

ORIGINAL ARTICLE

PERIODONTAL RESPONSE TO CYTOSTATIC DRUGS IN CHILDREN

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ABSTRACT

The aim: To study the effect of different types of cytostatic drugs on the periodontium in children with malignant tumors.

Material and methods: The material for generalization was based at the results of examination of 44 patients with malignant tumors of the abdominal cavity who underwent preoperative treatment in the oncohematology department of Poltava Children's City Clinical Hospital.

Results: In the absence of proper dental care in patients of this group, under the influence of chemotherapeutic drugs, significantly worsens the level of oral hygiene and the condition of periodontal tissues. There are also changes in the process of differentiation of the epithelial structures of the gingival margin, which is accompanied by an increase in smears - reprints of the number of inflammatory cells of the peripheral blood, both with preserved structure and destructive forms.

Conclusions: In children with malignant tumors, during antitumor therapy, there is a decrease in the level of hygiene of the oral cavity, accompanied by morphological destructive changes in the integumentary epithelial layer of the gingival margin. The severity of these disorders depends on the type and dose of cytostatic drugs, which should be considered in the formation of treatment and prevention measures for them.

KEY WORDS: children, periodontitis, malignant tumors, polychemotherapy, stomatotoxicity

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INTRODUCTION

Nowadays, a very important and priority direction of modern world medical science is to increase the effectiveness of treatment of patients with malignant tumors of different anatomical localization. Statistics provided by the WHO indicate a steady increase in the number of malignant tumors, and if for the period from 2011 their growth was 17.3%, then, in the short term, the number of their cases will increase 2 times over the same period [1, 2, 3].

According to the data that provided by the Center for Medical Statistics of the Ministry of Health of Ukraine, about 160,000 new cases of malignant neoplasms are registered in the country annually. Unfortunately, the annual cancer incidence among children increases by 5 - 9%, and their prevalence is 11 - 12 people per 100 thousand children [2, 4].

At the present stage of development of oncology, the use of chemotherapy remains one of the effective ways to influence the kinetics of malignant cells that have morphological signs of atypia. The essence of this approach is to synchronize the phases of tumor growth, which makes these structures quite sensitive to subsequent chemical contact. Unfortunately, the use of cytostatics is often limited to the appearance of severe side effects and unwanted consequences [5].

In particular, the frequency of stomatotoxicity of cytostatic drugs ranges from 30% to 90%, depending on the individual characteristics of the child's body. However, most scientists note that chemotherapy is primarily complicated by the manifestations of this phenomenon. The most common and debilitating form is the defeat of the mucous membrane of the gastrointestinal tract, including the oral cavity, as its initial department. Basically, it is an oral mucositis and all its clinical manifestations mainly depend on the ascending level of dental status and hygienic condition of the oral cavity, because the epithelial structures are rapidly renewed, which is due to the high frequency of signs of side effects at its level [4, 5, 6].

At this stage of medical science, the main direction of modern oncology is to develop an individual approach to the choice of cytostatic drugs, which provides targeted improvement of treatment results and reducing the intensity of their toxic effects, what, in combination, significantly increased the survival rate of children with solid tumors [5, 6].

THE AIM

The aim of the research is to study the effect of different types of cytostatic drugs on the periodontium in children with malignant tumors.

MATERIALS AND METHODS

In order to determine the response of periodontal tissues in children to various pharmacological antitumor drugs, we formed two clinical groups of children of 22 people each and who were treated in the oncohematological department of Poltava City Children's Clinical Hospital due to the presence of solid tumors of abdominal localization of different morphological type. Cytostatic treatment was

performed on the background of standard concomitant therapy, taking into account the daily physiological needs and the general somatic condition of patients. Diagnostics of malignant tumors was carried out in accordance with the scope of measures provided by the clinical protocols for the treatment of children with solid tumors, approved by the order of the Ministry of Health of Ukraine №649 from 28.08.2009. The diagnosis of the main disease was verified after a comprehensive in-depth examination with involving of all advances modern technologies.

The study of the hygienic condition of the oral cavity was performed by evaluation of the Greene-Vermillion index. To determine the presence of inflammation in periodontal tissues were used PMA index and PBI bleeding index [7].

In order to establish the cellular composition of smears-reprints from the vestibular surface of the gingival margin of the frontal part of the mandible used a method developed by the staff of the department. The smears were fixed and stained according to the Romanovsky-Gimse method. After that, the count of epithelial and cellular structures was performed in 10 fields of view, followed by their conversion to one field of view [8].

All absolute numerical indicators were statistically processed in accordance with existing requirements [9].

RESULTS

Patients of the first group in the complex treatment, according to the SIOP 2001 protocol, received: cyclophosphamide + MESNA 360 mg and doxorubicin 34 mg, and in the second group the drugs were: ifosfamide 3000 mg, uromitexan 3000 mg, etoposide 150 mg, vincristine 1,6 mg, doxorubicin 20 mg.

The duration of the therapeutic program, according to the requirements of the protocol, depended in each case on the situational circumstances, and for each patient an individual treatment program was developed taking into account its prognostic factors, but without proper stomatological care.

In studying the cytograms of 25 children from the control group, we were able to establish the prevalence of squamous epithelial cells with signs of focal keratinization, which had a different shape and structure of the nuclei, as well as single neutrophils.

At the primary dental examination, at the time of hospitalization, only 3 patients out of 44 (6.8%) focused on the appearance of bad breath and some discomfort when eating. Analysis of the anamnesis of patients revealed that before the diagnosis of the tumor 39 children (88.6%) were constantly hygienic measures for the care of the oral cavity and 3 of them (6.8%) had previously consulted with a dentist with complaints of edema, soreness and bleeding from gums. Unfortunately, 42 children (95.5%) and their parents at this time "forgot" about the importance of hygienic care for the oral cavity and the reason of it was an unforeseen stressful life situation in which the family immediately found itself.

In 35 patients (79.5%) a slight pallor of the skin and red border of the lips was visually detected, which had signs of dryness and single small crusts. The oral mucosa in all examined patients was moderately moisturized and had a pale pink color. The gums were close to the necks of the teeth in the absence of dental plaque, but in 5 patients (11.4%) the gingival margin had clinical signs of chronic inflammation: hyperemia of the mucous membrane, edema and bleeding when probing the gingival papillae.

When comparing both groups of patients, during this period of the survey, the hygiene indices, PMA index and bleeding index had no statistically significant differences and were identical in ascending parameters.

The cellular elements of the gingival margin were represented mainly by the epithelial structural component with signs of vacuolated substance of the cytoplasm and an increased number of cells with deformed nuclei, neutrophils were found to be both normal and destructive.

At the end of the first course of comprehensive treatment, 14 children (66.7%) of the 21 patients of the first group, who remained at this time of the examination, complained of increased level of dryness of the mucous membrane, feeling of thirst, difficulty in forming a food lump and swallowing. Thirteen patients (61.9%) complained of unpleasant sensations and bleeding gums, and among them - 8 patients (61.5%) noted pain and swelling of the oral mucosa, which also made it difficult to eat. It is noteworthy that 6 children (28.6%) emphasized that pain appeared in the areas of projection of the branch and body of the mandible and parotid-masticatory area, and their severity increased with articulation and chewing.

Visual examination attracted pale skin of the face and neck, as well as dryness of the abdominal border of the lips with exfoliation, which was observed in 18 children (85.7%) with their localization mainly on the lower lip, and in 9 children of them (50%) was combined with angular cheilitis. In all patients, there was a slight swelling of the oral mucosa, and this was especially noticeable along the line of closure of the dentition. Hyperemia and edema of the interdental papillae and of the marginal edge of the gums were also determined in 9 children (48.9%). The rest of the children had a pale complexion. During probing of the gingival sulcus, bleeding occurred in 10 cases (47.6%).

Lack of proper care of the oral cavity, due to the unenviable and ambiguous situation in which children and their parents found themselves, during the first course of polychemotherapy led to a deterioration of its hygienic condition in 2 times in comparing with the primary examination. The Greene-Vermillion index was increased by 3.6 times, PMA index - by 8.5 times, and PBI by 3.4 times. Such indicators correlated with the severity of clinical changes in the condition of the gingival margin, which ranged from satisfactory to "lite" and "medium" severity. The presence of signs of mucositis was found in 8 patients (38.1%).

At the time of the survey, 19 children (86.4%) of the 2nd group complained of dryness of the oral mucosa. It was accompanied by a feeling of thirst and significant discomfort at time of chewing food, in forming of a food lump and swallowing it, which caused some discomfort. The fact of bleeding of gums was found in 18 patients

Table I. The state of hygiene of the oral cavity and periodontal tissues (M+m)

Indicators	Control group (n=25)	1st group of patients		2nd group of patients	
		Before the first course of polychemotherapy (n=22)	After completing of the first course of polychemotherapy (n=21)	Before the first course of polychemotherapy (n=22)	After completing of the first course of polychemotherapy (n=22)
Greene-Vermillion index, points	0,52±0,02	0,95±0,05 p_1<0,05	1,89±0,04 p_2<0,05	0,87±0,08 p_1<0,05	3,58±0,07 p_2<0,05 p_3<0,05
PMA index, %	0	3,43±0,18 p_1<0,05	29,14±0,12 p_2<0,05	3,12±0,12 p_3>0,05	38,45±0,12 p_2<0,05 p_3<0,05
Bleeding index PBI (by H.P.Muhlemann), points	0	0,78±0,06 p_1<0,05	2,96±0,05 p_2<0,05	0,82±0,07 p_1>0,05	4,87±0,09 p_2<0,05 p_3<0,05

Footnote:
p_1 – the probability of the difference between the indicators of the control group and patients at the time of hospitalization;
p_2 – the probability of the difference between the indicators at the time of hospitalization and at the end of the first course of polychemotherapy;
p_3–вthe probability of the difference between the groups of comparison at the time of completion of the first course of polychemotherapy.

(81.8%), and in addition, 12 of them (66.7%) indicated the occurrence of pain in the location of the masticatory muscles and especially in the places of their attachment to the periosteum, moreover, the intensity of pain increased with multidirectional movements of the lower jaw.

Paleness of the visible skin and dryness of the red border of the lips were present in all children in this group. The presence of exfoliation was detected in 20 children (90.9%), and in 14 of them (63.6%) additionally coincided with the presence of angular cheilitis, with the mucous membrane, when it was illuminated, "sparkled" in all patients. In 18 patients (81.8%) was determined by severe swelling of the oral mucosa on the background of erythematous manifestations, and this was especially evident at the line of closure of the teeth where it had a scalloped shape. In addition, in 13 of 22 children (59.1%), single erosive elements were found, which indicated the presence of mucositis of the 1st and 2nd severity in these patients. Swelling and hyperemia of the interdental papillae and of the gingival margin were noted in 16 patients (72.7%). In the other 6 children (27.3%) interdental papillae were pale pink. Probing of the gingival sulcus provoked bleeding in 19 people (86.4%).

At the same time, the Greene-Vermillion index deteriorated compared to baseline values by 4.1 times, PMA index - by 12.3 times, and PBI - by 5.9 times. That is, in a comparative aspect with the results obtained in the first group of observations, these indicators were worse in 1.8, 1.3 and 1.6 times, respectively (Table I).

When comparing the cellular composition of smears-reprints in the observation groups, at the time of completion of the first course of polychemotherapy, more significant changes were observed in the second group of patients, ie in those who received more intensive cytostatic treatment. In particular, they determined the prevalence of epithelial cells that were in the intermediate stages of their differentiation, which, in turn, led to increased level of desquamation of the epithelial surface layer and to diapedesis of peripheral blood elements outside the epithelial layer of the gingival margin. The absence of normal physiological conditions prevented of the normal formation of cells, which could participate in the full restoration of the integrity of the epithelium of the gingival margin.

Also, in both groups, there was a decrease in nuclear epithelial and keratinizing non-nuclear components, which indicated the damaging effect of factors due to the influence of various cytostatics, directly on the nature of reparative regeneration of epithelial structures of the periodontium. There was an increase in the number of cells with signs of vacuolation of the cytoplasmic matrix, deformation of their nuclei and the appearance of a significant number of inflammatory cells of the peripheral blood, as well as diapedesis of erythrocytes. This was accompanied by a decrease in the rate of nuclear-cytoplasmic ratio by 1.3 times - in the 1st group and 1.5 times - in the 2nd group, which is confirmed by the data we received earlier, regarding the buccal epithelium [9].

DISCUSSION

The data published in this paper are the result of research, which was due to the goal - to study the effects on the periodontium of different types of cytostatic agents in children with malignant tumors. The originality of the research is determined by the fact that the contingent of pediatric patients with oncopathology, who receive drugs from the group of cytostatics, pharmacodynamics and pharmacokinetics of which are constantly improving to increase its effectiveness and safety of chemotherapy, require constant monitoring with appropriate changes to correct disorders of the oral cavity [4,5,6]. In addition, it determines the prospects of this

work in connection with the tendency to a steady increase in the number of children with this nosological form of the disease [1,2,8]. Restrictions on the availability of qualified dental care for this category of patients are often due to the lack of dentists in medical establishments and their non-acquaintance about this problem, or the refusal of relatives to conduct dental activities.

CONCLUSIONS

Thus, in children with malignant tumors of abdominal localization, on the background of treatment with cytostatic drugs, pathological complex of symptoms is formed in periodontal tissues, which is accompanied by deterioration of Greene-Vermillion, PMA and PBI indices. It is facilitated by the violation of the functional state of the integumentary epithelium of the gingival margin with the prevalence of morphological dystrophic changes and a variety of types of structural changes in it. The severity of these disorders largely depends on the composition and volume of cytostatic drugs prescribed to children, and what should be considered when forming for them the components of a set of treatment and prevention measures. Therefore, for this category of children, it is desirable to begin a mandatory study of quantitative and qualitative changes in cell composition in the epithelial layer of the gingival margin, which should facilitate the timely diagnosis of adverse changes and prevent its progression through the use of rational pharmacotherapy.

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The Authors declare no conflict of interest.

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