,2)	18(52.9)	0.041*
Microdontia	17(29.3)	4(11.4)	0.040*
Root malformations	13(22.0)	11(32.4)	0.273
Enamel defect	14(23.7)	8(23.5)	0.982
Hyperdontia	1(1.7)	-	1.000

Table 3: Comparison of the frequencies of dental anomalies according to gender, type of treatment, and tumor type.

Dental anomaly		Gender n(%)		**p**	Type of treatment n(%)		p	Type of tumor n(%)		**p**
		Female	Male		C	C+R		LT	ST	
DA	Yes	36(80.0)	42(87.5)	0.483	47(81.0)	31(88.6)	0.397	53(85.5)	25(80.6)	0.790
	No	9(20.0)	6(12.5)		11(19.0)	4(11.4)		9(14.5)	6(19.4)	
Microdontia	Yes	30(66.7)	30(62.5)	0.674	38(65.5)	22(62.9)	0.795	40(62.5)	19(61.3)	0.939
	No	15(33.3)	18(37.5)		20(34.5)	13(37.1)		22(35.5)	12(38.7)	
Hypodontia	Yes	11(24.4)	10(20.8)	0.677	17(27.6)	5(14.3)	0.137	12(19.4)	9(29.0)	0.430
	No	34(75.6)	38(79.2)		41(72.4)	30(85.7)		50(80.6)	22(71.0)	
Root malformations	Yes	10(20.8)	14(29.2)	0.444	7(12.1)	17(48.6)	*0.006	20(32.3)	4(12.9)	0.078
	No	35(79.2)	34(70.8)		51(87.9)	18(51.4)		42(67.7)	27(87.1)	
Enamel defect	Yes	12(26.7)	10(20.8)	0.676	11(19.0)	11(31.4)	0.211	17(27.4)	4(12.9)	0.188
	No	33(73.3)	38(79.2)		47(81.0)	24(68.6)		45(72.6)	27(87.1)	
Hyperdontia	Yes	-	1(2.1)		1(1.7)	-	1.000	-	1(3.2)	0.344
	No	45(100.0)	47(97.9)	0.330	57(98.3)	35(100.0)		61(100.0)	30(96.8)	

DA: Dental anomalies, ST: Solid tumor, LT: Lymphoproliferative tumor, C: Chemotherapy

C+R: Chemotherapy and Radiotherapy, *p<0.05

Table 4: Treatment characteristics

Diagnosis	Total n (%)	Chemotherapeutic agents						Radiotherapy dose			
		Alkylating agent	Anti-metabolite	Topoisomerase inhibitors	Tubulin binding drug	Others	Only CT (n)	≥20 Gy		<20 Gy	
								H+N(n)	Others (n)	H+N (n)	Others (n)
Leukemia	43(46.2)	+	+	+	+	+	28	13	-	1	1
Lymphoma	18(19.3)	+	+	+	+	+	7	2	-	6	3
Neuroblastoma	8(8.6)	+	-	+	+	+	5	-	-	-	3
Renal tumor	8(8.6)	+	-	+	+	-	5	-	1	-	2
STS	6(6.5)	+	-	+	+	-	5	-	-	-	1
GCT	3(3.2)	+	-	-	+	-	3	-	-	-	-
Hepatic tumor	3(3.2)	+	+	+	-	-	3	-	-	-	-
CNS tumor	2(2.2)	+	-	+	+	+	-	-	-	-	2
Retinoblastoma	1(1.1)	+	-	-	+	-	1	-	-	-	-
LCH	1(1.1)	-	+	-	+	+	1	-	-	-	-

STS: Soft tissue sarcoma, GCT: Germ cell tumor, CNS: Central nervous system, LCH: Langerhans cell histiocytosis, H+N: Head-Neck Alkylating agents (cyclophoshamide, ifosfamide, mechlorethamine, melphalan, busulfan, carmustine, dacarbazine, carboplatin, oksaliplatin, cisplatin, procarbazine, temozolomide), antimetabolites (methotrexate, 6-mercaptopürine, 6-thioguanine, azacytidine, gemcitabine), topoisomerase inhibitors (dactinomycin, daunorubicin, bleomycin, doxorubicin, epirubicin, idarubicin, topotecan, irinotecan, actinomycin D, etoposide, teniposide), tubulin binding drugs (vincristine, vinblastine, vinorelbine), and other chemotherapeutic agents (steroid, imatinib, L-asparaginase, rituximab, 13-cis retinoic acid)

Table 5: Distribution of teeth with anomalies

Teeth	Hypodontia n (%)		Microdontia n (%)		Enamel defect n (%)		Root malformations n (%)	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Central	-	-	-	-	15	15	16	2
Lateral	7	2	16	10	10	11	10	2
Canine	-	-	-	-	-	-	4	3
First premolar	18	3	66	6	6	7	6	20
Second premolar	19	-	23	-	5	6	5	22
First molar	-	-	-	-	5	10	20	4
Second molar	3	-	21	4	-	-	4	5
Total	47(90.4)	5(9.6)	126(86.3)	20(13.7)	41(45.6)	49(54.4)	65(48.9)	58(51.1)