

**ANALYSIS OF EFFICIENCY OF IMMUNOPHARMACOTHERAPY IN COMPLEX  
TREATMENT OF OVARIAN CANCER AND CERVICAL CANCER****\*Kamishov Sergey Viktorovich**

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**ABSTRACT**

The aim of the study was to evaluate the effectiveness of accompanying immunotherapy in the complex treatment of cervical cancer and ovarian cancer in stationary conditions. Materials and methods. For this purpose, patients with cervical cancer (cervical cancer) and cervical cancer (cervical cancer) T2-3N0-1M0 stages (II-III clinical stages) were examined at oncology clinics in oncogynecology and chemotherapy departments. Results. Carrying out EIPHT with plasmapheresis contributed to an even more pronounced decrease in the side effects of cytostatic treatment on the patient's body.

**KEYWORDS:** Ovarian cancer, cervical cancer, immunotherapy, polychemotherapy, evaluation of treatment efficacy, relapse-free current.

**INTRODUCTION**

The most difficult question in the study of the effectiveness of the use of immunomodulators is a correct assessment of the appropriateness of the appointment of immunocorrective treatment and its effectiveness. It is clear that the progressing tumor causes serious changes in the immune response, with which the immune system alone cannot cope and the inclusion of immunomodulators in the complex of treatment of cancer patients is justified. In modern oncology, the role of immunology has significantly expanded, which provides new methods for diagnosis, monitoring and treatment of cancer, as well as correction of complications of traditional treatment. The new cancer treatment strategy is based on the principle of "complementary oncotherapy" [3, P.242; 7, P. 153;8, P.15], which implies the synergistic therapeutic effect of existing traditional and immunological methods of treatment, taking into account the etiopathogenetic significance of each method. Immunological methods of treatment, in this case, are present at all stages of antitumor treatment, but at each stage they perform various tasks. At the present stage, despite the development of medical science, surgery and chemoradiotherapy remain the main methods of treatment of cervical cancer and OC. In general, the implementation of organ-preserving and functionally-sparing approaches in combination with the methods of immunotherapy in the treatment of oncogynecologic patients is an actual and promising scientific direction that allows not only to heal the patient, but also to preserve the basic functions of the female body,

significantly improve the quality of life, shorten the terms of social and psychological rehabilitation [4, P.383; 8, P.15;10, P.20.]. In patients with cancer after complex antitumor treatment, immunosuppression of mixed genesis is observed. First, the fact of development of the oncological process allows us to speak about the presence of an initial defect in the function of immune surveillance, which allows unhindered reproduction of malignant cells. Secondly, the tumor cells themselves have a local and immunosuppressive effect due to the development of various substances. Third, modern complex antitumor treatment (surgical treatment, radiation and chemotherapy) is a powerful factor that induces generalized immunosuppression [1, P.452; 2, <http://www-dep.iarc.fr/globocan.htm> ; 4, P.383; 8, P.15]. In this regard, a special group of patients who are shown to perform immunotherapy, are oncological patients. They, as a rule, have a pronounced concomitant pathology, advanced age, immunodepression, aggravated by preoperative radiation and / or several courses of chemotherapy. Currently, nonspecific active immunotherapy is more widely used in the clinic and more developed than other types of immunotherapy. As non-specific stimulants, bacterial vaccines, polysaccharide preparations (zymosan, manosine, propermyl, glucan, prodigiosan, pyrogenal), interferon and biologically active factors of the thymus, inducers of endogenous interferon formation and thymic serum activity, etc. are used. In the literature, data on the effectiveness of interferon inducers (neovir, cycloferon) in the treatment of cervical dysplasia and cancer in situ. Research materials have been published, according to

which the systemic administration of 13-cis retinoic acid in combination with the local application of interferon in the form of applications, allows complete remission in patients with cervical cancer of the IB stage [3, P.242]. T-activin and its analogue Timalin is widely used in oncology, including oncogynecology. These drugs are a complex of polypeptide fractions isolated from the thymus gland of cattle. The drugs are used as an immunostimulant and biostimulator in the complex therapy of diseases accompanied by a decrease in cellular immunity, including acute and chronic purulent processes and inflammatory diseases, with burn disease, trophic ulcers, etc., as well as in the suppression of immunity and hematopoietic function after radiation or chemotherapy in cancer patients. The results of clinical observation showed that the use of imunofan, amixin and lycopene in complex therapy of endometrial adenocarcinoma significantly reduces the frequency of radiation complications and exerts a pronounced immunocorrecting action.<sup>[5,7,8,9]</sup> A team of researchers at the Cancer Center of the Russian Academy of Medical Sciences developed a method of adaptive phototherapy, based on extracorporeal irradiation of leukocyte mass isolated from the patient's blood. In this case, a helium-neon laser (wavelength 632.8 nm) is used. Subsequently, re-fusion of the leukocyte mass into the bloodstream was performed. After this, stimulation of T-lymphocytes occurs. This method was used in patients with breast cancer, which slowed the timing of metastasis in the postoperative period. The procedure of plasmapheresis is accompanied by hemodilution, as evidenced by a decrease in hematocrit by 15% and total protein concentration by 20%. In this case, in comparison with the initial data, the viscosity of the blood decreases by 19%, fluidity increases by 20%, electrophoretic mobility of erythrocytes by 22%, their aggregation ability decreases by 35%, platelets by 32%. Plasmapheresis eliminates the blockade of the macrophage system and simultaneously optimizes the functions of damaged organs. Modern methods of extracorporeal immunopharmacotherapy (EIPHT) are inherently effective extensions of therapeutic plasmapheresis [8, P.15; 10, P. 20]. Numerous studies have shown that modern immunotherapy methods in the treatment of malignant tumors can have a normalizing effect on the immune status of cancer patients, provide an objective antitumor effect, and also contribute to the regression of tumor pleurisy and ascites in chemo-resistant forms of cancer. A promising direction in the treatment of malignant neoplasms at the present stage of development of immunotherapy is a combination of methods of activation of specific and nonspecific immunity. In contrast to the usual methods of immunotherapy, when immunomodulating drugs are taken in the form of tablets, or are administered intramuscularly or intravenously, the use of extracorporeal immunopharmacotherapy (EIPHT) methods makes it possible to selectively select from the blood directly the cells of the immune system - the leukocytes. The isolated leukocytes are processed by special technologies with

immunomodulating drugs and then, already activated, return back to the vascular channel, after which they are able to synthesize the activation factors of the immune system and activate other cells of the immune system. This direction of immunotherapy has great prospects in oncological practice in connection with the possibility of removing the consequences of cancer and chemoradiation intoxication, as well as activate its own system of antitumor protection of the body. However, in the literature there is very little information on the use of the EIPHT method in the treatment of cancer. Many methods of immunotherapy in the field of oncology are still used empirically, there are no clear criteria for indications and contraindications in the treatment of malignant tumors of various localizations. Determining the optimal doses of drugs, the sequence of various effects on the immune system, their duration, and the influence of immunotherapy methods on the immediate and long-term results of antitumor therapy, require the efforts of many researchers.

Based on the foregoing, the aim of the study was to evaluate the effectiveness of accompanying immunotherapy in the complex treatment of patients with cervical cancer under stationary conditions.

#### MATERIAL AND METHODS

For this purpose, patients with ovarian cancer (OC) and cervical cancer (CC) T<sub>2-3</sub>N<sub>0-1</sub>M<sub>0</sub> stages (II-III clinical stages) were examined at oncology clinics in oncogynecology and chemotherapy departments. All patients received complex treatment, including a two-stage combined radiotherapy, including a remote teletherapy (DTGT) split course at a 2 Gy ROD up to 50 Gy, 5 times a week, and intracavitary brachytherapy at a rhythm of 5 Gy to SOD 45-55 Gy, every other day. Systemic or intra-arterial polychemotherapy with a cisplatin regimen of 50 mg / m<sup>2</sup> + 5-fluorouracil 1000 mg / m<sup>2</sup> for 4 days for 4-6 courses was given once every 3 weeks. Radiation therapy and chemotherapy were performed in both adjuvant and neoadjuvant regimens. Surgical treatment was performed in the form of a radical operation. Extracorporeal immunopharmacotherapy was performed by exfusion of 500-1000 ml of autoblood in sterile "Gemakon" or "Terumo" containers and its centrifugation at 3000 rpm for 30 minutes. 50-80 ml of the supernatant of blood plasma, containing antibodies, circulating immune complexes, cytokines, products of cellular metabolism were removed. Then the obtained leukotrombomass and erythrocytic mass were incubated with thymalin in a total dose of 30 mg (for 3 procedures) at 37°C for 60-100 min, with the subsequent return of the conjugate to the circulatory system of patients. This method was carried out in a hospital, at the time when patients were admitted to chemotherapy and radiation therapy. In total, patients received 2 sessions of extracorporeal therapy at the beginning of admission to hospital and before discharge from the hospital. Depending on the type of extracorporeal therapy being performed, 4 groups of patients with cervical cancer and

OC were isolated. The 1st group included patients of the control group i.e. those patients with cervical cancer and OC who did not receive immunotherapy. In 2<sup>nd</sup> (34 patients) cervical cancer and 28 patients with osteoporosis, immunotherapy in the form of subcutaneous injections with thymomimetics (thymalin) was performed in standard doses for 10-14 days. The third group included 52 patients with cervical cancer and 36 patients with OC who underwent extracorporeal immunotherapy (EIPHT) by exfusion of 200-250 ml of autoblood in sterile containers "Gemakon" or "Terumo", incubation with immunomodulator thymalin in a total dose of 30 mg (for 3 procedures) at 37°C for 60-100 min followed by reinfusion of the resulting conjugate and group 4 comprised 44 patients with cervical cancer and 47 OC using EIPHT in combination with plasmapheresis. It should be noted that patients who received any type of immunotherapy, were subjected to it every time during the receipt of chemo- and radiotherapy. The overall cumulative five-year survival was assessed by Kaplan E.L. et Meier R. in patients with cervical cancer, depending on the different options of immunotherapy in complex treatment.

## RESULTS AND DISCUSSION

Evaluation of the effect of extracorporeal immunopharmacotherapy on long-term results of treatment was conducted by studying the indices of total and disease-free survival of patients with OC. Thus, the overall 5-year survival rates of patients with oncogynecologic diseases after complex therapy in combination with immunotherapy were as follows: in the 1st group of patients with cervical cancer receiving EIPHT without plasmapheresis -  $69.3 \pm 6.2\%$  ( $P = 0.037$ ); in the 2<sup>nd</sup> group of patients with cervical cancer receiving EIPHT with preliminary plasmapheresis -  $74.3 \pm 7.1\%$  ( $P = 0.041$ ); in the 3<sup>rd</sup> control group of patients with cervical cancer without immunotherapy -  $58.7 \pm 5.8\%$ ; in the 4th group of patients with OC receiving EIPHT without plasmapheresis -  $71.5 \pm 6.7\%$  ( $P = 0.036$ ); in the 5<sup>th</sup> group of patients with ovarian cancer receiving EIPHT with plasmapheresis -  $76.5 \pm 6.3\%$  ( $P = 0.043$ ) and in the 6th control group of patients with non-immunotherapy -  $62.5 \pm 6.1\%$ . The conducted studies made it possible to conclude that the greatest effectiveness in the complex treatment of patients with cervical cancer and stage II-III cancer has an immunotherapy scheme including intermittent plasmapheresis followed by EIPHT, the use of which in complex therapy of oncogynecologic diseases allowed to increase the five-year survival rates of patients. The median progression-free survival (PPhS) in patients with cervical cancer in the EIPHT group was 7.2 months. (95% CI 6.5-7.9), in the group with EIPHT and plasmapheresis - 7.7 months. (95% CI 7.2-8.2) and in the control group 5.7 months. (95% CI 4.8-6.6), ( $p = 0.0031$ ). The median overall survival (OS) in the EIPHT group was 13.5 months. (95% CI 11.3-15.7), in the group with EIPHT and plasmapheresis - 14.2 months. (95% CI 12.1-16.3) and in the control group 12.4 months. (95%

CI 10.8-13.9,  $p = 0.0027$ ). The observed risk ratio (hazard ratio, HR) of progression in the group of cervical cancer patients with EIPHT (HR 0.737, 95% CI 0.665-0.809,  $p = 0.035$ ) decreases by 26.3% compared with the control group and the death risk ratio (HR 0.911; 95% CI 0.868-0.954,  $p = 0.031$ ) by 8.9%. In the group with EIPHT and plasmapheresis, these indices were (HR 0.649, 95% CI 0.586-0.712,  $p = 0.037$ ) and (HR 0.855, 95% CI 0.794-0.916,  $p = 0.034$ ), and their decrease was 35.1% and 14.5% respectively. The median progression-free survival (PPhS) in patients with OC in the EIPHT group was 9.3 months. (95% CI 7.6-11.0), in the group with EIPHT and plasmapheresis - 10.2 months. (95% CI 8.5-11.9) and in the control group 7.8 months. (95% CI 6.5-9.1), ( $p = 0.036$ ). The median overall survival (OS) in the EIPHT group was 14.8 months. (95% CI 12.4-17.2), in the group with EIPHT and plasmapheresis - 15.6 months. (95% CI 13.2-18.0) and in the control group - 13.6 months. (95% CI 11.4-15.8,  $p = 0.041$ ). The observed hazard ratio (HR) of progression in patients with OI in the EIPHT group (HR 0.808, 95% CI 0.682-0.934,  $p = 0.035$ ) decreases by 19.2% compared with the control group and the death risk ratio (HR 0.912, 95% CI 0.878-0.946,  $p = 0.037$ ) by 8.8%. In the EIPHT and plasmapheresis group, these values were (HR 0.692, 95% CI 0.604-0.780,  $p = 0.040$ ) and (HR 0.855, 95% CI 0.787-0.923,  $p = 0.038$ ) and a decrease of 30.8% and 14.7% respectively. Carrying out EIPHT with plasmapheresis contributed to an even more pronounced decrease in the side effects of cytostatic treatment on the patient's body. In the patients of this group, in half the cases and more, the main clinical manifestations of the toxicity of chemotherapy were suppressed. Direct changes in the subjective state of patients with OC after treatment were determined according to the WHO ECOG scale. It was shown that the implementation of immunocorrection methods led to a decrease in the severity of the general condition of patients. In this case, a more pronounced effect on the reduction in the severity of the general condition of the patients was noted after the EIPHT with plasmapheresis. Assessment of the quality of life of patients with cervical cancer and OC after the treatment was determined by the SF-36 questionnaire. The study showed that the quality of life of patients with cervical cancer and OC after immunoregulatory measures was significantly higher than in the control group of patients without immunotherapy, which was expressed in an increase in both physical and mental health components. The parameters of the overall 5-year survival of patients with oncogynecologic diseases after complex therapy in combination with immunotherapy were: in the 1st group of patients with cervical cancer receiving EIPHT without plasmapheresis -  $69.3 \pm 6.2\%$  ( $P = 0.037$ ); in the 2nd group of patients with cervical cancer receiving EIPHT with preliminary plasmapheresis -  $74.3 \pm 7.1\%$  ( $P = 0.041$ ); in the 3rd control group of patients with cervical cancer without immunotherapy -  $58.7 \pm 5.8\%$ ; in the 4th group of patients with OC receiving EIPHT without plasmapheresis -  $71.5 \pm 6.7\%$  ( $P = 0.036$ ); in the 5th group of patients with ovarian

cancer receiving EIPHT with plasmapheresis -  $76.5 \pm 6.3\%$  ( $P = 0.043$ ) and in the 6th control group of patients with non-immunotherapy -  $62.5 \pm 6.1\%$ . The conducted researches made it possible to conclude that the greatest effectiveness in reducing the side effects of chemotherapy in the complex treatment of patients with cervical cancer and stage II-III stages as well as in improving the subjective state of patients and their quality of life, has an immunotherapy scheme that includes intermittent plasmapheresis followed by EIPHT, which reduces the main clinical manifestations of toxicity of chemotherapy, improves the subjective state of patients and their quality of life. In addition, the use of EIPHT techniques in the complex therapy of oncogynecologic diseases made it possible to increase the five-year survival rates of patients.

Therefore, the use of EIPHT techniques in the complex therapy of oncogynecologic diseases makes it possible to increase the parameters of the five-year total and disease-free survival of patients with cervical cancer and ovarian cancer. The extracorporeal immunopharmacotherapy (EIPHT) technique developed by us has great prospects in oncological practice in connection with the possibility to remove the consequences of cancer and chemoradiation intoxication, and also to activate our own system of antitumor protection of the organism<sup>[4,5]</sup>, which positively affects the outcome of the disease and leads to an increase in quality and the life expectancy of the patient.

## CONCLUSION

The conducted researches made it possible to draw a conclusion that the greatest effectiveness in reducing side effects of chemotherapy in the complex treatment of patients with cervical cancer and stage II-III stage II, as well as in improving the subjective state of patients and their quality of life, has an immunotherapy regimen including intermittent plasmapheresis followed by EIPHT, which reduces the main clinical manifestations of toxicity of chemotherapy, improves the indicators of the subjective state of patients and their quality of life. In addition, the use of EIPHT techniques in the complex therapy of oncogynecologic diseases made it possible to increase the five-year survival rates of patients.

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