УДК: 616.345-617-089.168.1-06

FEATURES OF IMMUNOBIOLOGICAL CORRECTION IN ONCOGYNECOLOGIC PATIENTS

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ОСОБЕННОСТИ ИММУНОБИОЛОГИЧЕСКОЙ КОРРЕКЦИИ У ОНКОГИНЕКОЛОГИЧЕСКИХ БОЛЬНЫХ

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ОНКОГИНЕКОЛОГИК БЕМОРЛАРДА ИММУНОБИОЛОГИК КОРРЕКЦИЯНИНГ АҲАМИЯТИ

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Цель: *изучение состояния клеточных и гуморальных факторов иммунитета у больных раком шейки матки на фоне применения иммунокоррекции, осуществляемой экстракорпоральной иммунофармакотерапией.* ***Материал и методы:*** *под наблюдением были 136 больных с диагнозом рак шейки матки T2-3N0-1M0, которые получили лечение в онкогинекологическом отделении в 2004-2014 гг.* ***Результаты:*** *у больных раком шейки матки выявлен Т-клеточный иммунодефицит, сопряженный с дефицитом CD4+Т-хелперов/индукторов, на фоне повышения содержания CD8+Т-лимфоцитов и повышенной активацией лимфоцитов с преобладанием апоптоза иммунокомпететных клеток. После проведения экстракорпоральной иммунофармакотерапии тималином наблюдается активация Т-клеточного звена иммунитета.* ***Выводы:*** *выявленный до и после химиолучевой терапии дисбаланс гуморального звена иммунитета был сопряжен с дисбалансом основных сывороточных иммуноглобулинов и повышенным уровнем мелких и крупных циркулирующих иммунных комплексов.*

Ключевые слова: *рак шейки матки, иммунокоррекция, экстракорпоральная иммунофармакотерапия.*

Мақсад: *тадкикот мақсади, бачадон бўйни саратонида иммунокоррекция фонида ҳужайравий ва гуморал ҳолатини аниқлаш иммунофармакотерапия ёрдамида аниқланади.* ***Материал ва усуллар:*** *2004-2014 йиллар онкогинекология бўлимида назоратда бўлган 136 та бемор бачадон бўйни саратони T2-3N0-1M0 ташхиси билан даво муолажаларини олган.* ***Натижа:*** *анализлар шуни кўрсатадики, бачадон бўйни саратонида Т- ҳужайравий иммунодифицит кузатилади. CD4+ Т-хелпер/индукторлар дефицити билан боғлиқ бўлган CD8+ Т-лимфоцитлар ошиб бориши ва иммунокомпонент ҳужайраларини апоптози тарқалиши лимфоцитлар активациясини ошиши билан кузатилади. Тималин билан ўтказилган экстрокарпорал иммунофармакотерапия (ЭИФТ) иммунитетнинг Т-ҳужайравий таркибий кисми фаоллашиву кузатилади.* ***Хулоса:*** *иммунитетнинг гуморал таркибий қисмида дисбаланс химиотерапия ва нур терапиясидан кейин зардоб иммуноглобулинлари ва айланиб юрувчи катта ва кичик иммун комплескарни дисбаланси билан баҳоланади.*

Калит сўзлар: *иммунокоррекция, эктракорпорал иммуннофармакотерапия, бачадон бўйни саратони.*

According to WHO, an increasing number of cervical cancer (cervical cancer) patients are diagnosed every year, especially among women of childbearing age [1,5]. Despite the success of clinical medicine, including modern methods of examination and treatment, cervical cancer steadily ranks among the first places among tumors of the female reproductive system. As is known, in most economically developed countries cervical cancer takes the third, in Russia - the second place among tumors of the female reproductive system, and in Uzbekistan there is a tendency to increase the number of oncological diseases of the reproductive system [5].

Thus, in recent decades, the following unfavorable trends have developed. At first, there is an increase in the incidence of cervical cancer in general, while the incidence of women of reproductive age is increasing. Secondly, the frequency of advanced forms of cervical cancer is increasing [4].

It should be noted that today the main role in the therapy of cervical cancer belongs to combined or complex treatment, which includes surgical, medicinal and radiotherapy, hormone therapy, immunotherapy. It is known that effective chemotherapy is often limited to the toxic effects of high doses of cytostatics that have myelosuppression, which increases the risk of developing severe bacterial and fungal infections, forming deep immunodeficiency, and which can lead to death [6,4]. According to the published data, in the course of chemotherapy, leukopenia of 1-2 degrees develops in 90% of cases, and in 30-40% of patients - 3-4 degrees, requiring maintenance therapy for several weeks. Taking into account the formation of an immunodeficiency state and the formation of leukopenia, various methods of immunotherapy are used, including extracorporeal pharmacotherapy [7]. Moreover, this method of immunotherapy is quite effective in stationary conditions, when the patient is on chemotherapy and / or radiation therapy. In connection with the foregoing, an alternative method of immunotherapy, which is the most promising area in oncology as it is extracorporeal immunotherapy, is actively being considered.

The aim of this study was to study the state of cellular and humoral factors of immunity in patients with cervical cancer, using extracorporeal immunopharmacotherapy.

Material and methods of investigation. 136 patients with cervical cancer T2-3N0-1M0 stages (II-III clinical stages) who were examined and treated in oncogynecology and chemotherapy departments of RSPMC of oncology and radiology and MOH RUz from 2004 to 2014 were included in the survey. As follows from the presented data, with cervical cancer IIA, the stage of the disease was observed in 18.7% of cases, IIB - in 20.9%, IIIA - in 16.0% and IIIB stage - in 44.4% of cases. As can be seen, the largest part of the patients was female cervical cancer at stage IIIB. The age of the examined cervical cancer patients was 21 to 74 years old, with an average age of 45.7 ± 7.07 years.

Since, in this article, the immunological features of the response will be described, it is necessary to take into account the presence of concomitant disease among patients with cervical cancer. Thus, it was revealed that 15.3% of the patients had inflammatory processes of the uterine appendages, 19% of the gastrointestinal tract, 15% of the disease of the cardiovascular system, 4% of the ovarian cysts, 3% of the nodular goiter and 6 % bronchial asthma.

Immunopharmacotherapy in patients with cervical cancer using immunomodulators was carried out during the period of radiotherapy and chemotherapy under stationary conditions. In accordance with the goal of the study, the following groups of patients were created, depending on the methods of therapy in the complex treatment: group 1 - 36 patients with cervical cancer before treatment; 46 patients with cervical cancer who received extracorporeal immunopharmacotherapy (EIPHT) with thymalin; Group 3 - 54 patients with cervical cancer who did not receive EIPHT. Also 39 persons of the control group with normative values.

The study of the immune system was carried out at the admission of patients to the hospital before the immunotherapy course and immediately a few days before discharge from the hospital. In patients who did not receive extracorporeal immunotherapy, studies of the immune system were performed on admission to the hospital and immediately before discharge from the hospital.

All patients with cervical cancer received standard polychemotherapy according to the protocol of the department, a complex treatment including a two-stage combined radiation therapy, including remote teletegammatherapy, a split course at a single focal dose of 2 Gy to summary focal dose 50 Gy, 5 times a week and intracavitary brachytherapy to summary dose 45 -55 Gy, every other day. Also, patients with cervical cancer received systemic or intra-arterial polychemotherapy under the scheme of cisplatin 50 mg / m² + 5-fluorouracil 1000 mg / m² for 4 days for 4-6 courses 1 time in 3 weeks.

Immunological studies included the study of cellular and humoral parameters of the immune system of patients with cervical cancer. Immunological studies were conducted in a clinical laboratory. Determination of cellular immunity (CD3 +, CD4 +, CD8 +, CD16 +, CD20 +), as well as identification of activation markers of lymphocytes (CD25 +, CD38 + and CD95 +) was carried out using monoclonal antibodies when counted using a fluorescent microscope using MCAB manufactured by Sorbent LTD (Russia) [2,6]. The humoral link of immunity was assessed by determining the main serum immunoglobulins IgG, IgA, IgM, CIC of small and large values in the serum of peripheral blood by the ELISA method. The results of the study were subjected to statistical processing using the Student-Fisher criteria, the data obtained were processed on a PC using the Statistica program No.6. For the sake of clarity of the results obtained, all the studied parameters of the state of the immune system of patients were translated into percentages relative to 100% for the norm.

The EIPHT method was designed primarily to reduce toxic effects after chemotherapy and radiotherapy, as well as improve the overall condition after chemotherapy and radiation therapy. The EIPHT method was carried out by exfusion of 200-250 ml of autoblood in “Gemakon” or “Terumo” sterile containers, by incubation with the thymalin immunomodulator in a total dose of 30 mg 37 ° C for 60-100 min, followed by reinfusion of the resulting conjugate into the circulatory system of patients. A total of 2 procedures of extracorporeal immunotherapy with timalin were performed during the period of patients’ stay in the hospital.

Results and discussion

So, in patients with cervical cancer, 2 courses of extracorporeal immunotherapy with the use of thymaline immunomodulator were carried out between periods of radiotherapy and chemotherapy. As indicated above, several groups were analyzed by us: group 1 - 36 patients with cervical cancer before treatment; 46 patients with cervical cancer who received EIPHT with thymalin; Group 3 - 54 patients with cervical cancer who did not receive EIPHT. Also 39 persons of the control group with normative values.

Immunological studies were conducted when patients were admitted to the hospital before the immunotherapy and chemotherapy course, and immediately a few days before discharge from the hospital.

The analysis of the obtained results allowed to reveal the following changes, so, the content of leukocytes in the group of patients before any type of therapy did not have a significant difference when compared with the control group, i.e. with normative values. It should be noted that a significantly reduced white blood cell count was observed in the group of patients after chemotherapy who did not receive EIPHT compared to the normative data and the data of cervical cancer patients who received EIPHT. Thus, the total leukocyte count in the cervical cancer group decreased to 51% after c/t and amounted to 3274.8 ± 236.6 cells / μl, while in the control group this figure was equal to 6500 ± 295.0 cells / μl ($p < 0.05$). It is known that the leading role in the antitumor protection of the body is attached to the cellular link of immunity, where the key role is played by T-lymphocytes and their subpopulations. It is known that phenotypic markers of T-lymphocytes include CD3 +, CD4 +, CD8 + receptors. It is shown that the initiation and regulation of the effectiveness of the immune response is largely determined by the specific antigen of T lymphocytes. It is known that the degree of surface expression of CD3 + receptors on the T-lymphocyte membrane reflects its transmissive function and allows the total number of T-lymphocytes to be identified [6]. The relative number of CD4 + T-helper/inducers in patients with cervical cancer before and after EIPHT was suppressed 1.5-fold, and when comparing the values of patients who did not receive EIPHT-it was inhibited 1.9-fold. Thus, the deficit of T-helpers / inducers before ch/t and radiotherapy was 76% relative to control, after ch/t - 64% relative to control, and after using EIPHT - 92% relative to control. Obviously, the deficit of the T-lymphocyte population in cervical cancer is due to the predominant suppression of the number of CD4 + T-helper / inducers, which are a necessary and important link in the formation of killer cells that directly eliminate tumor cells [2,3].

We also studied activation markers of peripheral blood lymphocytes in patients with cervical cancer. These markers began to be studied relatively recently, that is why in the literature there are few studies devoted to the study of their functional activity, in particular, in malignant processes, and this is the reason for their study in our studies. The analysis of activation markers of lymphocytes allows studying the processes of activation, proliferation, differentiation and apoptosis of immunocompetent cells [1]. Expression of CD25 +, CD95 + and CD38 + has been studied from the markers of lymphocyte activation. It is known that the CD25 + receptor is represented by the α-chain, which is expressed on activated T-lymphocytes. Moreover, in the group of patients with cervical cancer who received EIPHT, an insignificant increase in the expression of the apoptosis marker was observed, but not significantly different from the control group and the value of patients before treatment. The immunodeficiency state can be explained by the increased expression of the apoptosis marker in the course of cervical cancer. Expression of CD38 + on lymphocytes in the group of patients with cervical cancer before the treatment was significantly increased in comparison with the control data. In the group of patients with cervical cancer after treatment, those who did not receive EIPHT, expression of CD38 + significantly decreased, which again proves the energy of cells of the immune system, and in the group of cervical cancer patients who received EIPHT, this index was slightly elevated and had no significant difference with the control data. It is known that CD38+ is an early marker of activation of T- and B-lymphocytes [2].

The study of the humoral link of immunity made it possible to reveal an imbalance in the content of the main serum immunoglobulins in cervical cancer. So, expression of CD20 + on B-lymphocytes was significantly increased in the group of patients before treatment. Against the background

of EIPHT normalization of the content of B-lymphocytes is observed. It is known that immunoglobulins play an important role as mediators in the cascade development of the immune response and in part can cause the effectiveness of final, effector reactions of cellular immunity by inactivation and elimination of mutant cells [8]. The study of the concentration of serum immunoglobulins made it possible to reveal an imbalance in the content of the main immunoglobulins after a course of chemotherapy. But in the group of patients receiving EIPHT normalization of the ratio of the main immunoglobulins was observed, and in the group of patients with cervical cancer who did not receive EIPHT imbalance persisted, which manifested itself in an increase in IgA and IgG. Consequently, the humoral link of immunity was characterized by a significant increase in the serum concentration of IgA and IgG in the peripheral blood of patients with cervical cancer, especially in the group of patients who did not receive EIPHT. Thus, we analyzed the cellular and humoral parameters of immunoreactivity in patients with cervical cancer before and after chemotherapy and radiotherapy with and without EIPHT. Studies have revealed an imbalance in the state of cellular and humoral components of immunity before chemotherapy begins. Moreover, in the group of patients who did not receive EIPHT, inadequate restoration of the immune system is observed with the formation of T-cell immunodeficiency and activation of humoral immunity. The data obtained by us characterize the state of immunoreactivity of patients with cervical cancer before and after treatment, and can serve as a diagnostic and prognostic criterion for this disease against chemotherapy and EIPHT.

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Objective: *The aim of the study was to study the state of cellular and humoral factors of immunity in patients with cervical cancer against the background of immunocorrection, carried out by extracorporeal immunopharmacotherapy(EIPHT).* ***Materials and Methods:*** *136 patients with cervical cancer T2-3N0-1M0 stages (II-III clinical stages) who were examined and treated in oncogynecology and chemotherapy departments of RSPMC of oncology and radiology and MOH RUz from 2004 to 2014 were included in the survey.* ***Results:****The analysis showed that patients with cervical cancer showed T-cell immunodeficiency, which was associated with CD4 + T-helper / inducer deficiency against the background of an increase in CD8 + T-lymphocytes and increased activation of lymphocytes with the predominance of apoptosis of immunocompetent cells.* ***Conclusions.*** *After carrying out extracorpoeral immunopharmacotherapy with thymalin, activation of the T-cell link of immunity is observed. The revealed imbalance of the humoral link of immunity before and after chemo- and radiotherapy was associated with an imbalance of the main serum immunoglobulins and an increased level of circulating immune complexes of small and large sizes.*

Key words: *immunocorrection, extracorporeal immunopharmacotherapy, cervical cancer.*