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Practical Opportunities of Immunopharmacotherapy in Oncogenicology (Review of Literature)

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Abstract The review presents the results of the use of extracorporal immunopharmacotherapy (EIFT) techniques in medical practice for the treatment of infectious, autoimmune diseases and septic complications. EIFT studies are presented as an accompanying therapy in the treatment of malignant tumors. The widespread practical implementation of EIFT is hampered by insufficient clinical testing in various diseases, a small range of studied drugs and the lack of adequate methods for predicting efficacy. In our own studies on the example of patients with cervical cancer of II-III stages it has been shown that the most effective in complex treatment has an immunotherapy scheme including intermittent plasmapheresis with subsequent EIFT which improves blood indices, reduces leuko- and lymphopenia and normalizes indicators of cellular and humoral immunity, reduces the main clinical manifestations of chemotherapy toxicity, improves the indicators of the subjective state of patients and their quality of life and also allows to increase the indicators of five year survival.

Keywords Malignant tumors, Plasmapheresis, Cervical cancer, Extracorporeal immunopharmacotherapy

1. Introduction

In modern oncology, the role of immunology has significantly expanded which provides new methods for diagnosing, monitoring and treating cancer, as well as correcting the complications of traditional treatment.

Numerous studies have shown that modern methods of immunotherapy in the treatment of malignant tumors can have a normalizing effect on the immune status of cancer patients, give an objective antitumor effect and also contribute to the regression of tumor pleurisy and ascites in chemoresistant 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 for the activation of specific and nonspecific immunity [11-12, 24-25].

Modern methods of extracorporal immunopharmacotherapy (EIFT) are an effective enhancement of therapeutic plasmapheresis. If during the plasmapheresis cellular elements are returned to the patient immediately after their separation from plasma, then with EIFT there is an additional release of the leukocyte fraction which is then processed outside the body with a specific drug aimed at increasing or decreasing (depending on the disease) of functional activity of the participating inflammatory cells and immune responses.

After a short incubation (1-3 hours) with the drug at 37°C, the cells are washed from the drug and returned to the patient's circulatory system. As a result, an additional immunocorrective effect is achieved. Extracorporeal treatment of leukocytes by immunomodulators has the following advantages:

1) cells during drug treatment are beyond the control of factors that are formed in the patient's body and prevent the activation of cells in vivo;
2) the drug is not administered directly to the patient (on the one hand, it excludes adverse reactions and complications and at the same time allows its use in concentrations much higher than therapeutic ones);
3) EIPT implies a very accurate and strictly metered contact of cells with a pharmacological agent in time;
4) cells induced in vitro and introduced into the organism extend their function exclusively to physiologically intended points of application, and their action spectrum is much narrower than the preparation spectrum of action at injecting into the organism.

This direction of immunotherapy has great prospects in oncological practice in connection with the ability to remove the effects of cancer and chemoradiation intoxication, as well as activate its own system of antitumor defense of the body.

Cancer patients, as a rule, have a pronounced comorbid pathology, advanced age, immunodepression, aggravated by preoperative radiation therapy or several courses of

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chemotherapy. The secondary postoperative immunodeficiency arising in them when performing traumatic and extensive surgical interventions may contribute to the development of septic complications.

Still, the main methods of treatment of malignant neoplasms remain surgery and chemoradiation therapy.

It is believed that the implementation of organ-sparing and functionally sparing approaches in combination with immunotherapy methods in the treatment of cancer patients is a relevant and promising scientific direction, allowing to increase the effectiveness of the treatment as well as improve the quality of life and reduce the time of social and psychological rehabilitation [1-2, 27].

Conducting effective, intensified chemotherapy is often limited by the toxic effects of cytostatics high doses which have myelosuppression, increasing the risk of severe bacterial and fungal infections which can be fatal.

The severity of the myelosuppression onset, as the main manifestation of intoxication depends both on the mechanism of action and the combination of anticancer drugs included in the combination used, and on their dosages and duration of chemotherapy.

According to literary data, during chemotherapy, leukopenia of grade 1–2 develops in 90% of cases and grade 3-4 – in 30–40% of patients and requires maintenance therapy for several weeks. Terms of treatment are violated which also worsens patient survival. All this is a serious factor limiting the planned intensity of antitumor chemotherapy and, as a rule, requires a delay in the next course of treatment or a decrease in doses of cytostatics which affects the effectiveness of antitumor treatment [18-19, 26]. When traditional methods of stopping acute or chronic endotoxicosis, autoimmune or immunocomplex processes become untenable, extracorporeal methods of active immunocorrection may be required by clinicians.

Earlier limited range of treatment of renal failure, today extracorporeal methods are increasingly used in medical practice in order to replace the impaired functions of various organs and system. Various systems and techniques of extracorporal hemocorrection - diffusion, convection, filtration, sorption, apheresis and others directly affect the molecular and electrolyte composition of the blood and thereby affect all structures of the human body, allowing to correct, restore, replace and maintain homeostasis in severe multiorgan dysfunction. Opportunities of new extracorporeal molecular technologies allow them to be successfully introduced into intensive therapy of severe cardiac and respiratory failure, acute renal damage and acute hepatic dysfunction of various origins, in the complex treatment of severe septic diseases, gross metabolic disorders, and to correct the imbalance of immune homeostasis et al. [23]. Plasmapheresis which is widely used in clinical practice eliminates the blockade of the macrophage system and simultaneously optimizes the functions of injured organs. The receptor sensitivity to hormones is restored (both its own endocrine system and introduced into the body), receptors that bind to drugs are unblocked, which explains the increase in the body's sensitivity to drug therapy. One of the mechanisms that provide the therapeutic effect of plasmapheresis is the deplassing of cellular elements. Along with the plasma pathological elements adsorbed on the cell surface are removed, the vital activity of the cells changes, new interactions with other cells and regulatory facts arise [5, 15, 22]. There is a dynamic equilibrium of concentrations of substances in the intracellular, extracellular and intravascular spaces in the body. A change in concentration in one of them (in this case, in the intravascular) leads to a redistribution in the others. Therefore, immediately after plasmapheresis, a significant decrease in the level of pathological products is observed, but after a few hours their content increases due to the intake of substances from the vascular bed that were previously in the interstitium or even in the cells. The following plasmapheresis sessions contribute to the removal of these metabolites, which leads to a pronounced therapeutic effect, since the main part of the harmful products is in extravascular spaces [21, 22].

Modern methods of extracorporal immunopharmacotherapy (EIFT) are in essence an effective extension of therapeutic plasmapheresis. If during the latter cellular elements immediately after their separation from plasma are returned to the patient, then with EIFT there is an additional release of the leukocyte fraction, which is then processed outside the body with a specific drug aimed at increasing or decreasing (depending on the disease) the functional activity of the participating inflammatory cells and immune responses. After a short incubation (1–3 hours) with the preparation at 37°C, the cells are washed from the preparation and returned to the patient's circulatory system. As a result, an additional immunocorrective effect is achieved [5, 15]. The implementation of the idea of the directional transport of drugs using EIFT goes along the line of using red blood cells, leukocytes and platelets as containers for drug delivery. In the role of an object for directional transport may be antibacterial, chemotherapeutic agents, contrast agents, etc., moreover, the list includes more and more new drugs. The advantage of extracorporeal pharmacotherapy is in its point-like effect by incubating blood elements with the invitro preparation, which allows to avoid undesirable effects of drugs on the organism as a whole, as well as reduce the required doses [5, 6, 32].

With various diseases, including those of oncological nature, the immune system mobilizes all its reserves to fight infectious and other agents that are far from infinite and, ultimately, comes its depletion. The increase in endotoxemia acts overwhelmingly on all components of cellular and humoral immunity leading to even deeper immunosuppression which can be described as "immune distress syndrome." The development of endotoxemia in the described critical conditions is often described as a "systemic inflammatory response syndrome" which can be the answer not only to infection and sepsis, but also to any traumatic aggression and stress [4, 30].

Despite a wide range of effective antibiotics for treating infections, sepsis remains the main cause of morbidity and

mortality for patients admitted to the intensive care unit. Over the years, multiple extracorporal methods have been developed to affect circulating levels of inflammatory mediators such as cytokines and chemokines, the complement system, as well as coagulation system factors.

These include high molecular hemofiltration, the use of high-contrast membranes and adsorption-based systems such as bound plasma adsorption and a polymyxin-B column. In addition, new experimental systems have emerged that use human phagocytic cells and immobilized antibodies for targeted immunomodulation. In the context of limited resources and growing access to technology, a better understanding of these therapies is required before they can be properly integrated into standard clinical practice in the hope of influencing major clinical outcomes [29, 31].

In various studies, it has been shown that EIFT using such drugs as diucifon, IL-2, immunofan, prednisolone, leads to the development of a fast and lasting therapeutic effect in various pathological conditions: severe atopic syndrome, infectious bronchial asthma, thermal lesions, in patients with sepsis.

At the same time, the effectiveness of EIFT methods significantly exceeds the efficiency of standard drug therapy in intensive care of the multiple organ failure syndrome (MOFS) and is not accompanied by characteristic complications and side effects of traditional drug therapy. After treating diseases such as rheumatoid arthritis, autoimmune thyroiditis, glomerulonephritis, multiple sclerosis, systemic lupus erythematosus, dermatosclerosis, neurodermatitis, eczema, autoimmune hepatitis, diabetes mellitus and many others, remission of the disease was observed in more than 90% of patients after the first course of treatment. It is important to note that the duration of this treatment course is usually 10-14 days, and the duration of remission resulting from this treatment was 10-12 months and extended to 3 - 5 years or more in some patients. With the general therapy of these diseases, the treatment is usually not less than 3 weeks, but the remission rarely exceeds half a year [17, 28].

In the study of Mendelenko M.M. et al. (2001) the effectiveness of using cycloferon as a pharmaceutical preparation for EIFT was shown. For this purpose, leukocytes obtained from 5 ml of venous blood of 17 healthy individuals were stimulated with different doses of cycloferon for 1 hour. The obtained results indicate that incubation of blood leukocytes with cycloferon leads to an obvious increase in IFN-alpha production. The dose-dependent effect of stimulation is observed in the concentration range of cycloferon from 50 mg/l to 200 mg/l.

Cycloferon poorly induces IFN-alpha production by leukocytes (50-150 ng/l) compared with phytohemagglutinin and other nonspecific or bacterial stimulants.

However, this amount of IFN-alpha may be adequate to stimulate the immune response if the patient is reinfused with a large number of autologous leukocytes activated by cycloferon isolated from 100-400 ml of blood. The effect of cycloferon is less expressed in the production of TNF-alpha, IFN-gamma and IL-4 by leukocytes in the range of studied doses. It should be noted that some features of the reaction of donor leukocytes can be observed in response to cycloferon.

The results indicate that it is possible in principle to use autologous leukocytes extracorporeally activated by IFN inducers for immunotherapy [16].

In another work done by Snezhko T.A. (2015) the effect of EIPT on the efficacy of treatment of patients with primary resistant of Hodgkin's lymphoma and the first early relapse of the disease IIB-IVB stages was studied.

The study was based on 60 patients who received polychemotherapy for line II (DHAP scheme) for the first early relapse or Hodgkin's lymphoma resistant to therapy. All patients were divided into 2 groups of 30 people - the main and control. In patients of the main group, the treatment complex was supplemented with EIFT using RIL-2 and IFN-α2b. It was shown that the use of EIFT in the complex treatment of patients when compared with standard II-line chemotherapy according to the same scheme, significantly increases the overall response rate from 60% to 83.3% ($p \leq 0.05$), reduces the risk of progression on background therapy from 13.3% to 3.4% and allows high-dose chemotherapy with stem cell autotransplantation to more patients (16.6% versus 6.7%). There was a tendency to improve two-year overall and relapse-free survival in the group of patients who received immunopolychemotherapy (64.7% versus 60.9%). The inclusion of EIFT in the treatment regimen reduced the number of toxic complications of treatment: leukopenia –17.5% versus 40% ($p \leq 0.05$), dyspeptic phenomena - 33.3% versus 70.0% ($p \leq 0.05$). It was also shown that the EIFT method ensures the safety of the immune system under exposure to cytostatics and leads to a twofold decrease in their pro-apoptotic effect on immunocompetent cells (16.7 ± 4.25% versus 29.0 ± 4.37%, $p \leq 0.05$) which allows for better preservation of the T-cell component of the immune system in patients with recurrent and refractory Hodgkin's lymphoma compared with patients undergoing standard polychemotherapy [20].

In the studies of Ausheva T.V. (2005) the main study group included 30 patients with primary verified malignant bone tumors (19 men and 11 women). The use of preoperative autochemotherapy in combination with extracorporeal magnetic blood treatment in the complex treatment of malignant bone tumors reduced the frequency of performing operative surgical interventions to 6.7 ± 4.5% whereas in the traditional treatment of this pathology it reaches 56% ± 2.7. Autohemochemotherapy combined with extracorporeal magnetic blood treatment for malignant bone tumors leads to partial regression of the primary tumor in 76.7 ± 7.7%, stabilization -23.3 ± 7.7%, reduction of pain in 100% of patients, improvement of limb function in 26.7 ± 8.0%. The two-year survival rate when using autohemotherapy in combination with extracorporeal magnetic blood treatment is 90 + 5.5%, which is significantly ($p < 0.01$) higher than two-year survival of patients who used traditional methods of treatment of this pathology (69.3 ± 2.5%). At the same time, autohemotherapy

in combination with extracorporeal magnetic treatment of the blood does not have a toxic effect, as evidenced by a decrease in the level of creatinine from 130.0 ± 3.7 mmol / l to 102.1 ± 5.6 mmol / l and average weight molecules from 0.36 ± 0.04 to 0.25 ± 0.03 in the course of the treatment, as well as the lack of dynamics of the enzymatic activity of transaminases, creatine phosphatekinase, blood bilirubin level [3].

At the same time, it should be noted that widespread practical implementation of EIFT is hampered by insufficient clinical testing in various diseases, a small range of studied drugs, and the lack of adequate methods for predicting efficacy. The lack of scientific evidence that reveals specific mechanisms for the realization of the effect of leukocyte-modified drugs often leads to an empirical approach to the appointment of extracorporeal immunocorrection schemes in patients [7, 13, 14].

In our own research, we studied the efficacy of treatment of patients with cervical cancer (CC) II-III stages by developing and implementing methods of accompanying EIFT. The examination included 268 patients with cervical cancer of the T2-3N0-1M0 stages (stage II-III) who were examined and treated in the gynecological and chemotherapy departments of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology (RSSPMCOR) from 2004 to 2014. All patients with cervical cancer received complex treatment, including neoadjuvant polychemotherapy (NAPCT), surgery and / or chemoradiotherapy (CRT) or two-stage combined radiation therapy, including remote telegrammatherapy (DTGT) and intracavitary brachytherapy. DTGT was performed on a “Theratron” or “AGAT-R” apparatus in a split course with a single local dose of 2 Gy to a summary local dose of 50 Gy, 5 times a week. Brachytherapy was performed on the apparatus "Gammamed" with a single local dose of 5 Gy to a summary local dose of 45-55 Gy, every other day. At the first stage, all patients with cervical cancer have received systemic or intraarterial polychemotherapy according to the scheme: cisplatin 50 mg/m^2 + 5-fluorouracil 1000 mg/m^2 for 4 days, 4-6 courses once 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.

In accordance with the applied methods of immunopharmacotherapy as part of complex treatment, the patients were divided into the following groups: 1) control without immunotherapy - 118 (44.0%); 2) EIFT - 83 (31.0%); 3) EIFT + plasmapheresis (PF) - 67 (25.0%) patients.

The age of the examined patients in patients with cervical cancer was from 21 to 74 years (mean age 45.7 ± 7.07 years). Morphological analysis of the surgical material and biopsy results in patients with cervical cancer showed that the majority of the examined patients (255 (95.1%)) had a histological squamous cervical cancer, 13 (4.9%) patients had clear cell adenocarcinoma.

Methods of extracorporeal immunopharmacotherapy (EIFT) were designed, first of all, to reduce toxic manifestations after chemotherapy and radiation therapy as well as to improve the general condition of the patient after extensive surgery. After carrying out EIFT techniques in cervical cancer patients, hematopoietic improvement was observed, as well as normalization of the immune status which was expressed in an increase in the number of erythrocytes and leukocytes, normalization of the immunoregulatory index and humoral immunity, an increase in phagocytic reactions and an increase in the bactericidal ability of neutrophils, as well as a decrease in the level of proinflammatory cytokines. In addition, the imbalance in lipid peroxidation and antioxidant protection systems was significantly reduced.

The use of EIFT techniques allowed, in more than half of the cases, to stop the main clinical manifestations of chemotherapy toxicity, eliminate signs of III and IV degrees of toxicity and also reduce the levels of biochemical parameters of endogenous intoxication in patients with cervical cancer. Immunotherapy measures significantly reduced the degree of radiation reactions from the pelvic organs in patients with cervical cancer.

At the same time, the subjective state of the ECOG scale (WHO), as well as the indicators of the physical and mental components of their quality of life, according to the SF-36 questionnaire significantly improved in patients.

Indicators of total 5-year survival in patients with cervical cancer II-III stages after treatment were: in the group of patients receiving EIFT without plasmapheresis - 69.3 ± 6.2% (P = 0.037), in the group of patients receiving EIFT with preliminary plasma exchange - 74.3 ± 7.1% (P = 0.041) and in the control group without immunotherapy - 58.7 ± 5.8%.

The observed risk ratio (hazardratio, HR) of progression in the group of patients with cervical cancer with EIFT (HR 0.737; 95% CI 0.665-0.8009; p = 0.035) decreases by 26.3% compared to 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 EIFT and plasmapheresis, these indicators 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.

Molecular biological markers p53, VEGF and Ki-67 were present in the majority of patients with cervical cancer (73.3, 80.0 and 76.7%, respectively). At the same time, markers of Bcl-2 and EGFR were detected in 36.7 and 30.0% of patients, respectively.

A comparative assessment of the dependence of 5-year survival of patients on the level of molecular biological markers in tumor tissue showed that the markers of p53, VEGF and Ki-67, as well as the level of proliferative activity of the tumor, have the greatest prognostic significance in terms of the treatment effectiveness.

Based on the studies, an algorithm was proposed for applying EIFT methods in patients with ŠMII-III stages which takes into account such factors as tumor volume, degree of differentiation, level of tumor markers p53, VEGF, Ki-67, tumor proliferative activity and peroxidation lipids on

diene conjugates [8-10].

Studies have shown that the immunotherapy scheme, including intermittent plasmapheresis with subsequent EIFT, which improves blood parameters, reduces leuko- and lymphopenia, normalizes indicators of cellular and humoral immunity, reduces the main clinical manifestations of toxicity chemotherapy, improves the indicators of the subjective state of patients and their quality of life, and also allows to improve the five-year survival rate of the patients.

Since EIFT 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, if indicated, it is necessary to conduct hemostatic, general strengthening, cardiotropic, anesthetic, anticoagulant, neurotropic, hepatotropic therapy in standard regimens.

2. Summary

An analysis of current literature data makes it possible to conclude that the immune system is at the center of all attempts currently being made to improve the effectiveness of antitumor therapy and the task of activating the antitumor potential of the immune system is the most important in modern oncology.

With time, immunotherapy may be the most promising method for treating tumors as it is a physiologically adequate method which restores the natural forces of the patient's body to combat the neoplastic process and infectious complications often arising during the treatment.

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, plasmapheresis, perfusion of blood through sorbents, treatment with various activators and etc.

A promising direction in the treatment of malignant tumors at the present stage of immunotherapy development is a combination of methods for the activation of specific and nonspecific immunity. Unlike conventional immunotherapy methods, when immunomodulating drugs are taken as tablets, or introduced intramuscularly or intravenously, the use of extracorporeal immunopharmacotherapy (EIFT) methods allows us to selectively isolate the blood cells of the immune system (leukocytes) directly from the blood. The isolated leukocytes are processed by special technologies with immunomodulating drugs and then, already activated, they are returned back into the vascular bed after which they are able to synthesize the activating factors of the immune system and also to activate other cells of the immune system.

This direction of immunotherapy has great prospects in oncological practice in connection with the ability to remove the effects of cancer and chemoradiation intoxication, as well as to activate own system of antitumor defense of the body.

However, there is very little information in the literature about the use of the EIFT method for the treatment of oncologic diseases.

In addition, many methods of immunotherapy in the field of oncology are still empirically used. 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 effect of immunotherapy methods on the immediate and long-term results of antitumor therapy require the efforts of many researchers.

REFERENCES

[1] Alimhodzhaeva L.T. Cycloferon and extracorporal therapy in the optimization of neoadjuvant PCT of locally advanced breast cancer // Medical Journal of Uzbekistan. Tashkent: 2007; 1: 54-57.

[2] Antoneeva I.I. Immunopathology and immunotherapy of ovarian cancer. Monograph. Ulyanovsk: 2007; 143.

[3] Ausheva T.V. Autohemotherapy in combination with extracorporeal magnetic treatment of blood in the complex treatment of malignant bone tumors: author's abstract, PhD. - Rostov-on-Don: 2005.

[4] Voinov V.A. Tactics of efferent therapy in sepsis // Bulletin of Surgery named I. Grekov. –2013; 2: 75-78.

[5] Gushchin N.S., Leskov V.P., Prozorovsky N.S. Experimental justification of extracorporeal immunopharmacotherapy // Actual issues of immunopharmacotherapy. M; 1987; 71-82.

[6] Zharinov G.M., Molchanov O.E., Agafonova M.V., Rumyantseva S.Yu. The first experience of local immunotherapy of cancer patients // Cytokines and inflammation. 2002; 1(2): 75.

[7] Zinchenko S.V. Immunomodulators in the complex therapy of oncological patients (literature review) // Volga Cancer Bulletin. 2014; 1: 57-64.

[8] Kamishov S.V., Pulatov D.A., Nishanov D.A., Yuldasheva N.Sh. The effect of the expression of tumor markers on the results of the treatment of patients with cervical cancer who received accompanying immunotherapy // Euraz Oncolog Jour. 2017; 1: 68-76.

[9] Kamishov S.V., Pulatov D.A., Yuldasheva N.Sh. Study of the role of extracorporeal immunopharmacotherapy in reducing the toxic effects of chemoradiotherapy in patients with cervical cancer // Euraz Oncolog Jour. 2015; 7(4):28-34.

[10] Kamishov S.V., Pulatov D.A., Yuldasheva N.Sh., Balenkov O.Yu. Study of the effects of immunotherapy on peroxidation processes in the accompanying treatment of cervical cancer // Euraz Oncolog Jour.2015; 7(4): 60-66.

[11] Kiseleva E.A., Volkova S.D., Chechetkin A.V. Development of methods of gravitational blood surgery in a specialized medical institution // Bulletin of the blood service of Russia.

2016; 3:10-14.

[12] Clinical use of extracorporeal treatment methods / Ed. N.N. Kalinin. - M.: Trekpor Technology. 2006; 168.

[13] Korotky N.G., Ujukhu V.Yu., Flaks G.A. The first experience of cytapheresis with extracorporal therapy with leukinferon in patients with psoriasis // Russian Journal of Skin and Sexually Transmitted Diseases. 1998; 3: 36-38.

[14] Kostyuchenko A.L. Efferent therapy. SPb.: Foliant. 432.

[15] Leskov V.P., Gushchin I.S. Extracorporeal Immunopharmacotherapy // Pulmonology. 1994; 4: 10-14.

[16] Mendelenko M.M., Kravchenko I.N., Agadzhanyan K.V., Kravchenko A.I. Obtaining cytokines from blood leukocytes activated by cycloferon // Russ Immunolog Jour. 2001; 4(6): 377-382.

[17] Nikogosyan S.O., Kuznetsov V.V. Ovarian cancer: issues of diagnosis and modern methods of treatment // Doctor; p2010; 9: 2-9.

[18] Popovich A.M. Immunotherapy in oncology. Handbook of immunotherapy for the practitioner. -SPb: Dialogue; 2002P.335-352.

[19] Romanes M.A. Extracorporeal immunopharmacotherapy of patients with psoriasis: author's abstract, PhD. Moscow; 2010.

[20] Snezhko T.A. Extracorporeal immunotherapy in complex treatment of patients with relapses and refractory course of Hodgkin's lymphoma: author's abstract, PhD. Rostov-on-Don; 2015.

[21] Sumina D.S. Clinical and immunological efficacy of extracorporeal immunopharmacotherapy in the complex treatment of psoriasis: author's abstract, PhD. Kursk; 2009; 24.

[22] Yudina S.M. Extracorporeal immunopharmacotherapy of patients with sepsis and severe purulent infection // Bulletin of intensive therapy. 1995; 2: 44-48.

[23] Yarustovsky, MB, Abramyan, MV, Krotenko, NP, Komardina, EV, Methods of Molecular Transfusion in the Intensive Care of Critical Conditions, Bulletin of Russia Academy of Sciences. 2016; 4: 13-19.

[24] Bambauer R., Latzo R., Schiel R. Therapeutic plasma exchange and selective plasma separation methods. Fundamental technologies, pathology and clinical results. Pabst Science Publishers, Lengerich/Berlin; 2013; 395–402.

[25] Bhardwaj N. Harnessing the immune system to treat cancer // J. Clin. Invest. 2007; 117: 1130–1136.

[26] DiSaia P.J., Creasman W.T. (eds.). Clinical gynaecologic oncology. 7th ed. Mosby Elsevier: 2007; 812.

[27] Gattinoni L., Powell D.J., Rosenberg S.A., Restifo N.P. Adoptive immunotherapy for cancer: building on success // Nat. Rev. Immunol. 2006; 6: 383–393.

[28] Gavrusev A., Strotsky A., Malashchitsky D. Extracorporeal magnetic therapy for the treatment of chronic prostatitis // Eur. Urol. Suppl. 2017; 16(5): 2192.

[29] Panagiotou A., Gaiao S., Cruz D.N. Extracorporeal therapies in sepsis // J. Intensive Care Med. 2013; 5(28): 281-295.

[30] Rosenberg S., Restifo N., Yang J., Morgan R., Dudley M. Adoptive cell transfer a clinical path to effective cancer immunotherapy // Nature Reviews Cancer. 2008; 8: 299–308.

[31] Sakuraba A., Naganuma M., Hibi T., Ishii H. Intensive therapy of granulocyte and monocyte absorption apheresis induces rapid remission in patients with ulcerative colitis // Gastroenterology. 2003; 4(124): 1379.

[32] Yoshioka S., Fujiwara H., Nakayama T. Intrauterine administration of autologous peripheral blood mononuclear cells promotes implantation rates in patients with repeated failure of IVF–embryo transfer // Hum Reprod. 2009;21: 3290–3294.