International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 05, 2020
ISSN: 1475-7192

Methods of Extracorporeal Immunopharmacotherapy: From General Medical Clinical Practice to Oncologic Practice (Literature Review)

Mirzagoleb N. Tillyashaikhov, Sergey V. Kamishov and
Mahsuda A. Tillyashaikhova

Abstract--- *The review presents the results of the application of extracorporeal immunopharmacotherapy (EIFT) techniques in medical practice for the treatment of infectious, autoimmune diseases, as well as septic complications. EIFT studies as an accompanying therapy in the treatment of malignant tumors are presented. The widespread practical implementation of EIFT is hindered by inadequate clinical testing for various diseases, a small spectrum 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 the II-III stages, it was shown that the immunotherapy regimen is most effective in complex treatment, including intermittent plasmapheresis followed by EIFT, which improves blood counts, increases leuko- and lymphopoiesis, normalizes cellular and humoral immunity, reduces the main clinical manifestations of chemotherapy toxicity, improves indicators of the subjective state of patients and their quality of life, and also allows you to increase indicators of five year survival rate.*

Keywords--- *Malignant Tumors, Plasmapheresis, Cervical Cancer (CC), Extracorporeal Immunopharmacotherapy (EIPhT).*

I. INTRODUCTION

In modern oncology, the role of immunology has significantly increased, which provides new methods for diagnostics, monitoring and treating cancer and also correcting 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. At the present stage of immunotherapy development, combination of methods for the activation of specific and non-specific immunity is a promising way in treatment of malignant neoplasms [11,12,24,25].

II. MATERIAL AND METHOD

This work is literary review of extracorporeal immunopharmacotherapy methods, which are now widely used. The paper also discusses data of our own research on this subject.

Mirzagoleb N. Tillyashaikhov, Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology.
Sergey V. Kamishov, Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology.
Mahsuda A. Tillyashaikhova, The Uzbekistan State Institute of Arts and Culture.

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

This review discusses and summarizes the results of scientific works on the methods of extracorporeal immunopharmacotherapy since 1987. The review includes data both from domestic scientists and specialists from the CIS countries and other foreign countries. Preparing the review, data from the portal of the Russian scientific electronic library elibrary.ru, and the following on-line resources were widely used: Medicine: ref. database http://www.viniti.ru/bnd.html, Russian medicine: electronic catalog http://www.scsml.rssi.ru/, pubmed.gov, High Wire Press, The Cochrane Library, Google scholar.

III. Results And Discussion

As a rule, oncologic patients have a pronounced concomitant pathology, old age, immunosuppression, exacerbated by preoperative radiation or several chemotherapy courses. The secondary postoperative immunodeficiency that occurs in them when performing traumatic and voluminous surgical interventions can contribute to the development of purulent-septic complications. Surgery and chemoradiotherapy still remain the main methods of treating malignant neoplasms. Organ-preserving and functional-sparing approaches in combination with immunotherapy methods in the treatment of cancer patients are believed to be an urgent and promising scientific direction that can improve the effectiveness of treatment, and improve quality of life and reduce the period of social and psychological rehabilitation [1,2, 27].

Effective, intensified chemotherapy is often limited by the toxic effect of high cytostatics doses, which have myelosuppressive activity increasing the risk of severe bacterial and fungal infections, which can lead to death. The severity of the of myelosuppression, as the main manifestation of intoxication, depends both on the mechanism of action and combination of the anticancer drugs included in the combination used, and on their dosages and duration of chemotherapy. According to published data, chemotherapy results in 90% of cases in leukopenia of 1-2 degrees, and 3-4 degrees in 30-40% of patients, requiring maintenance therapy for several weeks. The terms of treatment are disturbed, which also worsens the survival of patients. All this is a serious factor limiting the planned intensity of antitumor chemotherapy and, as a rule, requires delaying the next course of treatment or lowering the doses of cytostatics, which affects the effectiveness of antitumor treatment [18,19,26].

When traditional methods of arresting acute or chronic endotoxicosis, autoimmune or immunocomplex processes are ineffective, clinicians can use methods of active immunocorrection. Being previously limited only by renal failure treatment, today extracorporeal methods are increasingly used in medical practice to replace impaired functions of various organs and systems. Different systems and methods of extracorporeal haemocorrection - diffusion, convection, filtration, sorption and others, immediately affect blood molecular and electrolyte composition and thus affect all structures of the human body, allowing to correct, restore, replace and maintain homeostasis in severe multiple organ dysfunction. Possibilities of new extracorporeal molecular technologies allow introduce them successfully in intensive therapy of severe heart and respiratory failure, acute renal damage and acute liver dysfunction of various genesis, in severe infectious septic conditions treatment, gross metabolic disorders, and also use to correct immune homeostasis imbalance et al. [23]. Plasmapheresis, which is wildly used in clinical practice, eliminates the blockade of the macrophage system and at the same time optimizes the functions of damaged organs. The sensitivity of the receptors to hormones (both of own endocrine system and those introduced

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

into the body) is restored, receptors that bind to drugs are relieved, thus explaining the increased body sensitivity to drug therapy. One of the mechanisms that provide the therapeutic effect of plasmapheresis is cellular elements deplasmation. Pathological elements adsorbed on the cell surface are removed with plasma, vital activity of the cells changes, new interactions with other cells and regulatory facts develop [5,15,22]. There is dynamic balance of substance concentrations in the intracellular, extracellular and intravascular spaces of the body. Change in concentration in one of them (in this case, in intravascular) leads to the redistribution in others. Therefore, immediately after plasmapheresis a significant decrease in the level of pathological products, is observed, but in a few hours their content increases due to the intake of substances which were previously in the interstitium or even in the cells from the vascular bed. The following plasmapheresis sessions contribute to the removal of these metabolites, resulting in a pronounced therapeutic effect, since the majority of harmful products are in extravascular spaces [19,21,22]. Modern methods of extracorporeal immunopharmacotherapy (EIPhT) are in fact an effective extension of therapeutic plasmapheresis. If in the latter cellular elements are immediately returned to the patient after their separation from the plasma, then EIPhT causes an additional release of the leucocytic fraction, which is then treated externally with a certain drug used to increase or decrease (depending on the disease) the functional activity of the cells participating in the inflammation 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 [5.15]. The idea of targeted drug transport using EIPhT is realized through the use of red blood cells, white blood cells, platelets as containers for drug delivery. Antibacterial, chemotherapeutic agents, contrast agents, etc. can be used for targeted transport, moreover, this list includes more and more new medications. The advantage of extracorporeal pharmacotherapy is in its point effect due to the incubation of blood elements with the drug in vitro, which allows to avoid undesirable effect of drugs on the body as a whole, and also reduces the necessary doses [5,6,31]. In different diseases, including cancer, the immune system mobilizes all its reserves to fight infectious and other agents, which are far from unlimited and, ultimately, its depletion occurs. Endotoxicosis increase supresses all components of cellular and humoral immunity, leading to even deeper immunosuppression, which can be described as "immune distress syndrome." Endotoxemia development of in the described critical conditions is often characterized as a “systemic inflammatory response syndrome”, which can be a response not only to infection and sepsis, but also to any traumatic aggression and stress [4,30].

Despite a wide range of effective antibiotics to treat infection, sepsis remains the main cause of morbidity and mortality in patients admitted to the intensive care unit. For many years, different extracorporeal methods have developed to influence circulating levels of inflammatory mediators such as cytokines and chemokines, complement system, and coagulation factors. These include high molecular hemofiltration, use of high-contrast membranes and adsorption-based systems, such as adsorption bound plasma and a polymyxin-B column. Besides, new experimental systems have appeared that use human phagocytic cells and immobilized antibodies for targeted immunomodulation. In the context of limited resources and increased access to technology, better understanding of these methods of treatments is required before they can be properly integrated into standard clinical practice with the aim to influence main clinical outcomes [29,31]. Different studies showed that EIPhT using such drugs as diutsifon,

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

IL-2, immunofan, prednisone can lead to quick and persistent therapeutic effect in various pathologies - severe atopic syndrome, infection-dependent bronchial asthma, thermal lesions, sepsis. The effectiveness of EIPhT much higher than the effectiveness of standard drug therapy for intensive multiple organ insufficiency syndrome (IMOI) 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 can be observed in more than 90% of patients after the first course treatment. It is necessary to note that the duration of this course of treatment is usually 10-14 days, and the duration of remission obtained as a result of this treatment is 10-12 months and extended to 3-5 years or more in some patients. In general treatment of these diseases, the course of treatment, as a rule, is at least 3 weeks and remission are rarely more than six months [17.28]. In the study performed by Mendelenko M.M. et al. (2001) the effectiveness of cycloferon as a pharmaceutical for EIPhT was showed. For this purpose, leukocytes obtained from 5 ml of venous blood from 17 healthy individuals were stimulated with different doses of cycloferon for 1 hour. The obtained results showed that leukocytes incubation with cycloferon leads to a significant increase in IFN-alpha production. The dose-dependent effect of stimulation is observed in cycloferon concentration 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 non-specific 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 pronounced in the production of TNF-alpha, IFN-gamma and IL-4 by white blood cells in the range of doses studied. It should be noted that certain features of a donor white blood cell reaction can be observed in response to cycloferon. The results indicate a fundamental possibility of autologous leukocytes use extracorporeally activated by IFN inducers for immunotherapy [16].

In the other work by T. Snezhko (2015) the effect of EIPhT on the treatment of patients with primary-resistant Hodgkin's lymphoma and the first early relapse of stage IIB-IVB disease was studied. The study included 60 patients who received second-line polychemotherapy (DHAP) for the first early relapse or treatment-resistant Hodgkin's lymphoma. All patients were divided into 2 groups of 30 persons - the main and control. In patients of the main group, the treatment complex was supplemented with EIPhT using RIL-2 and IFN-α2b. It was shown that EIPhT, comparing with standard second-line polychemotherapy done following the same scheme, significantly increases the frequency of the general response to treatment from 60% to 83.3% ($p \leq 0.05$), reduces the risk of progression by during therapy from 13.3% to 3.4% and allows you to perform high-dose chemotherapy with autologous stem cell transplantation to more patients (16.6% versus 6.7%). A tendency towards the improvement in two-year general and relapse-free survival in the group of patients receiving immunopolychemiotherapy (64.7% versus 60.9%) was noted. EIPhT use in the treatment scheme contributed to a reduction in the number of toxic complications of treatment: leukopenia –17.5% versus 40% ($p \leq 0.05$), dyspeptic symptoms –33.3% versus 70.0% ($p \leq 0.05$). It was also shown that the EIPhT ensures the preservation of the immune system under the influence of cytostatics and leads to a twofold decrease in their proapoptotic effect on immunocompetent cells ($16.7 \pm 4.25\%$ versus $29.0 \pm 4.37\%$, $p \leq 0.05$), thus allowing T-cell chain of the immune system better preservation in patients with

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

recurrent and refractory Hodgkin's lymphoma in comparison with patients who underwent standard chemotherapy [20].

In the studies by Ausheva T.V. (2005) the main studied group included 30 patients with primary proved malignant bone tumors, 19 men and 11 women. The use of preoperative autohaemochemotherapy in combination with extracorporeal magnetic blood treatment in the complex treatment of malignant bone tumors has reduced the incidence of crippling surgical interventions to 6.7 ± 4.5%, while in the traditional treatment of this pathology it was 56% ± 2.7. Autohemochemotherapy in combination 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%, decrease of pain syndrome in 100% of patients, improvement of limb function in 26.7 ± 8.0%. The two-year survival rate in use of autohemochemotherapy in combination with extracorporeal magnetic blood processing is 90 + 5.5%, which is significantly ($p < 0.01$) higher than the two-year survival rate of patients treated with traditional methods (69.3 ± 2, 5%). Aautohemochemotherapy in combination with extracorporeal magnetic blood processing has no toxic effects, as evidenced by a decrease in creatinine level from 130.0 ± 3.7 mmol / L to 102.1 ± 5.6 mmol / L and mean molecular weight from 0.36 ± 0.04 to 0.25 ± 0.03 during treatment, and lack of dynamics of transaminase enzymatic, creatine phosphate kinase activity, and blood bilirubin level [3]. It should also be noted that insufficient clinical test for various diseases, small number of studied drugs, and the lack of adequate methods for predicting efficacy hinders the wide practical use of EIPHT. lack of scientific data showing specific mechanisms of leukocyte-modified drugs efficiency is often due to an empirical approach to prescribing extracorporeal immunocorrection in patients [7,13,14].

In our own studies, the effectiveness of treatment of patients with cervical cancer (CC) of II-III stages by developing and using methods of accompanying EIPhT was assessed. 102 patients with cervical cancer T2-3N0-1M0 stages (II-III clinical stages) who underwent examination and treatment in the gynecological oncology and chemotherapy departments of the RSNPMTSOiR MH RUz took part in the study. All patients with CC received complex treatment, including NAPCT, surgery and / or CLT or two-stage combined radiation therapy, including remote telegammotherapy (RTGM) and intracavitary brachytherapy. RTGM was performed on "Theratron" or "AGAT-R" with a split rate at ROD 2 Gy to SOD 50 Gy, 5 times a week. Brachytherapy was performed on a Gammamed apparatus with ROD of 5 Gy to a SOD of 45-55 Gy, every other day. At the first stage, all patients with CC received systemic or intra-arterial chemotherapy cisplatin 50 mg / m2 + 5-fluorouracil 1000 mg / m^2 for 4 days for 4-6 courses once every 3 weeks. Radiation therapy and chemotherapy were carried out both in the adjuvant and neoadjuvant modes. Surgical treatment was performed as a radical operation. In accordance with the methods used with immunopharmacotherapy as part of complex treatment, patients were divided into the following groups: 1) control without immunotherapy - 44.0%; 2) EIPhT - 31.0%; 3) EIPhT + plasmapheresis (PF) - 25.0% of patients. The mean age of the examined patients with CC was 45.7 ± 7.07 years. Morphological analysis of surgical material and biopsy results in CC patients showed that in the majority - 95.1% of the examined patients histologically revealed squamous cervical cancer, in 4.9% of patients there was clear cell adenocarcinoma [8,9].

EIPhT methodology: 200-250 ml of autologous blood was taken into sterile "Gemakon" or "Terumo" containers, incubated with one of the following immunomodulators: neovir in a total dose of 750 mg (for 3 procedures);

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

cycloferon - 750 mg (for 3 procedures) or polyoxidonium - 36 mg (for 3 procedures) at 37 ° C for 60-100 min and then the received the conjugate was reinfused to a patient.

EIFT method with plasmapheresis (EIPhT + PPh). If in general plasmapheresis the cellular elements after their separation from the plasma are immediately returned to the patient, in EIPhT to enhance the immunocorrective effect, they are additionally treated outside the body with a specific immunomodulator. 500-1000 ml of autologous blood was exfused into sterile “Gemakon” or “Terumo” containers and centrifuged at 3000 rpm for 30 minutes. 50-80 ml of the supernatant blood plasma containing antibodies, circulating immune complexes, cytokines, products of cell metabolism were removed. The resulting leukothrombomass and erythrocyte mass were incubated with one of the following immunomodulators: neovir in a total dose of 750 mg (for 3 procedures); cycloferon - 750 mg (for 3 procedures) or polyoxidonium - 36 mg (for 3 procedures) at 37 ° C for 60-100 min, then the conjugate was returned to the circulatory system of patients.

Methods of extracorporeal immunopharmacotherapy (EIFT) were primarily intended for reducing toxic effects after chemo- and radiation therapy, and also for improving the general state of patients after extensive surgery. After EIPhT in patients with CC improvement in hematopoiesis, and normalization of the immune status was observed expressed in increased number of red blood cells and leukocytes, normalization of the immunoregulatory index and humoral immunity, increased phagocytic reactions and increased bactericidal ability of neutrophils, and also in decreased level of pro-inflammatory cytokines. Besides, the imbalance in lipid peroxidation and antioxidant defense systems was significantly reduced.

The use of EIPhT allowed in more than half of cases to eliminate the main clinical manifestations of chemotherapy toxicity, signs of grade III and IV toxicity, and reduce biochemical parameters of endogenous intoxication in patients with CC. Immunotherapeutic measures significantly reduced the degree of radiation reactions in pelvic organs in patients with CC. At the same time, the patients significantly improved indicators of their subjective state according to the ECOG scale (WHO), and indicators of the physical and mental components of their quality of life according to the SF-36 questionnaire.

The overall 5-year survival rate for patients with cervical cancer of the II-III stages after treatment was: in the group of patients receiving EIPhT without plasmapheresis - 69.3 ± 6.2% (P = 0.037), in the group of patients receiving EIPhT with preliminary plasmapheresis - 74.3 ± 7.1% (P = 0.041) and in the control group without immunotherapy - 58.7 ± 5.8%. Risk ratio (hazard ratio HR) of progression in the group of patients with cervical cancer 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 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.

The majority of patients with CC (73.3, 80.0, and 76.7%, respectively) had molecular biological markers p53, VEGF, and Ki-67. At the same time, Bcl-2 and EGFR markers were found in 36.7 and 30.0% of patients, respectively. Comparative assessment of the 5-year survival rate dependence on molecular biological markers level in the tumor tissue showed that p53, VEGF and Ki-67 markers, as well as the level of tumor proliferative activity,

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

have the greatest prognostic value. Based on the studies, an algorithm was proposed for the application of EIPhT methods in stage II-III cervical cancer patients, which takes into account factors such as tumor volume, degree of differentiation, level of tumor markers p53, VEGF, Ki-67, tumor proliferative activity, and lipid peroxidation level by diene conjugates [8,9,10].

IV. CONCLUSION

The studies performed have shown that the most effective in the complex treatment of patients with CC stage II-III is the immunotherapy scheme, which includes intermittent plasmapheresis followed by EIPhT, which improves blood counts, increases leuko- and lymphopoiesis, normalizes cellular and humoral immunity, and reduces the main clinical manifestations of chemotherapy toxicity, improves indicators of the subjective state of patients and their quality of life, and also allows to increase the five-year survival rate of patients. Since EIPhT methods 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 there are indications, it is necessary first to do hemostatic, restorative, cardiotropic, analgesic, anticoagulant, neurotropic, hepatotropic therapy according to standard schemes.

REFERENCES

[1] Alimkhodzhaeva L.T. Cycloferon and extracorporeal therapy in 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 p.*
[3] Ausheva T.V. Autohemochemotherapy in combination with extracorporeal magnetic blood processing in the complex treatment of malignant bone tumors: diss... cand.med. sciences. - *Rostov-on-Don,* 2005.
[4] Voinov V.A. Tactics of efferent therapy in sepsis // *Bulletin of Surgery named after I.I. Grekov.* 2013;2:75-78.
[5] Gushchin N.S., Leskov V.P., Prozorovsky N.S. Experimental substantiation of extracorporeal immunopharmacotherapy // *Actual issues of immunopharmacotherapy. Moscow*, 1987. P. 71 82.
[6] Zharinov G.M., Molchanov O.E., Agafonova M.V., Rumyantseva S.Yu. The first experience of the local immunotherapy of oncogynecological patients // *Cytokines and inflammation.* 2002. V.1. –№2. –P.75.
[7] Zinchenko S.V. Immunomodulators in the treatment of cancer patients (literature review) // *Volga Oncology Bulletin.* 2014;1:57-64.
[8] Kamyshov S.V., Pulatov D.A., *Nishanov D.A., Yuldasheva N.Sh.*
[9] The effect of the expression level of tumor markers on the results of treatment of patients with cervical cancer who received accompanying immunotherapy // *Evraz. oncologist. magazine.* 2017; 1:68-76.
[10] Kamyshov 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 *//Evraz. oncologist. magazine.* 2015;4. –V,7. –P.28-34.
[11] Kiseleva E.A., Volkova S.D., Chechetkin A.V. The development of methods of gravitational blood surgery in a specialized medical institution // *Herald of the blood service of Russia.* 2016; 3:10-14.
[12] Clinical use of extracorporeal treatment methods / Ed. N.N. Kalinin. - *Moscow: Trekpor Technology,* 2006.168 p.
[13] Korotky N.G., Ujuhu V.Yu., Flaks G.A. The first experience of using cytapheresis with extracorporeal 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. - *St. Petersburg: Foliant,* 2000. –432 p.
[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 // *Ross. immunologist. magazine.* 2001;6. V.4. –P.377-382.
[17] Nikogosyan S.O., Kuznetsov V.V. Ovarian cancer: diagnostic issues and modern treatment methods // *Doctor.* 2010;9:2-9.

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

[18] Popovich A.M. Immunotherapy in oncology. *Handbook on immunotherapy for a practitioner. -SPb: Dialog*, 2002. -P.335-352.
[19] Romanes M.A. Extracorporeal immunopharmacotherapy of psoriasis patients: diss... cand. med. sciences. – *Moscow*, 2010.
[20] Snezhko T.A. Extracorporeal immunotherapy in the complex treatment of patients with relapses and refractory Hodgkin's lymphoma: diss... cand. med. sciences. *Rostov-on-Don* - 2015.
[21] Sumina D.S. Clinical and immunological efficacy of extracorporeal immunopharmacotherapy in the complex treatment of psoriasis: author. dis. Cand. med. sciences. -*Kursk*, 2009. -24 p.
[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, Abrahamyan MV, Krotenko NP, Komardina EV. Methods of molecular transfusiology in intensive care of critical conditions // *RAMS.* 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. - P. 395–402.
[25] Bhardwaj N. Harnessing the immune system to treat cancer // *J. Clin. Invest*. 2007. –V.117. –P.1130–1136.
[26] DiSaia P.J., Creasman W.T. (eds.). Clinical gynaecologic oncology. - *7th ed.* - *Mosby Elsevier*, 2007.-- 812 p.
[27] Gattinoni L., Powell D.J., Rosenberg S.A., Restifo N.P. Adoptive immunotherapy for cancer: building on success // *Nat. Rev. Immunol*. - 2006. - N6. - P. 383–393.
[28] Gavrusev A., Strotsky A., Malashchitsky D. Extracorporeal magnetic therapy for the treatment of chronic prostatitis // *Eur. Urol. Suppl*. 2017. -N16. –V.5. –P.2192.
[29] Panagiotou A., Gaiao S., Cruz D.N. Extracorporeal therapies in sepsis // *J. Intensive Care Med.* 2013. –N5. –V.28. –P.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. –N8. –P.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. -N4. – V.124. -P. 1379.
[32] Yoshioka S., Fujiwara H., Nakayama T.I.

DOI: 10.37200/IJPR/V24I5/PR2020192
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020