

**EXTRACORPORAL IMMUNOPHARMACOTHERAPY IN COMPLEX TREATMENT OF
CERVICAL CANCER AND OVAR CANCER*****Kamishov S. V. and Tillyashaykhov M. N.**Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health
of the Republic of Uzbekistan, Tashkent.***Corresponding Author: Kamishov S. V.**Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of
Uzbekistan, Tashkent.

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SUMMARY

When prescribing EIPHT methods for patients with cervical cancer and OC, the results of clinical and diagnostic studies, anamnestic data, the presence of specific antitumor or nontraditional types of treatment before admission to the hospital, as well as the histological type of the tumor, the macroscopic form of growth and its prevalence were taken into account. EIPHT methods are recognized, first of all, to reduce toxic manifestations after chemotherapy and radiation therapy, as well as to improve the general condition after extensive surgery in patients with oncologic diseases. In the course of the surveys conducted, an algorithm was developed for preparing patients with cervical cancer and OC to perform EIPHT techniques, including 1) the study of anamnestic data (the presence of concomitant diseases and earlier symptomatic or specific treatment); 2) the study of general clinical and biochemical analysis of blood; 3) the study of immunological parameters; 4) study of urinalysis; 5) study of the degree of toxicity of chemotherapy on the CTC-NCIC scale; 6) study of the subjective general condition of patients (Performance status) on the Karnofsky scale and ECOG (WHO); 7) an assessment of the quality of life of patients according to the SF-36 questionnaire; 8) the conclusion of the cardiologist; 9) if necessary, conservative fortifying, cardiotropic, hepatotropic and other types of therapy were given to patients.

KEYWORDS: Ovarian cancer, ovarian cancer, immunotherapy, extracorporeal immunopharmacotherapy, plasmapheresis, cytokines, interleukins, polychemotherapy.

Topicality of the theme. Increased attention to the problem of increasing cancer incidence is one of the characteristic features of the modern health care system of all developed countries. This is due, above all, a steady trend of increasing malignant neoplasms among the population, which has reached rather high rates and will increase in the foreseeable future. Oncological diseases are initially detected every year in 12 million people worldwide, while the number of cancer cases in the world over the past ten years has increased by twenty percent. This is the second cause of death after cardiovascular diseases in developed countries, and the common cause of 10% of all deaths in the world, which is about 6 million deaths per year.^[4,8,12]

In recent years, progress has been made in the study of immunology and cancer immunotherapy, including malignant tumors of the female reproductive system. Evidence has been obtained that the majority of malignant tumors develop on the basis of pronounced disorders of the immune system, arising already in pre-tumor diseases, are determined by the prevalence of the tumor process and are aggravated by the therapeutic effect used. These data, as well as information about a more favorable course of the disease with preserved

immunity, encourage many researchers to further study the state of the immune system and develop on this basis more effective treatment regimens for patients with malignant tumors with the inclusion of immunotherapy methods.^[1,2,5,9]

Ovarian cancer (OC) currently continues to be the fourth leading cause of cancer mortality among women and is still the most fatal of gynecological tumors.^[3,4,12] Cervical cancer (cervical cancer) is also one of the most common malignant tumors of the female genitalia. The incidence rate throughout the world varies from 10 to 40 per 100 thousand of the female population, and almost half of the patients die within the first year due to late diagnosis of the disease.^[3,5,6,10] Common forms of the disease worsen the prognosis and require the use of combined and complex treatment methods. At the same time, it is necessary to take into account the high toxicity of many anticancer drugs, which also leads to the limitation of surgical intervention in elderly patients and in the presence of severe comorbidities.^[5,7] The percentage of recurrences in patients with OC is approximately 75%, which is equivalent to approximately 2500 patients per year. Relapse therapy is the most controversial section of gynecological oncology

and is predominantly palliative, and with this in mind, its main purpose is to prolong life and improve its quality.^[8] Five-year survival for cervical cancer according to different authors in the presence of stage III-IV of the disease is 17-22%. The main cause of mortality is also recurrence of cancer, ranging from 37% to 50% of all treated patients.^[3,9,12] In this regard, the improvement of methods of drug therapy in order to extend and improve the quality of life of patients is a very urgent problem of clinical oncology.^[6,9] For many years, cancer treatment has focused on surgery, chemotherapy, and radiation therapy, but as knowledge of the immune system's capabilities in the fight against cancer deepened, treatment methods using the immune system against malignant tumors began to develop. Although immunotherapy of malignant tumors is a relatively new scientific trend, the results obtained in the last decade allow us to count on the important role of immunotherapeutic approaches in the treatment of oncological diseases.^[8,11] Immunosuppression of mixed genesis is observed in patients with oncological diseases after conducting a comprehensive antitumor treatment. First, the fact of the development of the oncological process allows us to speak about the presence of an initial defect in the function of immune surveillance, which allows tumor cells to multiply unhindered. Secondly, the tumor cells themselves have a local and immunosuppressive effect due to the production of various substances. Thirdly, modern complex antitumor treatment (surgical treatment, radiation and chemotherapy) turns out to be a powerful factor inducing generalized immunosuppression. In this regard, cancer patients make up a special group of patients who have been shown immunotherapy.^[6,8] Currently, the main objectives of immunotherapy in oncology have been formulated - these are basic immunotherapy of tumors with the aim of obtaining a direct antitumor effect, reducing the side effects of traditional antitumor therapy (treatment of myelosuppression and immunosuppression, correction of general toxic effect, antioxidant effect), prevention of tumor recurrence and the appearance of new other tumors, prevention and treatment of concomitant infectious complications (viral, bacterial and fungal infections).^[1,4] Obtaining new unique immunomodulatory drugs has created a qualitatively new basis for the correction of immunity disorders, it became possible to act more selectively on individual components and links of this system. On the other hand, there are prospects for methods that have a positive effect on the immune system as a whole - the use of adaptogens, plasma exchange methods, perfusion of blood through sorbents, treatment with various activators.^[8,10] One of the methods that have been successfully used for the relief of intoxication for a long time is therapeutic plasmapheresis, which consists in removing blood plasma containing antibodies, circulating immune complexes, cytokines, products of cellular metabolism, etc. Modern methods of extracorporeal immunopharmacotherapy (EIPHT) are in essence an effective extension of therapeutic

plasmapheresis. If during the latter the cellular elements immediately after their separation from the plasma are returned to the patient, then with EIPHT there is an additional release of the leukocyte fraction, which is then subjected to treatment outside the body with a specific drug. Leukocytes activated in this way, after returning to the bloodstream, are able to synthesize the factors that activate the immune system and, consequently, activate other cells of the immune system. Thus, EIPHT is a separate direction, born at the junction of immunology and extracorporeal hemocorrection.^[5] At the same time, it should be noted that clinical trials of various immunological approaches in oncology are still episodic, and their implementation is still difficult due to technical problems, the toxicity of the complexes used, their not always sufficient efficiency, the lack of criteria for assessing the feasibility of the appointment immunocorrective treatment and its effectiveness. The development, study and introduction into clinical practice of various methods of immunotherapy is an actual problem of modern oncology, since the application of these techniques can expand the therapeutic possibilities of standard treatment methods and reduce their side effects, which will improve the quality of life of patients with malignant tumors.

The aim of the study is to conduct extracorporeal immunopharmacotherapy in patients with ovarian cancer and cervical cancer.

Material and methods of research. The examination included 268 patients with cervical cancer $T_{2-3}N_{0-1}M_0$ stages (stage II-III), as well as 261 patients with stage 2-3 clinical stage $T_{2-3}N_{0-1}M_0$ (stage II-III) who were examined and treated in the gynecological oncology and chemotherapy departments of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of Ministry of Health of the Republic of Uzbekistan from 2004 to 2014 In accordance with the objectives of the study, the following groups of patients were created according to the methods of immunotherapy as part of complex treatment.

The 1 group - 83 (31.0%) patients with cervical cancer who received extracorporeal immunopharmacotherapy (EIPHT) without plasma exchange (PPh);

The 2 group - 67 (25.0%) of cervical cancer patients who received EIPHT with preliminary PPh;

The 3 control group - 118 (44.0%) patients with cervical cancer without immunocorrective therapy;

The 4 group - 78 (29.9%) patients with OC who received EIPHT without PPh;

The 5 Group - 73 (28.0%) patients with OC treated with EIPHT with PPh;

The 6 control group - 110 (42.1%) patients with OC without immunocorrective therapy.

Morphologically, non-squamous squamous cell carcinoma was determined in 147 (54.9%) patients and

keratinous squamous cell carcinoma in 121 (45.1%). According to the degree of tumor differentiation, 138 (51.5%) patients were diagnosed with low-grade cancer, 46 (17.2%) moderately-differentiated, and 84 (31.3%) patients had highly-differentiated cervical cancer. The analysis of histological preparations in patients with OC showed that in the majority - 222 (85.1%) of the examined patients were diagnosed with cystadenocarcinoma, in 39 (14.9%) patients had other forms of OC.

All patients with cervical cancer received complex treatment, including NAPC, surgery and / or CRT or two-stage combined radiation therapy, including remote telegraphmathery and intracavitary brachytherapy. At the first stage, all patients with cervical cancer have systemic or intraarterial polychemotherapy according to the cisplatin 50 mg / m² + 5-fluorouracil 1000 mg / m² scheme for 4 days, 4-6 courses 1 time in 3 weeks. Radiation therapy and chemotherapy were carried out both in the adjuvant and in the neoadjuvant mode. Surgical treatment was performed as a radical operation.

The results of the study

When prescribing methods of extracorporeal immunotherapy for patients with cervical cancer and OC, they tried to take into account the results of clinical diagnostic studies to the greatest extent. Analysis of anamnestic data of cervical cancer patients showed that the majority - 196 (73.1%) patients from the first visit to the gynecologist about complaints before the diagnosis of cervical cancer was treated with conservative anti-inflammatory therapy. 33 (12.3%) patients were treated independently with unconventional methods, and 16 (4.9%) electrocoagulation was performed without histological examination. Specific anticancer treatment before admission to the hospital most of the patients did not receive. A small part of patients with cervical cancer was given specific antitumor treatment. Thus, 15 (5.6%) patients had previously been treated with RTGT (SOD 40-50 Gy) without any special effect and 8 (3.0%) patients had SLT (RTGT + brachytherapy). Of these, 3 managed to achieve partial regression of the tumor, and in 5 patients - stabilization of the tumor process with some subsequent improvement in symptoms. The analysis of the anamnestic data of patients with OC has made it possible to establish that in the period from the first visit to the gynecologist about complaints to the diagnosis of OC, most of the 215 (82.4%) patients underwent conservative anti-inflammatory therapy. Patients with OC did not receive specific anticancer treatment before admission to the hospital. 33 (12.6%) patients were treated independently using unconventional methods, and 13 (5.0%) were given hormone therapy for nodular goiter and ovarian cysts. Morphological analysis of the surgical material and biopsy results in patients with cervical cancer showed that in the majority - 255 (95.1%) of the examined patients had a histological squamous cervical cancer, 13 (4.9%) patients had clear cell adenocarcinoma.

In 147 (56.3%) patients, serous cystadenocarcinoma was detected, in 50 (19.2%) - endometrioid cystadenocarcinoma, in 28 (10.7%) - mucinous cystadenocarcinoma, in 20 (7.7%) - clear cell cystadenocarcinoma and in 16 (6.1%) patients, mixed-type cystadenocarcinoma. According to the degree of tumor differentiation, 72 (27.6%) patients were diagnosed with low-grade cancer, 129 (49.4%) had moderately-differentiated cancer, and 60 (23.0%) patients had high-grade cancer. Using clinical and instrumental methods of research in all patients with cervical cancer, the macroscopic form of tumor growth and the extent of the tumor process were determined.

As mentioned earlier, in the majority, 119 (44.4%) patients were diagnosed with stage IIIB of the disease. In most cases, 140 (52.2%) of the examined patients showed tumor volume in the range from 10 to 15 cm³. It was not possible to determine the initial tumor in the majority of patients - in 164 (61.2%) using clinical and instrumental methods. In the majority - in 118 (44.0%) patients, the tumor spread to the upper third of the vagina. In the case of OC, the majority — 107 (41.0%) of the examined patients were diagnosed with stage IIIC of the disease.

According to the ultrasound examination, a tumor of more than 10 cm was detected in 143 (54.8%) patients and up to 10 cm in 118 (45.2%) patients. At the same time, one-sided lesion was observed in 113 (43.3%) of them and bilateral - in 148 (56.7%) patients. Dissemination of the peritoneum was absent in 107 (41.0%) patients, had insignificant dimensions - in 91 (34.9) and up to 2 cm - in 63 (24.1%) patients. The presence of ascitic fluid in the abdominal cavity was absent in 145 (55.6%) patients, was determined in the amount of up to 2 liters - in 65 (24.9%) and more than 2 liters - in 51 (19.5%) patients. Tumor cells in ascites or abdominal flushing were detected in 73 (62.9%) patients and were absent in 43 (37.1%) of 116 patients with ascites.

All patients with cervical cancer received a complex treatment: two-stage combined radiation therapy, including remote telegraphmathery (RTGT) with a split course at the ROD of 2 Gy to SOD 50 Gr, 5 times a week and intracavitary brachytherapy at the Giving 5 Gr to SOD 45-55 Gr, every other day. Also, all patients with cervical cancer have received systemic or intraarterial polychemotherapy according to the cisplatin 50 mg / m² scheme + 5-fluorouracil 1000 mg / m² for 4 days, 4-6 courses 1 time in 3 weeks. Radiation therapy and chemotherapy were carried out both in the adjuvant and in the neoadjuvant mode. Surgical treatment was carried out in the form of a radical operation of Wertheim-Megeiss. Combined therapy was carried out in all patients with adjuvant or neoadjuvant regimen, polychemotherapy according to the cisplatin 75 mg / m² + cyclophosphamide 1000 mg / m² scheme for 1 day, 4-6 courses 1 time per 3 weeks and surgical treatment in

the amount of radical or cytoreductive surgery. The frequency and severity of reactions depended on the initial state of these organs and comorbidities. Among the early forms of bladder reactions, radioepitheliitis should be distinguished, most often appearing in the middle or at the end of the course of combined irradiation. Clinically, these complications were manifested by pollacyuria and cystalgia. In some cases, late radiation damage to these organs occurred. Most patients had reversible cystalgia, pollakiuria, hematuria, rectitis, epithelium, ulceration, stenosis, necrosis. Rektita appeared later than cystitis, and were accompanied by tenesmus, itching and diarrhea. Late rectitis was more common than late cystitis. Also encountered radiation dermatitis, accompanied by swelling and pain. Methods of extracorporeal immunopharmacotherapy (EIPHT) were designed, first of all, to reduce toxic manifestations after chemotherapy and radiation therapy, as well as to improve the general condition after extensive surgery in patients with oncological and gynecologic diseases. For the implementation of EIPHT techniques it was necessary to develop indications and contraindications for their implementation in this category of patients. In the process of the conducted examinations, we developed an algorithm for preparing patients with cervical cancer and OC to perform EIPHT techniques. We also developed clinical and laboratory criteria for the inclusion of patients with cervical cancer and OC in the study on conducting methods of EIPHT. Accordingly, criteria were developed for excluding patients with cervical cancer and OC from the EIPHT study. Since EIPHT techniques involve taking from 200 to 1000 ml of blood from the bloodstream of patients with its special treatment and subsequent return to the bloodstream, conservative medical measures in some patients were carried out as prevention of exacerbation of concomitant diseases.

Immunotherapy in patients with cervical cancer and OC was performed in the pre- and postoperative period. In the 1st group, 83 (31.0%) patients with cervical cancer and in the 4th group - 78 (29.9%) patients with OC were performed with EIPHT by exfusion of 200-250 ml autologous blood into sterile containers "Gemakon" or "Terumo", incubation with immunomodulators: neovir in a total dose of 750 mg (for 3 treatments), cycloferon in a total dose of 750 mg (for 3 treatments) or polyoxidonium in a total dose of 36 mg (for 3 treatments) at 37 ° C for 60-100 minutes, followed by reinfusion the resulting conjugate. In the 2nd group, 67 (25.0%) patients with cervical cancer and in the 5th group - in 73 (28.0%) patients with OC, EIPHT was used, which was an extension of plasmapheresis. If during normal plasmapheresis, the cellular elements immediately after their separation from plasma are returned to the patient, then with EIPHT, in order to achieve an additional immunocorrective effect, they are further processed outside the body with a specific drug. 500-1000 ml of autologous blood were placed in sterile containers "Gemakon" or "Terumo", then it was centrifuged at 3000

rpm for 30 minutes. 50-80 ml of the blood plasma supernatant containing antibodies, circulating immune complexes, cytokines, and products of cell metabolism were removed. Then, the obtained leukotrombossa and erythrocyte mass were incubated with the above immunomodulators, in a total dose of 30 mg (for 3 procedures) at 37 ° C for 60-100 minutes, followed by return of the conjugate to the circulatory system of patients. In the 3rd control group, 118 (44.0%) patients with cervical cancer and in the 6th control group - 110 (42.1%) patients with OC did not receive immunotherapy. Thus, when prescribing EIPHT methods to patients with cervical cancer and OC, we tried to take into account the results of clinical diagnostic studies to the greatest extent. Anamnestic data, the presence of specific antitumor or non-traditional types of treatment before admission to the hospital, as well as the histological type of the tumor, the macroscopic form of growth and the degree of its prevalence were taken into account. EIPHT methods were designed, first of all, to reduce toxic manifestations after chemotherapy and radiation therapy, as well as to improve the general condition after an extensive surgery in patients with oncological diseases. In the process of the conducted examinations, we developed an algorithm for preparing patients with cervical cancer and OC to perform EIPHT techniques, including 1) the study of anamnestic data (the presence of concomitant diseases and previously conducted symptomatic or specific treatment); 2) the study of general clinical and biochemical analysis of blood; 3) the study of immunological parameters; 4) study of urinalysis; 5) study of the degree of toxicity of chemotherapy on the CTC-NCIC scale; 6) study of the subjective general condition of patients (Performance status) on the Karnofsky scale and ECOG (WHO); 7) an assessment of the quality of life of patients according to the SF-36 questionnaire; 8) the conclusion of the cardiologist; 9) if necessary, conservative fortifying, cardiotropic, hepatotropic and other types of therapy were given to patients. We also developed clinical and laboratory criteria for the inclusion of patients with cervical cancer and OC in the study on EIPHT techniques, which included: 1) a histologically confirmed diagnosis of cervical cancer and OC; 2) age from 21 to 75 years; 3) Stage IIA-IIIB in patients with cervical cancer and stage IIA-IIIC in patients with ovarian cancer; 4) condition after surgical treatment and ongoing chemotherapy or radiation therapy; 5) Performance status 40-80% on the Karnofsky scale and 1-3 points for ECOG (WHO); 6) the degree of toxicity of chemotherapy I-IV on the CTC-NCIC scale; 7) deterioration of the physical and mental components of health according to the questionnaire SF-36; 8) the absence in the history of other malignant diseases and severe comorbidities; 9) hemoglobin > 10 g / l, leukocytes > 4,000 / mm³, neutrophils > 1.5000 / mm³, platelets > 100.00 / mm³; 10) indicators of kidney function: creatinine ≤ 100 μmol / l; if creatinine ≥ 100 and ≤ 130 μmol / l, creatinine clearance should be > 60 ml / min. The patient does not turn on if plasma creatinine >

130 $\mu\text{mol} / \text{l}$; 11) liver function indicators: total bilirubin $<1.5 \times \text{VGN}$ (upper limit of normal), ALT and AST $<1.55 \times \text{VGN}$, alkaline phosphatase $<5 \times \text{VGN}$. Accordingly, criteria were developed for excluding patients with cervical cancer and OC from the EIPHT study, which included: 1) current or previous treatment with research drugs; 2) the presence of a severe pathology of the gastrointestinal tract (Crohn's disease, ulcerative colitis, partial or complete intestinal obstruction, chronic diarrhea or maldabsorption syndrome); 3) the presence of severely controlled associated diseases, such as diabetes or infectious diseases; 4) the presence of a history of mental disorders; 5) a history of severe renal disease; 6) the presence of initially peripheral polyneuropathy or auditory neuropathy $> 1 \text{ tbsp}$; 7) the presence of a known hypersensitivity to immunomodulators (neovir, cycloferon, polyoxidonium); 8) disseminated intravascular coagulation syndrome; 9) myocardial infarction for the last 6 months, hereditary heart diseases, decompensated heart failure, any cardiovascular pathology of the III-IV art. (according to the classification of the New York Heart Association NYHA), therapeutically uncorrected.

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