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IMPACT OF POLYCHEMOTHERAPY ON THE ORAL SOFT TISSUES IN CHILDREN WITH MALIGNANT ABDOMINAL TUMORS

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ABSTRACT

Introduction: According to modern standards of treatment of malignant neoplasms conducting polychemotherapy requires up to 90% of cancer patients. However, in addition to the expected cytotoxic effects, it is accompanied by disorders in dental health in the vast majority of patients.

The aim: To study the effect of cytostatics on soft tissues of the oral cavity in children with malignant tumors of the abdominal cavity.

Materials and methods: Material for writing this scientific work served as a synthesis of results for 25 people aged 7 to 15 years with malignant tumors of the abdominal cavity, in which a comprehensive oral examination was performed to determine the manifestations of dental toxicity cytostatics.

Results: At the end of the first course of chemotherapy, all patients had dry redness of the lips, 20 - (80,0%) with eruptions, in 18 - (20,0%) erosion. The Green-Vermillion, PMA, and PBI indices grew by 1,8; 7 and 3,3 times respectively. In cytograms with buccal epithelium an increase in the number of cells of polymorphic sizes and forms with signs of gidropic dystrophy was found. The nuclear-cytoplasmic ratio decreased by 1,4 times compared with the primary examination.

Conclusions: This situation creates the preconditions for the development of inflammatory process in the tissues of the oral cavity and requires the use in this category of patients of a substantiated pathogenetic correction of existing disorders.

KEY WORDS: children, malignant tumors, abdominal cavity, oral cavity, polychemotherapy

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INTRODUCTION

Currently, the growing effectiveness of treatment of oncologic patients is one of the priority aspects of the development of the world medical industry. The urgency of this issue is determined by the constant rise of the prevalence of malignant pathology among different segments of population. The WHO experts report that the annual increase in cancer cases is accounted for 3%, and by 2020 it will be twice higher worldwide [1,2].

Generally, the tumor chemotherapy is based on the principle of selective harmful effect of specific drugs on a malignant cell. Its conduct is rational and more effective when chemosensitivity of tumor has been confirmed. According to current state-of-the-art treatment standards, up to 90% of cancer patients require chemotherapy. Therefore, currently, one of the promising areas of scientific research in the field of oncology is the pharmacogenetic testing of antitumor drugs, which is based on the study of associations between the gene polymorphism and pharmacological response, followed by the assessment of the effectiveness, resistance and probability of occurrence of side effects [3-6].

Currently, polychemotherapy (PCT) is considered a promising aspect in the treatment of malignant pathology, based on a rational combination of pharmacological agents with a different mechanism of action to synchronize tumor growth phases, which makes the cells particularly sensitive to the subsequent chemical component [1,3,4].

However, the major disadvantage of cytostatics is their incomplete selectivity, which leads to the occurrence of undesirable effects. Among them, the reactions, caused by the affection of normal cellular structures with a high degree of proliferation, prevail, resulting in the development of cytotoxic disease, which may prevent the achievement of the maximum therapeutic effect of the regimens of the administration of antineoplastic agents. Unfortunately, no single active antitumor substance without negative effect on healthy organs and tissues has been found to date [1,2,4,5].

In addition to the expected cytotoxic effect on the kinetics of malignant tumors, long-term polychemotherapy is accompanied by disorders of dental health. Thus, many investigators report that the incidence of dental toxicity ranks the second after hematologic one and varies in a rather wide range from 30% to 90%, depending on the individual characteristics of the body, gender and age. Moreover, one of the risk factors for the development of adverse reactions is childhood, which predetermined the subject of the present research [1,2,5,6].

THE AIM

The paper was aimed at the study of the effect of cytostatics on the oral soft tissues in children with malignant abdominal tumors.

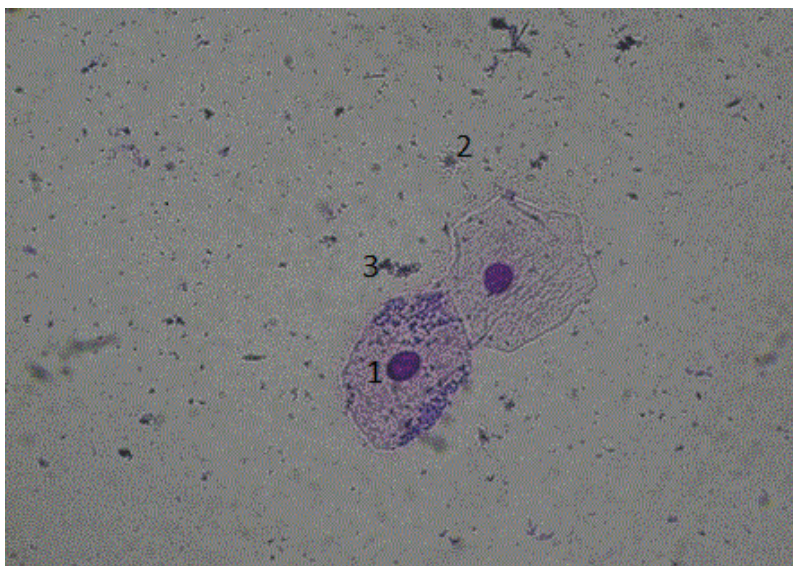


Fig. 1. Microimage of impression smear from the surface of the buccal mucosa of the 14 year-old patient R., at the time of the initial examination. Diagnosis: hepatoblastoma of the right lobe of the liver. PRETEXT IIp. T3N1M0. Grouped epithelial cells with clearly contoured nuclei (1); indistinct contours (2); moderate amount of microorganisms (3).

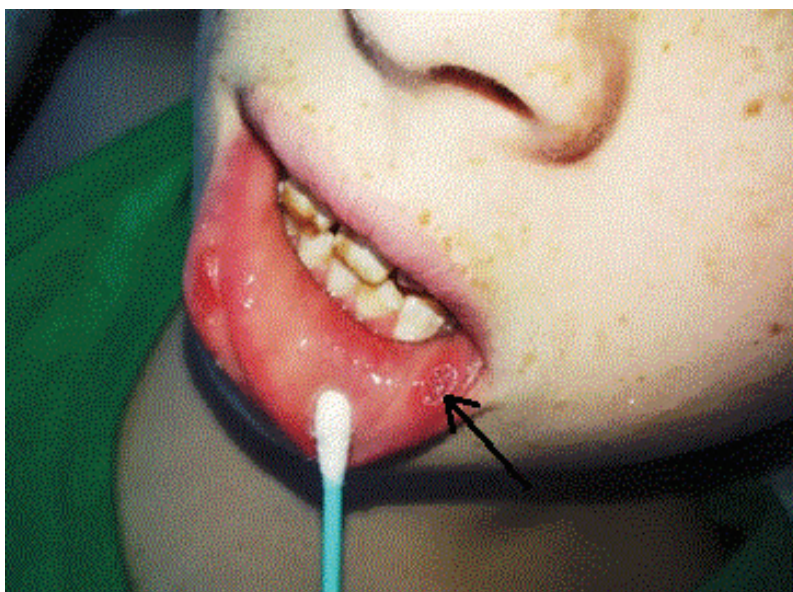


Fig. 2. The view of erosion on the lower lip mucosa of the 6 year-old patient Ch., at the end of the 1st course of PCT. Diagnosis: Nephroblastoma, Stage II, Clinical Group II. Stage II oral mucositis, chronic catarrhal generalized gingivitis of the first degree.

MATERIALS AND METHODS

The paper is based on the generalization of the results of the clinical-laboratory and instrumental examination, supplemented with special research methods, of 48 patients aged 1 to 15 years with malignant tumors of the abdominal cavity tissues of various morphological nature. All patients were on the inpatient treatment in the Oncohematology Department of the Children's Municipal Clinical Hospital in Poltava.

The research was conducted in compliance with the ethical standards of the Bioethical Committee, developed in accordance with the Helsinki Declaration of the World Medical Association (1964), supplemented by the 59th General Assembly of the WMA, Seoul, 2008. All relatives of children, involved in the study, were informed about their rights and solely voluntarily gave their informed consent.

Out of 48 patients a group of 25 individuals aged 7 to 15 years old, who underwent thorough examination of the oral cavity organs to identify manifestations of the dental

toxicity, caused by the same type protocol chemotherapy treatment, was formed.

The common clinical methods of examination included complaints from children and their relatives, life and disease medical history. In clarifying the complaints, the issues that directly concerned disorders of the oral cavity organs as the initial part of the gastrointestinal tract have been identified. The dental status has been studied utilizing the WHO conventional methodology and in compliance with the standards of medical care provision.

The state of oral hygiene has been estimated on the basis of the analysis of the Green-Vermillion index (1964). To detect inflammatory process in the periodontal tissues, the papillary-marginal-alveolar (PMA) index (modified by G. Parma, 1960) and the PBI index (Papilla Bleeding Index, H.P. Muhlemann (1977) have been used; in children of the control group the hygiene index was $0,52 \pm 0,02$, and the PMA and PBI indices had the value of 0.



Fig. 3. The view of the gingival margin of the 14 year-old patient D., at the end of the 1st course of PCT. Diagnosis: Nephroblastoma, Stage II, Clinical Group III. Stage I oral mucositis, chronic catarrhal gingivitis.

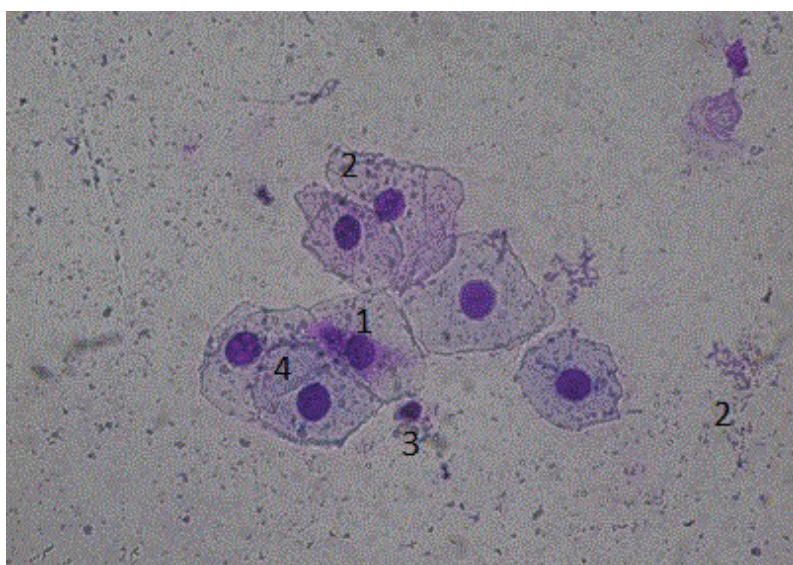


Fig. 4. Microimage of impression smear of buccal mucosa of the 12 year-old patient R., at the time of repeated examination. Diagnosis: hepatoblastoma of the right lobe of the liver. PRETEXT IIp. T3N1M0. Aggregations of epithelial structures of various shapes and size (1); marked contamination with microorganisms of the background field and epithelial cells (2); the remnants of "bare nuclei" (3); signs of hydropic dystrophy (4).

The material was collected for cytological study of the cell composition of the impression smears taken from the buccal mucosa using the proposed device [2]. The smears were Romanowsky-Giemse stained, and calculation of the cellular elements was made in 10 fields of view; their structure was visually evaluated. To determine the severity of the effect of the toxic factor, additional determination of the nuclear-cytoplasmic ratio in the buccal epithelium cells and its colonization resistance was made [2].

All children underwent antitumor therapy in the amount prescribed by the clinical protocols for treatment of children with solid tumors, taking into account their morphological type and the risk group according to the histological variant (Ministry of Health of Ukraine Order No. 649 dated 28 August, 2009). The study of all characteristics was carried out before and after the completion of the 1st course of PCT.

RESULTS AND DISCUSSION

The objective dental examination at the time of the initial treatment of children of the formed group showed a minor pallor of the face with characteristic grayish tinge. The prolabium in 12 individuals (48,0%) looked pale; in the rest 13 individuals (52,0%) it had a natural coloring. Its prominent dryness, combined with the oral type of respiration, was detected in 4 patients (16,0%). The oral mucosa was moderately moistened, colored pale pink without visible lesions. In 5 children (20,0%) abnormal attachment of the frenulum of the lower lip and shallow vestibule of the mouth was detected. Combination of pathological attachment of the frenulum of the tongue and upper lip was detected in 4 individuals (16,0%).

Examination of the tongue revealed its lesions in the form of "geographical tongue" in 3 children (12,0%) and presence of white patches in 4 children (16,0%).

The gingival status of 6 patients (24,0%) met the criterion of "clinically healthy" and at the time of the examination

the gums were colored pale pink, painless in palpation, adhered tightly to the surface of the necks of the teeth; no patches were noted. Gums of 10 patients (40,0%) looked pale, pasty and painless in palpation; no dental plaque was noted. In 9 patients (36,0%) the mucous membrane of the gingival margin was congested hyperemic, interdental papillae were swollen and bled in diagnostic sounding. Instrumental examination revealed layers of soft plaque within the frontal teeth of both jaws. Such clinical picture indicated about manifestations of chronic generalized catarrhal gingivitis of the first degree. The Green-Vermillion index in the group was consistent with the value of $1,13 \pm 0,04$, which is 1.2 times higher the control, the score of the PMA and PBI indices was $4,78 \pm 0,16$ and $0,92 \pm 0,03$, respectively.

The cytograms obtained from impression smears of buccal epithelium, revealed single epitheliocytes, as well as groups of 2-3 per power field with rounded centric nuclei of the same size; disintegration of the cell membrane of some epithelial structures was noted. Moderate contamination with microorganisms of both the background field and cellular elements was detected (Fig. 1). The index of nuclear-cytoplasmic ratio in the buccal epithelium cells was $0,018 \pm 0,006$ against $0,024 \pm 0,006$ in healthy children, and the score of colonization resistance of the mucous membrane of the buccal areas in both the controls and patients was 1 point.

At the end of the 1st course of PCT, 19 individuals (76,0%) indicated a marked feeling of dryness in the oral cavity, increased thirst, change in food tastes and difficulty in swallowing, and 12 out of them (48,0%) experienced a pronounced speech impairment. 17 patients (68,0%) complained of burning pain in the gums and their bleeding and 9 patients (36,0%) complained of painful sensations due to the presence of lesions of the oral mucosa that aggravated the intake of food and worsened their well-being. Another 5 individuals (20,0%) clearly felt pain in the area of the angle of the mandible and soft tissues in the projection of parotid salivary glands, the intensity of which increased in mouth opening and chewing.

Physical examination revealed pallor face, dryness of the prolabium in all patients, in 20 of them (80,0%) it was accompanied by the formation of exfoliations, mostly on the lower lip. In 14 individuals (56,0%), angular cheilitis was noted that restricted the opening of the mouth and hampered dental examination.

Examination of the oral mucosa showed individual differences. Thus, in 18 individuals (72,0%), its erythema was noted, causing single erosive lesions in 5 of them (20,0%), which were located on the lower lip mucosa and the mucogingival fold in the area of premolars, molars and soft palate that corresponded to oral mucositis of the second degree (Fig. 2). In the rest 7 patients (28,0%), the oral mucosa was pale with signs of pasty.

Visual assessment of the gingival margin mucosa in 19 patients (76,0%) revealed cyanotic hyperemia of the interdental papillae and their marginal portion; swelling and tenderness in palpation. Gums of the rest 6 individuals (24,0%) were

pale. Diagnostic sounding in the area of the dentogingival sulcus provoked bleeding in all patients (Fig. 3).

Repeated studies conducted after the completion of the first course of PCT showed deterioration of the oral hygiene status, indicated by increased value of the Green-Vermillion index by 1,8 times and a decline in the quality assessment to "unsatisfactory". In addition, the PMA index increased by 7 times, which was concordant with the significant proliferation of inflammatory events in the gums, although the severity of the manifestations of lesions varied from minor to severe, and it was selective. Apparently, such lesions were caused by the individual sensitivity of the oral tissues, including sensitivity of the mucous membrane to the cytostatics. Thus, in 12 patients (48,0%), the PMA index was in the range of 60%, indicating proliferation of inflammation and in 9 individuals (36,0%) it was associated with painful lesions of erosive nature, coated with a fibrin film, and sometimes with a tendency to confluence. Moreover, voluntary bleeding from the gingival margin was noted. In 10 patients (40,0%), the index score showed moderate degree of inflammation, and only in 3 individuals (12,0%) it was minor.

The PBI index at the end of the 1st course of PCT was 3,3 times higher than the reference value. Diagnostic sounding of the gingival sulcus revealed bleeding with the score of 4 points in 9 people (36,0%), in 10 patients (40,0%) its intensity score was 3 points and in 6 patients (24,0%) this index was within the score of 2 points.

Repeated study of the cytograms with buccal epithelium revealed elevated amount of epithelial cells with polymorphic shapes and size, their increased contamination, as well as the background field, with aggregations of microorganisms and the remnants of "bare nuclei"; in places the signs of hydropic dystrophy were noted (Fig. 4).

The nuclear-cytoplasmic ratio of buccal epithelium cells was 1,4 times lower in comparison with the previous survey and constituted $0,013 \pm 0,004$, whereas the score of colonization resistance of the oral mucosa increased to 2 points.

Thus, at the time of completion of the 1st course of PCT deterioration of the dental status was noted. In this way, the mean values of the Green-Vermillion, PMA, and PBI indices indicated unsatisfactory oral hygiene and the presence of inflammation in periodontal tissues, namely, cyanotic hyperemia, edema of the gingival margin mucosa and interdental papillae with signs of both spontaneous bleeding, and during irritation with a dental instrument during diagnostic sounding, combined with manifestations of mucositis of the I and II degree. The study of the cytograms of the impression smears of the buccal epithelium revealed an increase in the degree of its desquamation and contamination by microorganisms and elevated amount of destruent cells. Significant decrease of the nuclear-cytoplasmic ratio indicates the marked destructive and dystrophic changes in the epithelial cellular structures of the mucous membrane, and the growth of its colonization resistance score to 2 points indicates a high level of contamination with microbial flora, promoting the development of inflammatory process in the oral tissues.

Findings of the study are related to the outcomes of toxic effect of cytostatics on the mucous membrane, deterioration of the oral hygiene status and impairment of certain components of oral homeostasis components in children with solid tumors of the abdominal cavity, who underwent the first preoperative course of polychemotherapy. Unfortunately, little information is available in the fundamental publications, presented without considering the pathogenetic mechanisms that lead to above impairments in this category of patients. Moreover, the sporadic research data found in publications mainly concern children with hemoblastomas, and sometimes the provided information is controversial.

CONCLUSIONS

In conclusion, manifestations of dental toxicity, detected in children with solid abdominal tumors during polychemotherapy require mandatory application of the rational pathogenetic correction of existing disorders.

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According to the order of the Authorship.

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The Authors declare no conflict of interest.

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