соответсвенно 43,75% и 59,37% случаев. В обеих группах доминировали слабо окрашенные стромальные и железистые клетки: в первой группе слабая экспрессия LIF в строме наблюдалась в 74,36% случаев и немного реже во второй группе 65,625 %, железы в первой группе слабо окрасились в 82,05% и практически столько же во второй группе 84,375% от общего количества.

Выводы

Таким образом, при гипоплазии эндометрия репродуктивные неудачи могут быть связаны с низкой экспрессией LIFR и LIF не только стромальными, но главным образом железистыми клетками. Подобная картина эндометрия набюдается у женщин с нормальной толщиной эндометрия, страдающими бесплодием, обусловленным другой патологией слизистой матки.

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ANALYSIS OF THE IMPACT OF IMMUNOTHERAPY ON IMMUNE SYSTEM OF THE PATIENTS WITH OVARIAN CANCER

S. V. Kamyshov, O.M.Akhmedov, M.S.Gildieva, Sh.Kh. Niyozova

Republican specialized scientific-practical medical center of oncology and radiology of Ministry of health of the Republic of Uzbekistan

Summary

The aim of the study was to study the effect of immunotherapy on immunopathogenetic elements of the immune system in patients with ovarian cancer with concomitant immunopharmacotherapy. Thus, based on the results obtained, it can be seen that in ovarian cancer, a marked imbalance of the cellular and humoral parts of the immune system is observed. Moreover, the imbalance in the cell elements of immunity is expressed in the suppression of IRI by reducing the number of T-helpers/inducers and increasing T-cytotoxic lymphocytes. CICs of large and small values are also increased, however, the highest increase in CIC was observed in patient groups prior to chemotherapy and immunotherapy, and after the use of chemotherapy without immunotherapy. Increase in T-cytotoxic lymphocytes, which indicates the suppression of T-cell immunity and the presence of cytotoxic action at the cellular level is more typical for terminal stages of cancer. The increase of the main immunoglobulins indicates the presence of a humoral imbalance, and, the increase in the CIC indicates the intoxication of the organism either due to the disintegration of the tumor cells themselves, or against chemotherapy or radiotherapy. An increase in the CIC4% always indicates a progression of the pathological process and is a marker of the progression or deterioration of the clinical course. CIC3% quickly decay in the body, so they have no pathological potential. It has been established positive clinical efficacy of the combination of immunotherapy.

Key words: ovarian cancer, immunotherapy, extracorporeal immunopharmacotherapy, immunomodulators, lymphocytes, polychemotherapy

Actuality. The ovarian cancer (OC) is the fifth most frequent cause of death from malignant neoplasms in women, and the most common cause of death of patients with various tumors of female genital organs [1,3,7]. The main reasons for the ineffectiveness of efforts to improve long-term results of treatment of patients with ovarian cancer are the absence of clear notions of etiology and pathogenesis, pathognomonic symptoms of various stages of the disease, as well as low efficacy of treatment in the terminal stages and the absence of specific immunological methods of treatment [2,3,4]. It is not for nothing that this issue is of concern to many specialists, both scientists and oncologists, in connection with the expansion of research opportunities in the field of tumor growth biology, especially in OC, factors that are of practical importance for understanding the immuno-pathogenetic mechanisms of development, metastasis, tumor recurrence, and also to be a theoretical justification for the introduction of new approaches to the treatment of this disease. Recently, a lot of facts have accumulated, indicating the immunogenicity of various tumors, including cancer. To date, there is still no complete description of tumor-associated antigens expressed by tumor cells of the ovarian cancer, but even now they have identified: the protein cdr2 (associated with cerebellar degeneration); p53; HER-2/neu; mesotheliene; cancer-testicular antigens, such as human survivin and reverse transcriptase of human telomerase, etc. [5,6]. The results of such studies suggest that the evaluation of the immune profile of the tumor can make a difference in the conditions of personalized medicine. Therapeutic approaches of antitumor immunotherapy are based on the stimulation of antitumor immunity as a result of action on the non-specific or adaptive effector unit of the immune system. At the same time, the severity and mechanisms of the development of immunodepression inherent in any oncological disease are different at different stages of tumor progression [1,4]. In connection with what was said above, ovarian cancer immunotherapy is a relatively new direction used in medicine, and at the same time, leaving high hopes [9]. Approaches to its implementation, the described methods, the timing of implementation, the possibility of combining with other methods of conservative and surgical treatment remain insufficiently studied and developed. Especially, the mechanisms of immune changes that affect the effectiveness of therapy and predict the course of the disease are not sufficiently disclosed. When evaluating the results of immunotherapy, their influence on the key mechanisms of antitumor immunity should be taken into account. Until now, such are considered, first of all, cellular mechanisms that are reflected in the quantitative composition and functional activity of cytotoxic lymphocytes [5]. It should be noted that the great achievements in the field of molecular genetic studies stimulated a broad study of the possibilities of immunotherapeutic methods for the treatment of cancer patients. As shown in the literature, the use of immunotherapy is aimed at the induction of both innate and adaptive immunity of the organism for the realization of antitumor activity.

The aim of the research: to study the effect of immunotherapy on immunopathogenetic elements of the immune system in patients with ovarian cancer during accompanying immunopharmacotherapy.

Materials and methods of research. 197 patients with $T_{2-3}N_{0-1}M_0$ stage (II-III clinical stages) who were examined and treated in oncogynecology and chemotherapy departments, from 2004 to 2014 were included in the survey. In accordance with the objectives of the study, the following groups of patients with OC were randomized to perform a comparative analysis of the immunological results, depending on the immunotherapy method used, which was included in the complex treatment: group 1 - 34 practically healthy individuals; group 2 - 38 patients with OC before treatment; group 3 – 40 patients with OC who received immunotherapy - extracorporeal immunopharmacotherapy (EIPHT); group 4 - 39 patients with OC who received immunotherapy - extracorporeal immunopharmacotherapy and plasmaphoresis (EIPHT+PHh); 5 group - 46 patients without immunotherapy. All patients underwent clinical laboratory blood tests and instrumental methods of research, which included the study of a general analysis of blood and urine, biochemical and immunological indices, as well as a blood coagulation system.

Combined therapy in adjuvant or neoadjuvant regimen was carried out in patients with ovarian cancer, including polychemotherapy with the Cisplatin regimen of 75 mg/m^2 + Cyclophosphamide 1000 mg/m^2 for 1 day for 4-6 courses 1 time every 3 weeks and surgical treatment in the volume of a radical operation. Chemotherapy was performed in both adjuvant and neoadjuvant regimens. The EIPHT and EIPHT+PPh to the patients with OC using immunological drugs were carried out during the period of radiotherapy and chemotherapy in the hospital.

The method of extracorporeal immunopharmacotherapy (EIPHT) was used to reduce toxic effects after chemotherapy and radiation therapy. Extracorporeal immunopharmacotherapy was performed by exfusion of 500-1000 ml of autoblood in sterile containers "Gemakon" or "Terumo" and its centrifugation at 3000 rpm for 30 minutes. 50-80 ml of the supernatant of the blood plasma were removed. Then the obtained leukotrombomass and erythrocytic mass were incubated with an immunotropic drug in a total dose of 30 mg at 37°C for 60-100 min, with the subsequent return of the conjugate to the circulatory system of the patients. To stimulate the cellular immunity, an immunological drugs - oxidehydrogenation sodium (Pharm-Sintez, Russia) was used. Immunotherapy was performed in the hospital, when patients were admitted to chemotherapy and radiation therapy. In total, patients received 2 EIPHT sessions at the beginning of admission to hospital and before discharge from the hospital.

The immunological studies included the study of cellular and humoral parameters of the immune system in patients with ovarian cancer. Determination of cellular immunity (CD3+, CD3+CD4+, CD3+CD8+, CD16+, CD20+) was performed by flow cytometry on Accuri C6 (USA) using monoclonal antibodies. The humoral unit of immunity was assessed by the determination of the main serum immunoglobulins IgG, IgA,

IgM, CIC (circulating immune complexes) of small and large values in the serum of peripheral blood by the ELISA method. During the statistical analysis of the data presented in the work, the results of the research were entered into databases prepared in Microsoft Excel XP. Numerical (continuous) values were presented as mean arithmetic values and mean error (M±m). A comparison of the quantitative traits was carried out with the help of the Student's test, for continuous variables - the paired Student test. As a boundary comparative criterion for the statistical significance of reliability, $p<0.05$ was assumed. On the diagrams presented below for control i.e. the normative values were taken as 100%.

The obtained results of the research and their discussion. It is known that all malignant processes are recognized as immunodeficiency states, accompanied by immunodepression of any parts of the immune system [7,9]. Consequently, the study of the immunoreactivity of patients with ovarian cancer is an important factor in determining the depth of immunodeficiency, predicting the disease and, most importantly, identifying the most radical ways of therapy, including immunotropic therapy. We have randomized the following study groups to perform a comparative analysis of the immunological results, depending on the immunotherapy method used. The analysis of the results obtained is presented in Figure 1. It has been established that phenotypic markers of lymphocytes include such markers as CD3+, CD3+CD4+, CD3+CD8+, CD20+. In the literature it is widely 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 [9,10,11]. Thus, the analysis of the immunophenotype CD3+ T-lymphocytes in patients with ovarian cancer, depending on the type of immunotherapy, showed that the presence of significant suppression of CD3+ expression on T-lymphocytes is observed in all groups of patients with OC compared with the control group, and there are significant differences between the values of patient groups ($p<0.05$). The lowest value of CD3+ was noted in the group of patients with OC after the application of polychemotherapy without the use of immunotherapy. Moreover, reliable suppression of CD3+ expression in the group of patients after chemotherapy without the use of immunotherapy is observed in comparison with the values of patients with OC in the groups where EIPHT and EIPHT+PHh were used. It should be noted that in the group of patients after chemotherapy without the use of immunotherapy, a decrease in CD3+ expression was noted. This is most likely to a toxic and depressive effect of polychimotherapy on factors of cellular immunity. Obviously, the decrease in the total pool of T-lymphocytes (CD3+) was mainly due to suppression of CD3+CD4+ expression. The study of expression of CD3+CD4+ on T-lymphocytes, which are the main regulatory cells of immunity, showed that the lowest value was noted in groups of patients with OC without the use of immunotherapy and before treatment ($p<0.05$).

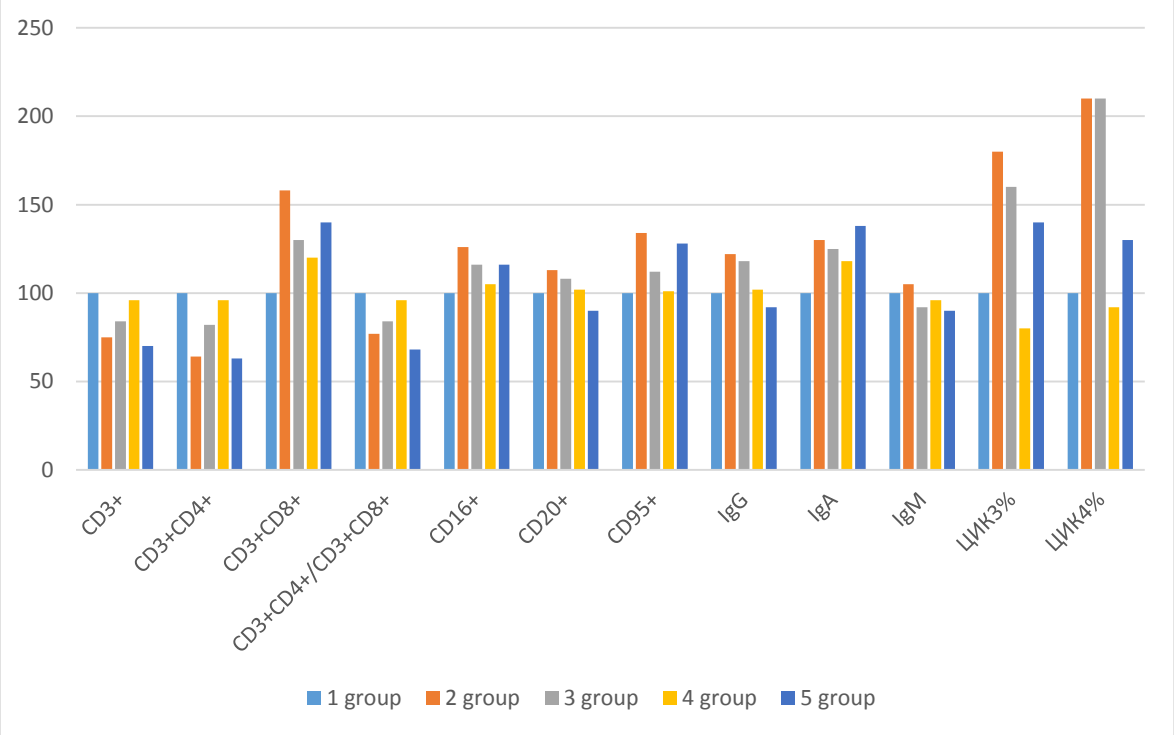

Fig. 1. The results of the study of cellular immunity in patients with ovarian cancer

But, in the groups of patients with OC who received EIPHT and EIPHT+PPh, it was found that the expression of CD3+CD4+ was slightly approximated to the normative value. It has been shown in the literature that CD4+ T cell response to tumor proteins is an

important cellular defense mechanism for the macroorganism, since CD4+ T-helpers stimulate the production of antibodies by B-lymphocytes and activate CD8+ T-lymphocytes specific for tumor cells [12,14]. The analysis showed that in the group of patients with OC without the use of immunotherapy CD3+CD4+ expression was 21,8±1.2%, whereas in the groups of patients after EIPHT - 26.7±1.4%, after EIPHT+PPh - 29,2±1,3%, and in the group of patients before the start of therapy - 20,5±1,2%, in the group of practically healthy persons - 36,8±1,2%.

Cytotoxic CD3+CD8+ T-lymphocytes play an important role in the pathogenesis of cancer [5,9,15]. CD3+CD8+ T-lymphocytes play a major role in eliminating the virus, which is due, on the one hand, to their ability to cause the death of infected cells expressing the corresponding peptides presented by MHC class I molecules, and on the other hand, the ability to secrete antitumor factors-cytokines [3,5]. Analysis of the expression of CD3+CD8+ on T-lymphocytes revealed a significant increase in all groups of patients with OC compared with the value of a group of practically healthy individuals. It should be noted that the maximum increase in CD3+CD8+ was detected in the group of patients before treatment and after polychotherapy without the use of immunotherapy ($p<0.05$). When analyzing the CD3+CD8+ values on T-lymphocytes between the study groups of patients, it was seen that before the treatment, the expression of CD3+CD8+ was significantly increased and amounted to 36.8±2.3%, in the group of patients after polychemotherapy without immunotherapy was an average of 32,9±0,94%, and in the groups of patients after the application of EIPHT and EIPHT+PPh a significant decrease in the number of cytotoxic T-lymphocytes and an approximation to the values of the normative group is observed, which indicates a decrease in immunosuppression against the background of different variants of immunotherapy with the help of polyoxidonium which is detoxification and drug has an expressed immunotropic properties. Immunoregulatory index (IRI), which is the ratio of CD3+CD4+/CD3+CD8+ values, is of significant importance in secondary immunodeficiency states. It is known that, in healthy IRI, an average of 1.62±0.04. Obviously, suppression of CD3+CD4+ expression on the background of increased expression of CD3+CD8+ leads to IRI decreasing. According to our data, the least decrease of IRI is observed in the group of patients before and after treatment without the use of immunotherapy. It was noted that in the group of patients with ovarian cancer who underwent EIPHT after polychemotherapy, a reduced IRI was also observed in comparison with the data of patients receiving EIPHT+PPh. Thus, the lowest value of IRI in the group of patients after polychemotherapy without immunotherapy was 0.62±0.03, and the highest value was noted in the group of patients after EIPHT+PPh and amounted to 1.42±0.03 ($p<0,05$). Consequently, expressed immunosuppression was characteristic of patients with OC in the groups of patients prior to treatment and after polychemotherapy without the use of immunotherapy. It is obvious that a decrease of IRI is an important criterion for the depth of the T-cell immunodeficiency state, especially when assessing the effectiveness of treatment for ovarian cancer. Further, expression of killer cells, which are the third population of lymphocytes providing maintenance of genetic homeostasis, which phenotypically and functionally differ significantly from T and B lymphocytes, was studied [14]. Killer lymphocytes are classified as the main effectors of natural or innate immunity, which are capable of lysing target cells or carrying out antibody-dependent cellular cytotoxicity. It is their inherent performance of the functions of the first line of defense before the emergence of immune T-lymphocytes and specific antibodies [4,5,10]. We have studied killer cells with the phenotypes CD16+. A significant increase in CD16+ expression was revealed in all groups of patients with OC. The data obtained are shown in Figure 1. It was shown that the greatest expression of CD16+ is observed in the group of patients with OC before treatment and after polychemotherapy without immunotherapy, which was significantly increased in comparison with other groups of patients ($p<0.05$). Thus, in the group of patients before treatment, CD16+ expression was 25.6±1.3%, in the group of patients after polychemotherapy without immunotherapy - 23.2±1.24%, in the group of patients after EIPHT - 21.5±1.1%, in the group after EIPHT+PPh - 18,2±1,3%, in the group of practically healthy persons - 16,8±1,2%. Consequently, the greatest expression of CD16+ was noted in groups of patients with OC before and after polychemotherapy without the use of immunotherapy. As you can see, immunotherapy has a beneficial effect on the immune system, reducing its tension. The study of CD20+ expression on B-lymphocytes, which are the main regulatory cells of the immune system and which are of great importance in the development of humoral immunity, showed that CD20+ expression was significantly increased in all groups of OC patients, except for a group of patients after polychemotherapy without the use of immunotherapy, which is apparently due to immunodepression bone marrow after polychemotherapy ($p<0.05$). The highest expression of CD20+ was detected in the group of patients before treatment, and the lowest expression of CD20+ was observed in the group of patients after polychemotherapy without the use of immunotherapy. Obviously, this indicates an immunosuppressive effect of polychemotherapy on the body. CD20+ expression in the group of patients after EIPHT was 23,7±1.3%, in the EIPHT+PPh group - 22.7±1.4% at the normative value of 19.5±0.82%. Therefore, in the group of patients with ovarian cancer, activation of CD20+ expression is observed, which is sharply suppressed on the background of polychemotherapy and dynamically decreases after the application of immunotherapy. Thus, the analysis of the results obtained revealed expressed changes in the cell unit of immunity, which are manifested by suppression of the expression of CD3+, CD3+CD4+, IRI, increased expression of CD3+CD8+, CD16+ and CD20+ cells.

It has been established that the functional usefulness of B-lymphocytes in the immune response is characterized by the production of immunoglobulins

[10,11]. 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 end effector reactions of cellular immunity by inactivation and elimination of antigens [13,14]. We analyzed serum concentrations of the main immunoglobulins IgG, IgA, IgM in ovarian cancer. As can be seen from the presented data, the content of the main serum immunoglobulins varied within wide limits. The highest serum IgG content was detected in the group of patients before the start of treatment, and the smallest amount was noted in the group of patients after treatment without the use of immunotherapy, which may also be related to immunodepression of the immune system against polychemotherapy. The best situation is typical for patients with OC after EIPHT+PPh, where the IgG level is approximated to the norm. Serum IgM content in practically all groups of patients with ovarian cancer was within the normative values, and no special deviations between groups of patients were detected. Serum content of IgG was in the group of patients with OC before treatment of 1298.8±57.9 mg%, in the group of patients after EIPHT - 1258.4±52.6 mg%, in the group of patients EIPHT+PPh - 1185.0±44,6 mg %, in the group of patients without immunotherapy - 1110.5±50,6mg%, at the normative value - 1150.9±42,8mg%. Analysis of the IgA content revealed a significant increase in IgA in the blood serum in all groups of patients with OC. Moreover, the greatest content was noted in the group of patients after polychemotherapy without immunotherapy. Approximate values of IgA to the normative value were noted in the group of patients after EIPHT+PPh, which is explained by the immunocorrecting effect of plasmaphoresis and the effect of polyoxidonium as a detoxification and immunotropic drug. Consequently, the humoral unit of immunity was characterized by an increase in serum concentrations of IgG and IgA in groups of patients with OC, especially after chemotherapy without immunotherapy and before treatment. One of the most important humoral immunity markers is the circulating immune complexes (CIC). It has been established that one of the most important biological functions of immunoglobulins is antigen binding and CIC formation [2,4,8,12]. An important characteristic of the CIC is their magnitude, which can be large and small. The analysis showed that the CIC of large and small sizes in all groups of patients with ovarian cancer were significantly increased. Thus, the CIC of large quantities were significantly increased before treatment and after treatment without immunotherapy. And in the groups of patients after EIPHT and EIPHT+PPh, the CIC of large values significantly decreased. This may be indicative of desintoxication effects after plasmaphoresis and the use of immunological drugs. As for the CIC of small quantities, there is also a significant increased content. Apparently, this is due to the lack of the necessary detoxification and the impact on the immune system. The CIC4% of small values is the smallest value close to the norm in the group of patients after EIPHT+PPh, which again indicates the beneficial effect of this immunotherapy on the functioning of the immune system. It is known that the CIC3% of large values formed with an excess of antibodies, although capable of binding complement, but are large in size, insoluble and have low pathogenicity [1,2]. Consequently, activation of the humoral unit of immunity is observed along with a expressed depression of the cellular immunity. Thus, based on the results obtained, it can be seen that in ovarian cancer, a marked imbalance of the cellular and humoral parts of the immune system is observed. Moreover, the imbalance in the cell link of immunity is expressed in the suppression of IRI by reducing the number of T-helpers/inducers and increasing T-cytotoxic lymphocytes. CICs of large and small values are also increased, however, the highest increase in CIC was observed in patient groups prior to chemotherapy and immunotherapy, and after the use of chemotherapy without immunotherapy. Increase in T-cytotoxic lymphocytes, which indicates the suppression of T-cell immunity and the presence of cytotoxic action at the cellular level is more typical for terminal stages of cancer. The increase of the main immunoglobulins indicates the presence of a humoral imbalance, and, the increase in the CIC indicates the intoxication of the organism either due to the disintegration of the tumor cells themselves, or against chemotherapy or radiotherapy. An increase in the CIC of 4% always indicates a progression of the pathological process and is a marker of the progression or deterioration of the clinical course. CIC 3% quickly decay in the body, so they have no pathological potential. Positive clinical efficacy of the combination of immunotherapy has been established.

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REMOTE RESULTS OF TREATMENT OF PATIENTS WITH CERVICAL AND OVARIAN CANCER ON THE BACKGROUND OF IMMUNOTHERAPY

Kamishov S.V., Pulatov D.A., Yusupova N.B., Niyozova Sh.Kh.

Republican Specilized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan, Tashkent

Summary

The aim of the investigation was to study the remote results of treatment of accompanying immunopharmacotherapy in patients with cervical cancer and ovarian cancer. Studies have concluded that the greatest effectiveness in reducing the side effects of chemotherapy in the complex treatment of patients with cervical cancer and ovarian cancer stage II-III, as well as in improving the subjective condition of patients and their quality of life, provides immunotherapy plan, which includes intermittent plasmapheresis followed by extracorporeal immunopharmacotherapy (EIPHT), which reduces the main clinical manifestations of chemotherapy, improve the indicators of the subjective condition of patients and their quality of life. The use of EIFT methods in the treatment of oncogynecological diseases can improve the five-year overall and one-time survival of patients with cervical cancer and ovarian cancer. Developed technique has great potential in cancer practice due to the possibility of eliminating the effects of cancer intoxication, as well as increased own system of antitumor protection of the body, which positively affects the outcome of the disease, as well as improves the quality and life expectancy of the patient.

Key words: ovarian cancer, cervical cancer, immunotherapy, extracorporeal immunopharmacotherapy, plasmapheresis, polychemotherapy, remote results of treatment.

Cervical cancer (CC) is one of the most common oncological diseases of the reproductive system in women and accounts for about 12-20% of malignant neoplasms of female genital organs [1,2]. Currently, cervical cancer ranks second place in the world in terms of incidence among all malignant tumors of the female reproductive system, and second in the structure of mortality from cancer of women under the age of 45, second only to breast cancer. In the structure of oncogynecologic diseases CC ranked 3rd in the overall oncological morbidity structure with a frequency of 4.7 cases per 100,000 population in 2015 in Uzbekistan [3,7].

Ovarian cancer (OC) continues to be the fourth leading cause of cancer death among women and continues to be the most fatal of gynecological tumors. The recurrence rate of patients with OC is approximately 75%, which is equivalent to approximately 2500 patients per year. In this group of patients with relapses, many patients have a life expectancy of 2 to 3 years, therefore, OC can be classified as a "chronic disease" [6,8].

It is known, that in CC and OC the 5-year survival rate is 30% excluding stage disease. Such treatment disappointing results due to the fact that 75% of patients with cervical cancer and ovarian cancer enter to the oncological establishment on III-IV stage of the process [10,12]. As the research data show, the survival of patients with CC and OC is determined not only by the stage of the disease and the chosen method of treatment. At present, it is known that the development of the oncological process is accompanied by violations of the state of adaptive (specific) immunity, which deepen in the conditions of extensive surgical interventions. It is established that immune dysfunctions make a significant contribution to the pathogenesis of generalized inflammation in the oncological process, and are not only a sign of its development, but largely ensure its occurrence and subsequent progress [3,4]. Proceeding from this, it is obvious that immunotherapy methods are needed for this category of patients that can effectively correct developing immune dysfunctions. Now it is proved that the most rational means of immunocorrection is the usage of immunotropic drugs. The versatility of the biological activity of these drugs makes it possible to rely on their correction not only to correct the manifestations of immune deficiency, but also to optimize the functioning of the entire immune system and its adequate interaction with other body systems [1,2]. Thus, according to modern literature, the most promising area of immunotherapy is extracorporeal