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ORIGINAL ARTICLE

Dynamics of saliva cytokine levels during intraoperative photodynamic therapy in patients with locally advanced oral cancer

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ABSTRACT

Purpose of the study. Assessment of the level of certain cytokines in the saliva of patients with primary locally advanced cancer of the oral mucosa in addition to surgical treatment with intraoperative PDT (IPDT).
Patients and methods. Patients with primary locally advanced cancer of the oral mucosa T3-4aN0-2M0 were divided into 2 groups: the main group (30 patients) underwent radical tumor removal supplemented with IPDT and the control group (30 patients) without addition. IPDT was performed using Latus-T (farah) and a chlorin E6 photosensitizer. Cytokine levels were determined in unstimulated whole saliva the day before, on the 3rd and on the 7th day after the operation by the ELISA multiplex analysis method.
Results. A similar dynamic of the cytokine profile of patients of both groups was shown: on the 3rd day after surgery, the levels of G-CSF, IL-6, MIP-1β increased, and GM-CSF and IFN-γ decreased compared with baseline values. On the 7th day, the dynamics of G-CSF, GM-CSF, IL-6 persisted, while IL-8, IL-10, IL-12 changed to the opposite.
Intergroup differences were revealed in the level of IL-1β – on day 3, an increase in the main group and a decrease in the control group. The level of IL-7 on day 7 decreased sharply in the control group and increased statistically significantly in patients receiving IPDT. The main group showed a 4.8-fold increase in IL-8 on day 3 and its 3.6-fold drop on day 7 with the opposite dynamics in the control group. The TNF-α level increased only in the main group on day 7, and in the control group it decreased by 3 and recovered on day 7. On day 3, the MCP-1 level increased in the main group and decreased in the control group. The level of IL-17 in the main group increased on the 3rd day with a further decrease below the baseline, and in the control group it decreased on the 3rd day, followed by a recovery on the 7th. An increase in IL-5 and IL-13 levels on day 3 was noted only in the control group, however, the level of IL-5 in both study periods in the main group was lower than in the control group.
Conclusion. IPDT in patients with primary locally advanced oral cancer causes changes in the cytokine composition of saliva during the first week after surgery, some of which can be associated with an elongation of the relapse-free period in such patients.

Keywords: intraoperative photodynamic therapy, cytokines, saliva, primary locally advanced oral cancer

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Compliance with ethical standards: the work followed the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Ethics Committee of the National Medical Research Center of Oncology (extract from the protocol of the meeting No. 15 dated 10/12/2021). Informed consent was received from all participants of the study

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Динамика уровней цитокинов слюны при проведении интраоперационной фотодинамической терапии у больных местно-распространенным раком полости рта

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РЕЗЮМЕ

Цель исследования. Оценка уровня некоторых цитокинов в слюне больных первичным местно-распространенным раком слизистой оболочки полости рта при дополнении хирургического лечения интраоперационной ФДТ (ИФДТ).
Пациенты и методы. Пациенты первичным местно-распространенным раком слизистой оболочки полости рта T3-4aN0-2M0 были распределены в 2 группы: основная группа (30 больных) – проведено радикальное удаление опухоли, дополненное ИФДТ и контрольная группа (30 пациентов) – без дополнения. ИФДТ проводили с помощью «Латус-Т» (фара) и фотосенсибизатором хлорин Е6. Уровни цитокинов определяли в нестимулированной цельной слюне за сутки до, на 3-и и на 7-е сутки после проведения операции методом ИФА мультиплекс-анализа.
Результаты. Показана сходная динамика цитокинового профиля больных обеих групп: на 3-и сутки после операции уровни G-CSF, IL-6, MIP-1β повышались, а GM-CSF и IFN-γ снижались по сравнению с исходными показателями. На 7-е сутки характер динамики G-CSF, GM-CSF, IL-6 сохранялся, а IL-8, IL-10, IL-12 менялся на противоположный. Межгрупповые различия выявлены по уровню IL-1β – на 3-и сутки повышение в основной и снижение в контрольной группе. Уровень IL-7 на 7-е сутки резко снижался в контрольной группе и статистически значимо повышался у больных, получавших ИФДТ. В основной группе показано 4,8-кратное повышение IL-8 на 3-и сутки и его 3,6-кратное падение на 7-е с противоположной динамикой в контрольной. Уровень TNF-α возрастал только в основной группе на 7-е сутки, а в контрольной отмечено его снижение на 3-и и восстановление на 7-е сутки. На 3-и сутки уровень MCP-1 возрастал в основной и снижался в контрольной группе. Уровень IL-17 в основной группе нарастал на 3-и сутки с дальнейшим снижением ниже исходного, а в контрольной группе снижался на 3-и сутки с последующим восстановлением на 7-е. Нарастание уровней IL-5 и IL-13 на 3-и сутки отмечены только в контрольной группе, однако, уровень IL-5 в оба срока исследования в основной группе был ниже, чем в контрольной.
Заключение. ИФДТ у больных первичным местно-распространенным раком полости рта вызывает изменения цитокинового состава слюны в течение первой недели после операции, часть из которых можно связать с удлинением безрецидивного периода у таких пациентов.

Ключевые слова: интраоперационная фотодинамическая терапия, цитокины, слюна, первичный местно-распространенный рак полости рта

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено этическим комитетом ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 15 от 12.10.2021 г.). Информированное согласие получено от всех участников исследования

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INTRODUCTION

Currently, it is recognized that under the influence of inflammation, neoplastic and stromal cells interact and control the evolution of the tumor, producing cytokines that modulate the antitumor immune response [1–3]. The similarity of the cytokine pattern for tumors of different localization and histogenesis has been demonstrated [4], however, there is no consensus on whether cytokines play a decisive pro-oncogenic or anti-oncogenic role [5]. Both can be assumed based on the known biological properties of cytokines as stimulants, on the one hand, proliferation and neo angiogenesis, and on the other hand, the immune response.

In recent decades, the participation of various pro- or anti-inflammatory cytokines of the tumor microenvironment of squamous cell carcinoma of the oral cavity in the oncogenesis of a tumor of this localization has been shown [6–8]. Most studies describe elevated levels of IL-1β, 6, 8, 10, TNF-α in patients with oral cancer compared with healthy ones at both the local and systemic levels [9, 10]. Moreover, a higher content of IL-1β and IL-6 was demonstrated in tumors of the oral mucosa than in areas of unchanged mucosa [11]. Literature data show that hyperproduction of cytokines by tumor cells and its microenvironment in patients with oral cancer is one of the causes of tumor spread.

Thus, when developing approaches to the treatment of oral cancer, it is important to analyze the local and systemic cytokine status of such patients, as well as the induction of an antitumor immune response. The latter can be achieved with photodynamic therapy (PDT), one of the mechanisms of antitumor effectiveness of which is immunogenic cell death [12]. PDT induces it through the release of damage-associated molecular patterns (DAMPs) [13]. PDT-induced acute inflammation and immunogenic cell death are considered the initial step in the implementation of its immunostimulating effect [14], which manifests itself in a tumor-specific immune response [15]. The role and place of immune mechanisms in the realization of the antitumor effect of PDT are summarized in a recent review [14].

The purpose of the study was to assess the level of certain cytokines in the saliva of patients with primary locally advanced cancer of the oral mucosa in addition to surgical treatment with intraoperative PDT (IPDT).

PATIENTS AND METHODS

The study group included 60 patients with primary locally advanced cancer of the oral mucosa who were being treated by the Department of Head and Neck Tumors of the Federal State Budgetary Institution "National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation. The average age of the patients was 63.1 ± 14.3 years. The distribution of patients by gender was as follows: male – 48 people, female – 12 people. In all patients, the diagnosis was morphologically verified and corresponded to stages III–IV (T3-4aN0-2M0) of cancer. According to the morphological structure, the tumors were represented by squamous cell carcinoma, of which moderate–differentiated – 79 %, highly differentiated – 16 % and low–differentiated – 5 %.

The patients were randomized into 2 groups: the main group (30 patients) – patients who underwent radical tumor removal supplemented with IPDT and the control group (30 patients) – without the supplement. The patients in the groups were comparable in age, gender and location of the primary focus. All patients underwent surgical intervention in the volume of radical removal of the tumor of the tongue and oral mucosa with cervical lymphadenectomy in a volume adequate to the prevalence of the tumor process, on the affected side or bilateral (with damage to the anterior parts of the oral cavity).

The study was approved by the Ethics Committee of the National Medical Research Center of Oncology Protocol No. 15 dated 10/12/2021, all patients signed a voluntary informed consent.

Intraoperative PDT was performed in accordance with the developed and patented method (RF Patent No. 2797433) [15]. At the first stage, patients with locally advanced cancer of the mucous membrane of the oral cavity and tongue underwent surgical treatment, and then, after hemostasis of the postoperative wound of the oral cavity, PDT was performed after covering the healthy surrounding tissues around the surgical field with sterile eight-layer gauze wipes. Latus-T (headlight) was used for the session, with parameters: wavelength 662 nm,

power density 45 MW, light energy 200–300 J/cm^2. The lamp was placed in such a way that the area of laser light emission covered both the bed of the removed tumor and the edges of the surgical wound. The duration of exposure was calculated depending on the size of the bed of the removed tumor of the oral cavity according to the formula: T = T0 × nw/kp, where T0 is the tabular value of the irradiation time, nw is a coefficient showing how many times the energy density WS (J/ cm^2) to be collected by the surface differs from the tabular WS/0 = 100 J/cm^2: nw = WS/100, kp is a coefficient showing how many times the laser power differs from the tabular P0 = 100 MW: kp = P/100. After completion of the photodynamic therapy stage, plastic surgery of the postoperative defect was performed. Chloride E6 was used as a photosensitizer, which was administered intravenously in a single dose of 2 mg per 1 kg of patient weight 3–3.5 hours before the expected end time of tumor removal. The immediate results of complex treatment supplemented with IPDT were evaluated in patients with locally advanced oral mucosal cancer.

Cytokine levels (G-CSF, GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, MCP-1, MIP-1β, TNF-α) were determined in saliva by ELISA multiplex analysis (Bio-Plex Pro Human Cytokine Assays 17-Plex Panel, Bio-Rad, USA). The collection of unstimulated whole saliva for the study was carried out from 8 to 9 a. m. the day before the operation, on the 3rd and on the 7th day after it. The results were expressed in pg/ml.

Statistical analysis of the study results was carried out using the Statistica 12.0 program (StatSoft Inc., USA), MedCalc (version 9.3.5.0). Since the distribution was not normal, the Mann-Whitney criterion was used to compare intergroup indicators, and the Wilcoxon criterion was used to compare indicators in dynamics; the differences were considered statistically significant at $p < 0.05$. The data are presented as a median with upper and lower quartiles (Me [LQ, UQ]).

STUDY RESULTS AND DISCUSSION

The results of the study are shown in Fig. 1A-1G, 2A-2G.

On the 3rd day after surgery in patients of both groups, the levels of G-CSF, IL-6, MIP-1β increased (Fig. 1A), and GM-CSF and IFN-γ decreased (Fig. 1B) compared with baseline values; the content of the remaining cytokines was multidirectional in the compared groups of patients.Some of the indicators changed statistically significantly in only one of the groups, which is apparently related to the effect of PDT (Fig. 1B, 1G).

On the 7th day, the dynamics of G-CSF, GM-CSF, IL-6 persisted, IL-8, IL-10, IL-12 changed to the opposite, the levels of other cytokines changed in the main and control groups in different ways (Fig. 2A-D).

Differences were revealed between the main and control groups in terms of colony-stimulating factors: an increase in G-CSF and a decrease in GM-CSF on both the 3rd and 7th days after surgery compared with baseline values, and in the main group, changes in G-CSF are less pronounced than in the control group, and in both The duration of the study was at lower values (Fig. 1A, 2A). So, in the control group, the level of G-CSF increased 22.8 times on the 3rd day after surgery, and 13 times in the main group, and on the 7th day it was 22.2 and 4.8 times higher than the initial one, respectively, i. e. the decrease on the 7th day after the initial increase by 3 occurred only after the effect of PDT.

IL-1β levels on day 3 increased in the main group from 410.1 [321.9; 522.6] to 550.8 [528.7; 590.6] pg/ml and decreased in the control group to 102.1 [22.1; 159] pg/ml, and on the 7th the reverse pattern was observed (Fig. 1B, 2B).

There was a 3.3-fold increase in IL-6 in the saliva of patients of both groups on day 3 compared with the baseline, which continued on day 7 with higher rates in the main group (1856.2 [1753.1;1975] versus 1356.9 [1261.3; 1450.7] pg/ml, $p < 0.05$), (Fig. 1A, 2A).

The dynamics of IL-7 consisted in an increase in the level of this cytokine in the saliva of patients of both groups on the 3rd day after surgery, statistically significant only in the control group (by 53 %) and multidirectional on the 7th day – a sharp drop (to 0) in the control group and a continued increase that reached statistical significance (15.3 [13.6; 17.2] versus 10.2 [6.8; 13.5] before treatment; $p < 0.05$) in patients receiving IPDT.

In the main group, there was a pronounced (4.8-fold) transient increase in IL-8 content on day 3 and its 3.6-fold drop on day 7; in the control group, on the contrary, it decreased on day 3 and increased on day 7, exceeding the indicator of the main group

in the last period (Me 2883.1 [2621.8;3338.2] and 2006.4 [1934.3;2310.4] pg/ml, respectively, $p < 0.05$), (Fig. 1A, 2B). The TNF-α level increased only in the main group on day 7, and in the control group it decreased by 3 and recovered on day 7 (Fig. 1D, 2D). On the 3rd day, there was a multidirectional dynamics of MCP-1 levels: an increase in the main group and a decrease in the control group (Fig. 1D), and on the 7th in both groups, the indicators become 3.5 and 4.6 times lower, respectively, than the initial one (Fig. 2D). The content of MIP-1β has a similar dynamics in both groups, increasing by 3 and returning to the baseline on the 7th day after surgery (Fig. 1A, 2G).

There was a decrease in IFN-γ and IL-4, expressed in the main group only on the 7th day with indicators at this time lower than the control ones (Fig. 2B). The median level of IFN-γ in the main group on day 7 was 4.7 [4.2; 5.2] pg/ml, and in the control group 6.8 [6.3; 7.4] pg/ml versus 10.6 [8.4; 12.4] pg/ml before treatment; for IL-4, the indicators were 4.1 [3.2; 4.7] and 8,6 [7,2; 8,9] versus 10,9 [8,7; 14,2]

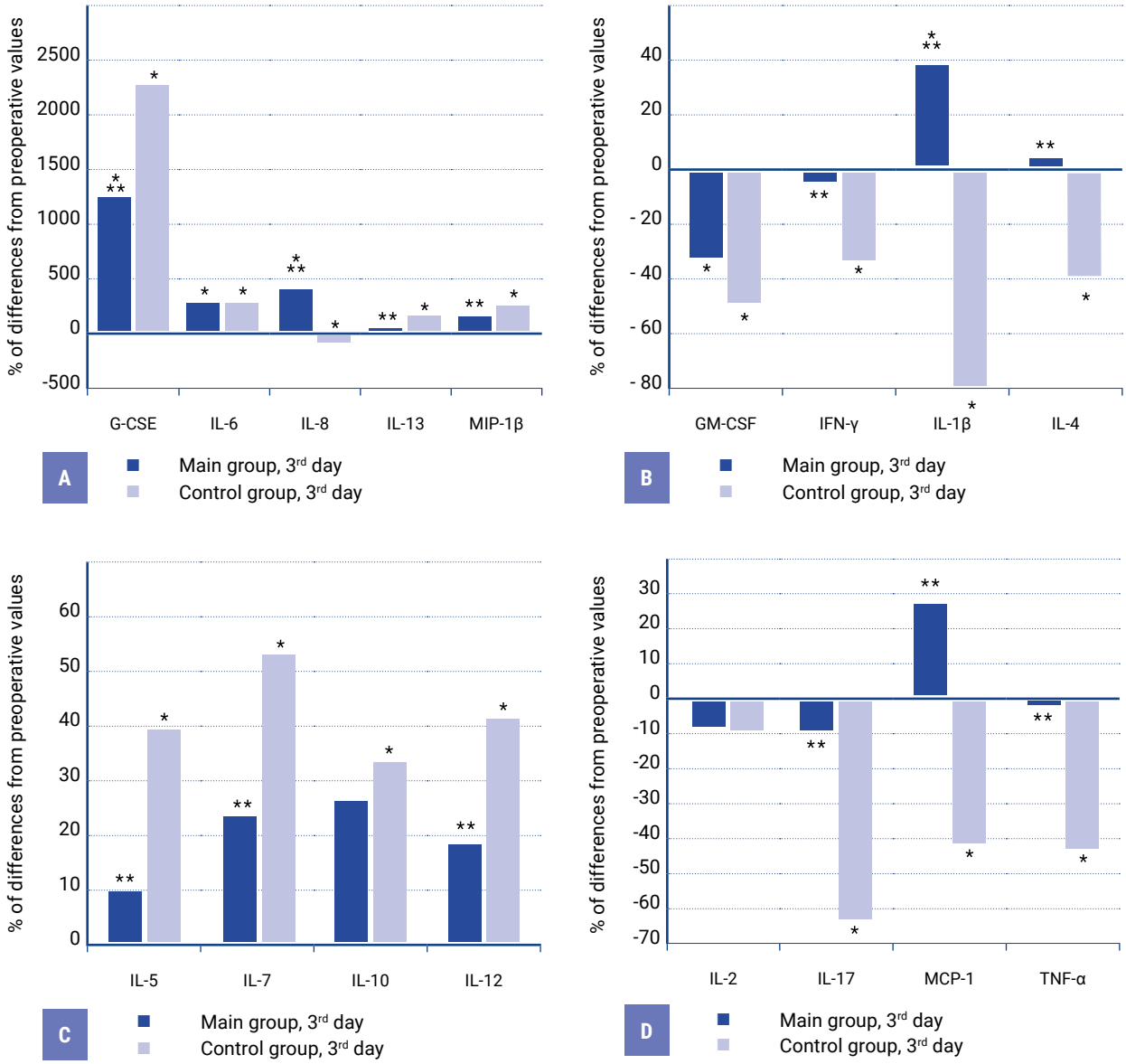

Fig. 1. The concentration of cytokines in the saliva of patients on the 3rd postoperative day.
Note: * – statistically significant differences compared to the level before surgery, $p < 0.05$; ** – statistically significant differences compared to the level of the control group, $p < 0.05$

pg/ml, respectively; for both cytokines, the differences between the indicators of the main and control groups are statistically significant ($p < 0.05$). The dynamics of IL-2 levels in the form of an increase was detected only in the control group on day 7 (Me 29.6 [26.9; 30.7] versus 21.4 [17.4; 25.5] pg/ml before treatment, $p < 0.05$), (Fig. 2B).

A decrease in IL-12 levels occurs in both groups on day 7 (Fig. 2B), and it is less pronounced in the main group than in the control group (Me 11.7 [10.6; 12.8] and 7.9 [7.2; 9.3], respectively, versus 14.7 [13.5; 16.7] pg/ml before treatment; $p < 0.05$) only for the control group), which can be regarded positively, given the role of this cytokine in the polarization of T-helper cells in Th1, providing cellular immunity.

IL-17 levels demonstrate different phases of changes: in the main group, a transient increase on the 3rd day with a further decrease below the initial one, and in the control group, a decrease on the 3rd day followed by a recovery on the 7th (Fig. 1G, 2G). The increase in the levels of cytokines polarizing

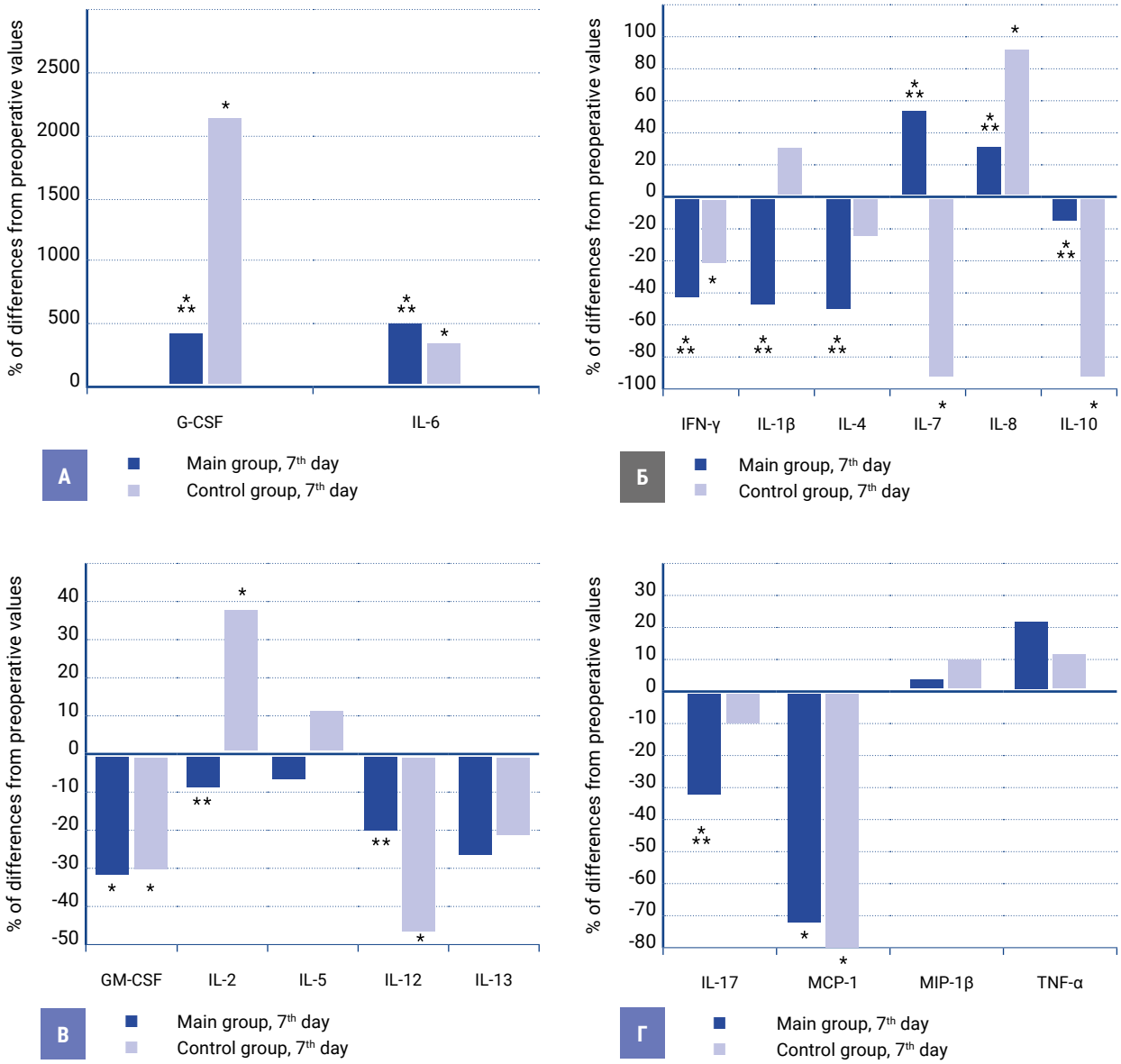

Fig. 2. The concentration of cytokines in the saliva of patients on the 7th postoperative day.
Note: * – statistically significant differences compared to the level before surgery, $p < 0.05$; ** – statistically significant differences compared to the levels in the control group, $p < 0.05$

CD4+ in Th2, IL-5 and IL-13 on day 3, noted only in the control group, is also transient. However, the level of IL-5 in both study periods in the main group was lower than in the control group (Fig. 1B, 2b): on day 3, 136.3 [130.2; 144.4] versus 173.6 [168.7; 176.8] pg/ml, on day 7, 117.4 [106.6; 125.2] versus 138.5 [131.7; 147.2] pg/ml, respectively, at both periods $p < 0.05$), which, taking into account the data described in the literature on its association with the recurrence of some tumors [16], is probably one of the positive aspects of the action of IPDT.

The importance of chronic inflammation and its accompanying cytokine production in tumor growth is known. The pro-oncogenic role of most known cytokines in neoplasia has been repeatedly described, realized through the activation of various transcription factors and signaling pathways, stimulation of proliferation, neoangiogenesis, epithelial-mesenchymal transition, and other processes [4]. However, it seems difficult to distinguish the importance of cytokines for malignant growth and for the immune response, of which they are an integral component, as a result of which their antitumor activity is carried out. Probably, a lot depends on their number, ratio, expression of receptors to them, etc. Unlike chronic, acute inflammation, moreover, is not microbial, but induced by a physical factor such as PDT, apparently exhibits an inhibitory effect on tumor growth both directly by destroying its cells and indirectly through the immune system [15]. In this regard, PDT-induced hyperproduction of cytokines in the lesion, especially after removal of the tumor, not only contributes to its sanitation, accelerating wound cleansing and healing, but also may have positive long-term consequences associated with an increase in the recurrence-free period due to the destruction of residual tumor cells and induction of an immune response to DAPMs. Our results partially confirm this. Oxidative stress caused by PDT stimulates the release of proinflammatory cytokines into the tumor microenvironment, which also affects their content in saliva. At the beginning of PDT-induced inflammation, tumor vessels become permeable to adhesion proteins (ICAM 1, VCAM 1, selectins), thus contributing to massive infiltration of the tumor by immune cells producing a wide range of cytokines, of which the literature emphasizes the importance of TNF-α, IL-6, IL-1β, as well as heat shock proteins, metabolites of arachidonic acid [17]. In this regard, cytokines that have a pro-inflammatory effect, in particular, the ability to increase vascular permeability, and are usually considered pro-oncogenic due to their stimulating effect on neoangiogenesis, have a positive value in PDT for the realization of its effect. The comparative dynamics of saliva cytokines obtained by us in patients of the main and control groups suggests earlier peaks in IL-1β and IL-8 concentrations occurring on the 3rd day after intraoperative PDT and high local levels of TNF-α and IL-6, which persist throughout the follow-up period. On the contrary, anti-inflammatory cytokines, for example, IL-10 and TGF-β, suppress the effects of PDT [18]. It is known about the importance of IL-7 in inflammation that its local content increases due to the production of macrophages, dendritic cells, fibroblasts, and its target are T lymphocytes expressing a receptor for it. IL-7 stimulates mainly Th1 and Th17 lymphocytes mediating cellular immunity [19]. A recent review on the role of IL-7 in tumors indicated that it inhibits the growth of melanoma, enhances the action of IFN-γ, restores the activity of CD8+ T lymphocytes by reducing their expression of PD-1 [20]. Based on this, it can be assumed that the decrease in the level of this cytokine observed by us after a transient increase in the saliva of patients in the control group is prognostically unfavorable for the state of local cellular immunity, and, on the contrary, its stable increase in the saliva of patients receiving IPDT reflects stimulation of the T-cell link.

The role of granulocytes and related cytokines in the body of the tumor carrier is twofold. There are numerous literature data on the pro-oncogenic effect of neutrophils [21], as well as chemokines that attract them to the focus. Neutrophilic "traps" promote the survival of circulating tumor cells in the blood and tumor metastasis [22, 23]. Nevertheless, neutrophils, as participants in the generation of ROS, are given important importance in the action of PDT [24]. However, since G-CSF promotes the release of immature granulocytes with immunosuppressive effects (MDSC) from the bone marrow into the peripheral blood and tissues, we consider a lower level of it in our patients receiving IPDT compared with the control group as a positive moment.

CONCLUSION

Intraoperative use of PDT in patients with locally advanced oral cancer causes changes in the cytokine composition of saliva that develop during the first week after surgery, some of which can be associated with the resulting clinical effect, consisting in prolongation of the relapse-free period in such patients (RF Patent No. 2797433). However, further studies are required to clarify the role of cytokines in the antitumor effectiveness of the applied photodynamic effect in patients with locally advanced oral cancer.

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