

Dental Development in Children After Chemotherapy

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Chemotherapy, as a treatment method in paediatric oncology, coincides with the physiological process of tooth development. The interference between cytostatic agents and the cycle of the cells with specialised functions in the formation and mineralisation of dental structures leads to the appearance of abnormalities in the development of the tooth buds, structural defects and disorderly eruption. We have looked into the distribution of developmental tooth disorders in a group of children suffering from malignant ailments. The study reveals a high occurrence of microdontia and agenesis of premolars among children diagnosed with high-risk acute lymphoblastic leukemia at the age between 1 and 6, as well as tooth eruption disturbances in 70% of the children. The nature and the severity of dental abnormalities depend on the type of cytostatic medication, the dosage and the frequency of therapeutic cycles, the age of the child at the beginning of the oncological therapy, as well as on the stage of the odontogenesis.

Keywords: chemotherapy, leukemia, dental development

Tooth development or odontogenesis represents an extremely complex process, which occurs over a long period of time, beginning in the intrauterine life and continuing up to the age of 14-15. Each tooth, in its evolution, goes through a series of distinct stages of development, represented by cell proliferation, histodifferentiation, morphodifferentiation, and the interference of certain extrinsic or intrinsic factors throughout the process of odontogenesis leads to the appearance of defects in the development as far as shape, structure, number and eruption of the teeth are concerned.

Malignant tumours represent the main cause of death in children between 0-14 years, registering a particular incidence in the first years of life. Leukemias are the most frequent forms of neoplasia in children, representing, in Romania, 45% of the total number of malignant illnesses in children under the age of 16: 25% of it corresponds to acute lymphoblastic leukemia (ALL), 15% to acute myeloblastic leukemia, while chronic myeloid leukemia represents 5% of the total number of cases of leukemia in children. The incidence of ALL, on the global level, is appreciated at 1:25,000 children/year, reaching a peak at the age of 4; 85% of the cases are diagnosed between the ages of 2 and 10 [1, 2].

Leukemias are illnesses with an indisputable and constant influence on the oral cavity. The oral manifestations and complications are caused both by the leukemic condition, being secondary to thrombocytopenia, anaemia and neutropenia and by the specific treatment with cytostatic agents, representing complications typical for the respective drug [3-7].

The purpose of modern oncotherapy is to treat the patient with minimal risks as far as the specific toxicity of the drug is concerned, and to obtain a long-term remission. According to the risk level of the acute lymphoblastic leukemia (high, standard), the oncological treatment is individualised. Thus, in the case of standard-risk leukemia, chemotherapy follows the steps of induction, consolidation, intensification (re-induction) and maintenance, while in the case of high-risk leukemia, the cytostatic treatment is longer and in higher doses, including the induction stage, followed by the aggressive cytostatic therapy (6 blocks of polychemotherapy high doses - Block HR), the induction phase and maintenance [8-10].

In children with malignant illnesses, chemotherapy, as a treatment method in paediatric oncology coincides with the physiological process of odontogenesis. The interference of the cytostatic agents with metabolism and with the cell cycle of ameloblasts and odontoblasts – cells with specialised functions in the formation and mineralisation of dental structures – affects the processes of amelogenesis, dentinogenesis, the appearance of abnormalities in the development of the tooth buds, defective mineralisation, microdontia and agenesis [1, 11, 12].

The nature and the severity of these abnormalities depend on the type of cytostatics, dosage and the frequency of therapeutic cycles, the age of the child at the beginning of oncologic therapy, the nutritional status, and the stage of tooth development (odontogenesis) [13-19].

Our purpose is to measure the prevalence and the distribution of disturbances in tooth development in a group of children suffering from malignant ailments.

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Experimental part

Materials and Methods

The study involves the evaluation of 36 children with mixed dentition, of ages between 10 and 12, being registered at the Department of Hematology-Oncology of the Paediatric Hospital I Tirgu Mures; the children have been diagnosed with acute lymphoblastic leukemia of standard or high-risk, and have undergone chemotherapy according to ALL-BFM 95 Protocol. In the standard form of leukemia, the cytostatic treatment has involved the following cytostatics: Vincristin (VCR), Asparaginase (L-Asp), Daunorubicin (DNR), Methotrexate (MTX), Cyclophosphamide (CPM), Cytosar (Ara-C), Purinethol (6-MP), Thioguanine (TG). For the high-risk leukemia, polychemotherapy has been much more aggressive, in higher doses of the following cytostatics: Vincristin, Vindesine (VDS), Asparaginase, Daunorubicin, Methotrexate, Cyclophosphamide, Ifosfamide (IFO), Etoposide (VP-16), Cytosar, Purinethol, Thioguanine (table D).

20 of the children have been diagnosed with ALL between the ages of 1 and 6 (10 children with standard-risk ALL, 10 children with high-risk ALL) and 16 of the age

between 7 and 12 (8 children with standard-risk ALL and 8 children with high-risk ALL). We have measured the disturbances of tooth development by direct clinical examination and/or radiological examination: hypoplasia (hypomineralisation) of the enamel, microdontia and atypical eruption.

Results and discussions

Dental abnormalities (table 2)

The most important development disturbances were represented by eruption disturbances (fig.1), almost 70% of the children having delayed eruptions or early eruptions. 18 of these children have been diagnosed with ALL at the age of 1-6 years.



Fig.1. An 8 year-old child, diagnosed with standard-risk ALL at the age of 1.5 years; agenesis of lower premolars and delayed eruption

Table I
CYTOSTATIC TREATMENT IN ALL

Risk	ALL-BFM 95 PROTOCOL			
	Cytostatic medication, total dosage/m ² /protocol			
	Induction	Consolidation-ALL SR/ Blocks HR-ALL HR	Intensification	Maintenance
ALL SR (Standard Risk)	VCR 6 mg/m ² iv; DNR 120 mg/m ² iv; L-Asp 40.000U/m ² iv; CPM 2000mg/m ² iv; Ara-C 1200 mg/m ² iv; 6-MP 1680 mg/m ² po; MTX 60 mg i.theal	MTX 20.000 mg/m ² iv; MTX 48 mg/m ² i.theal; 6-MP 1400 mg/m ² po	VCR 6 mg/m ² iv; DNR 120 mg/m ² iv; L-Asp 20.000 U/m ² iv; CPM 1000 U/m ² iv; Ara-C 600 mg/m ² iv; TG 840 mg/m ² po; MTX 24 mg i.theal	6-MP 36.000 mg/m ² po; MTX 1920 mg/m ² po; VCR 18 mg/m ² iv; MTX 96 mg i.theal
ALL HR (High Risk)	VCR 6 mg/m ² iv; DNR 120 mg/m ² iv; L-Asp 40.000U/m ² iv; CPM 2000mg/m ² iv; Ara-C 1200 mg/m ² iv; 6-MP 1680 mg/m ² po; MTX 60 mg i.theal	VCR 6 mg/m ² iv; VDS 6 mg/m ² iv; Ara-C 16.000 mg/m ² iv; MTX 20.000 mg/m ² iv; MTX 72 mg i.theal; CPM 2000 U/m ² iv; IFO 8000 mg/m ² iv; DNR 60 mg/m ² iv; VP-16 500 mg/m ² ; L-Asp 150.000 U/m ² iv	VCR 6 mg/m ² iv; DNR 120 mg/m ² iv; L-Asp 20.000 U/m ² iv; CPM 1000 U/m ² iv; Ara-C 600 mg/m ² iv; TG 840 mg/m ² po; MTX 24 mg i.theal	6-MP 36.000 mg/m ² po; MTX 1920 mg/m ² po; VCR 18 mg/m ² iv; MTX 96 mg i.theal

Table 2
THE DISTRIBUTION OF DENTAL ABNORMALITIES BY ALL RISK AND AGE AT ALL DIAGNOSIS

Dental abnormalities	High-risk ALL		Standard-risk ALL		Total children
	Age 1-6	Age 7-12	Age 1-6	Age 7-12	
First premolar microdontia	7 children 17 premolars	1 child 1 premolar	4 children 8 premolars	- -	12 (33.33%)
Second premolar agenesis	6 children 10 premolars	1 child 2 premolars	4 children 4 premolars	1 child 1 premolar	12 (33.33%)
First molar hypoplasia	8 children 20 molars	- -	6 children 18 molars	- -	14 (38.88%)
Incisor hypoplasia	8 children 18 incisors	- -	8 children 15 incisors	- -	16 (44.44%)
First molar and incisor hypoplasia	10 children	- -	7 children	- -	17 (47.22%)
First molar with shortened roots	- -	3 children 5 molars	- -	2 children 4 molars	5 (13.88%)
Abnormal emergence	9 children	4 children	9 children	3 children	25 (69.44%)

The mineralisation disturbances (hypoplasia) that have affected both first molars and the incisors have been noticed in 17 of the children diagnosed with ALL between the ages of 1 and 6.

The percentage of microdontia and of dental agenesis is of 33.33%, being also poignant in the children diagnosed with ALL between the ages of 1 and 6 years. The radiological examination has also shown root development disturbances, represented by molar shortened roots in 5 of the children diagnosed with ALL between the ages of 7 and 12 years.

According to the specialised literature, dental abnormalities do not occur in children who are clinically healthy; but they occur under the influence of genetic factors, children with the Down syndrome being frequently affected [20-22]. Given this, we have not performed any statistical correlations with healthy children with regard to the occurrence of dental development abnormalities.

38.88% of the children diagnosed with ALL have shown hypoplasia at first molars, 44.44% at the level of incisors and approx. 47% of them have shown defective mineralisation both at first molars and incisors. We have noticed the absence of hypomineralisation in children diagnosed with ALL between the ages of 7 and 12 years.

Hypoplasia is caused by the damage of the ameloblasts during the process of odontogenesis, represented by the change in the reproduction of the ameloblasts, of the secretory function, of the membrane permeability and of the exchange of Ca^{2+} through the cell membrane. It is clinically manifested by opacities of the enamel [23]. The children with ALL who underwent chemotherapy are frequently affected by these disturbances of the enamel mineralisation. Chemotherapy and cranial radiotherapy are the main methods of treatment used for acute lymphoblastic leukemia. Chemotherapy destroys the tumour cells, but with minimal toxicity for the normal cells. Chemotherapy has a selective toxic effect on the cells which proliferate actively through the interference with DNA synthesis and the replication, the transcription of RNA and with cytoplasmic mechanisms of streaming.

Although chemotherapy is a systemic treatment in malignant ailments, it can have effects on the oral cavity. Unlike radiotherapy, which affects only the cells around the area that is being radiated, chemotherapy has a systemic effect. As a consequence, odontogenic cells under development are sensitive to chemotherapy. The longer and more frequent the therapeutic cycles, and the higher the dosage, the higher the risk of affecting the ameloblasts [2, 7, 24]. Vincristine [6-7], as well as cyclophosphamide [4] and alkylating agents [1, 4, 25] have been associated with dental abnormalities among the children who have survived cancer.

The influence of the cytostatic therapy on odontogenesis has been evidenced by the insufficient development of first premolars (microdontia), as well as by the absence of the development of second premolars buds (agenesis) [20, 22]. The results of our study show the highest percentage of microdontia and agenesis among the children diagnosed with high-risk ALL between the ages of 1 and 6 years. The development of premolars occurs around the age of 2 [21], a stage in life which coincided with the diagnosis of the acute lymphoblastic leukemia and with the beginning of the cytostatic treatment according to the ALL-BFM-95 protocol. Practically, the whole process of mineralisation and development of the premolars intersected with the therapeutic cytostatic medication.

Pedersen et al. [26] emphasised the distribution of microdontia and of agenesis in childhood cancer survivors

after chemotherapy. The therapeutic protocol of leukemias and of malignant lymphoma included as cytostatic agents, vincristine and at least alkylating agent plus a combination of etoposide and a platinol and/or an antibiotic derivative as antracyclin. The protocols of leukemia and lymphoma also included methotrexate and asparaginase. The results of this study indicate a number of 88 premolars with microdontia and 27 cases of premolar agenesis in a group of 150 children with leukemias and lymphomas; our study shows a number of 26 microdontias and 17 ageneses in a group of 36 children with ALL.

Also, the cytostatic treatment interfered with the processes of root edification in the temporary teeth, therefore the roots of these teeth showed an intensified resorption, before the physiological age. The consequences consisted in premature loss of these teeth from the dental arches and disturbances in the eruption of permanent teeth. 25 of the children included in the study (69.44%) showed abnormal emergences, 18 of them being diagnosed with neoplasia between the ages of 1 and 6 years.

The eruption of the first molars in the oral cavity started at the age of 6, while their root edification continued post-eruption until the age of 10, which explains the presence of shortened roots in children of 7-12 diagnosed with ALL that were considered in our study. Chemotherapy may delay the development of Hertwig epithelial root sheath, an anatomical tissue with a role in the formation of the root [11]. The effect on the activity of the odontoblasts, a consequence of the abnormal secretory function of microtubules and of changes between inter- and intracellular relationships, could lead to abnormal and shortened roots [23, 27-29].

Conclusions

The study shows the effects of chemotherapy on the processes of dental development and mineralisation in children diagnosed with ALL. The nature and the severity of these abnormalities depend on the type of cytostatic medication, dosage and frequency of therapeutic cycles, the age of the child at the moment of initiation of oncological therapy, and the stage of the odontogenesis.

It also shows the necessity of monitoring the children having oncological conditions, with the view of optimising their oral-dental health, in order to increase the quality of their life and to prevent the worsening of the children's suffering. Thus, we consider that the presence of a dentist as a member of the oncological team can reduce the morbidity connected to the complications of the antineoplastic treatment.

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