При ГА изменения (больше или меньше M±SD) показателей Ca выявлены в 98% наблюдений, Mg – в 92%, P – в 6%, ПГ – в 54%, КТ – в 36%, ОК – в 63%, активности ЩФ – в 47%. Показатели N при ГА составляют 3,3±2,39±0,24 о.е., а повышенный N (>2 о.е.) обнаружен у 57% от числа обследованных пациентов. С N обратно соотносятся показатели в крови Ca, Mg и P. Существуют прямые корреляционные связи между N и индексом тяжести ГА. Как показывает ANOVA, имеет место зависимость от N показателей кальцемии и магнемии. По данным анализа Брауна-Форсайта с выраженностью N связаны также параметры тяжести ГА.

После проведенного ANOVA/MANOVA установлено, что содержание КТ и ОК достоверно влияет на интегральные сонографические признаки ГА. Однофакторный дисперсионный анализ показал влияние активности ЩФ на степень сужения суставных щелей, развитие эпифизарного остеопороза и изменения рогов менисков, уровень КТ – на формирование кист Бейкера, ОК – на интраартикулярные тела Гоффа. С учетом полученных результатов мы считаем, что содержание в крови КТ<2 пг/мл (<M-SD больных с кистами Бейкера) является фактором риска развития кист Бейкера, а гипокальцитонинемия <4 пг/мл (<M-SD здоровых) участвует в патогенетических построениях этого процесса. Высокие значения N (>2 о.е.) могут у больных ГА влиять на развитие внутрисуставных кальцинатов, кист Бейкера и тел Гоффа.

Как показал анализ Уилкоксона-Рао, ни один из МКМ не оказывал достоверного влияния на интегральные признаки магнитно-резонансной томографии. По данным Брауна-Форсайта параметры кальцемии влияют на развитие трабекулярного отека в мыщелках бедренной кости и остеокистоза, а также изменения заднего рога медиального мениска, уровень магнемии оказывает воздействие на появление трабекулярного отека в мыщелках большеберцовой кости, ПГ – на изменения переднего рога латерального мениска, ОК – на формирование внутрисуставных хондромных тел. Интегральный показатель N влияет на появление внутрисуставных хондромных тел и на изменения заднего рога медиального мениска.

Выводы. У больных ГА наблюдаются значительные изменения в крови МКМ, которые проявляются дисбалансом остеоассоциированных макроэлементов (Ca, Mg, P) с развитием гипокальцемии, которая регистрируется соответственно в 98%, высокой активностью ЩФ (в 47% случаев), признаками гиперпаратиреоидизма и гипероксикальцининемией. Нарушения костного метаболизма при ГА связаны с темпами прогрессирования заболевания и распространенностью суставного синдрома, а показатели МКМ могут иметь прогностическое значение. МКМ (остеоассоциированные макроэлементы и гормоны – ПГ, КТ, ОК, а также фермент ЩФ) участвуют в патогенетических построениях ГА, определяя развитие отдельных рентгенологических, сонографических и магнитно-резонансных артикулярных и периартикулярных признаков патологии коленных суставов (степень сужения суставных щелей, эпифизарный остеопороз, трабекулярный отек в мыщелках бедренной и большеберцовой костей, изменения рогов менисков, формирование кист Бейкера, интраартикулярных хондромных тел и тел Гоффа).

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SUPPORTIVE IMMUNOTHERAPY IN COMPLEX TREATMENT OF PATIENTS WITH ONCOGYNAECOLOGICAL DISEASES

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Abstract

The aim of the study was to study molecular-biological markers of the tumor as criteria for selecting methods of extracorporeal immunopharmacotherapy (EIFT) in patients with ovarian cancer (OC) and cervical cancer (cervical cancer) in the combined therapy. The objective of the study was 235 patients with cervical cancer and 198 patients with OC with II-III clinical stages of the disease. All patients with cervical cancer received combined and

complex treatment. 95 (40.4%) patients with cervical cancer and 78 (39.4%) had no immunotherapy. 76 (32.3%) patients with cervical cancer and 67 (33.8%) received EIFT by incubating autoblood with Thymalin immunomodulator followed by reinfusion of the resulting conjugate. 64 (27.2%) patients with cervical cancer and 53 (26.8%) of cervical cancer received EIFT with plasmapheresis. The best results after carrying out after treatment after treatment of patients with ovarian cancer and cervical cancer were observed in the group of patients in which EIFT with plasmapheresis was used as an accompanying treatment. This was expressed in improving the overall blood count, reducing leukopenia and lymphopenia, normalizing B-lymphocyte counts, CD4 +, CD8 + and NK, as well as in reducing the toxicity of chemotherapy and increasing the life expectancy of patients. The best effect was observed after the accompanying EIFT with plasmapheresis.

Keywords: cervical cancer, ovarian cancer, extracorporeal immunopharmacotherapy, plasmapheresis.

Importance. In the past 10 years, an increase in the prevalence of malignant neoplasms of female reproductive system has been observed worldwide. Cervical cancer is the 3rd most common cancer globally, in terms of both incidence (500,000 per year) and mortality (233,000 per year) [2,9]. Whereas, ovarian cancer is the 4th most common cancer of female reproductive system worldwide and has a very high fatality rate, exceeding (50-65 %) [3].

Chemoradiation exposure is a major component of treatment of oncogynecological diseases, but it causes a great number of negative side effects, such as, depression of the reactions of cellular and humoral immunity. Performing traumatic and large surgical interventions often leads to secondary post-operative immunodeficiency, which may contribute to the development of septic complications. Therefore, application of immunotherapy during the combined and complex treatment in this category of patients is promising. [1,3,9,12].

Over the last few years, progress has been made in the study of immunology and immunotherapy of cancer, including malignant neoplasms of the female reproductive system [4,6,11,12]. Therapeutic plasmapheresis has been successfully used for the treatment of various diseases. Therapeutic plasmapheresis is a method of removing blood plasma, containing the antibody “guilty” in disease development, circulating immune complexes, cytokines, products of cellular metabolism. Modern methods of extracorporeal immunopharmacotherapy (EIFT) are inherently effective expansion methods of the therapeutic plasmopheresis methodics. [5,6,7,8,10].

The purpose of the study – to research the use of extracorporeal immunopharmacotherapy as a method of supportive care in patients with cervical cancer and ovarian cancer of II-III stages in order to reduce the toxic effects of chemo radiotherapy during the phases of combined and complex treatment, and to improve the quality of life of the patients.

Material and methods. The study included 235 patients with cervical cancer $T_{2-3}N_{0-1}M_0$ stage (II-III clinical stages), as well as 198 patients with ovarian cancer $T_{2-3}N_{0-1}M_0$ stage (II-III clinical stage), who underwent examination and treatment at the Republican Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan Tashkent from 2004 to 2014.

All patients with cervical cancer received combined and complex treatment including polychemotherapy (PCT), surgery and radiation therapy (RT). In the first stage cervical cancer patients received systemic or intra-arterial poly chemotherapy (PCT) by cisplatin regimen 50 mg/m2 + 5-fluorouracil 1000 mg/m2 for 4 days for 4-6 courses 1 time in 3 weeks. PCT was conducted both in neoadjuvant and adjuvant regimens. In the second stage, a radical surgery or combined radiation therapy were employed, according to the radical program. In the third stage, radiation therapy was carried out, which included distance radiation therapy and intracavitary brachytherapy. RT was carried out on «Theratron» or «AGAT-R" equipment by split-rate Nature 2 Gy to 50 Gy in total, 5 times a week. Brachytherapy was performed on the "Gammamed" Nature 5 Gy to 45-55 Gy of total dose.

Combined therapy in neoadjuvant regimen was performed on all patients with ovarian cancer, which included polychemotherapy by the cisplatin 75 mg/m2 + cyclophosphamide 1000 mg/m2 scheme during 4 days for 2-4 courses every 3 weeks, and surgical treatment consisting of radical or cytoreductice surgery. Subsequently, 6 courses of adjuvant polychemotherapy every 3 weeks regimen were performed.

In accordance with the objectives of the study, patients were divided into the following groups according to the methods of immunotherapy in as a part of the complex treatment (Table 1). Immunopharmacotherapy, using extracorporeal methods, was performed in the postoperative period.

Table 1

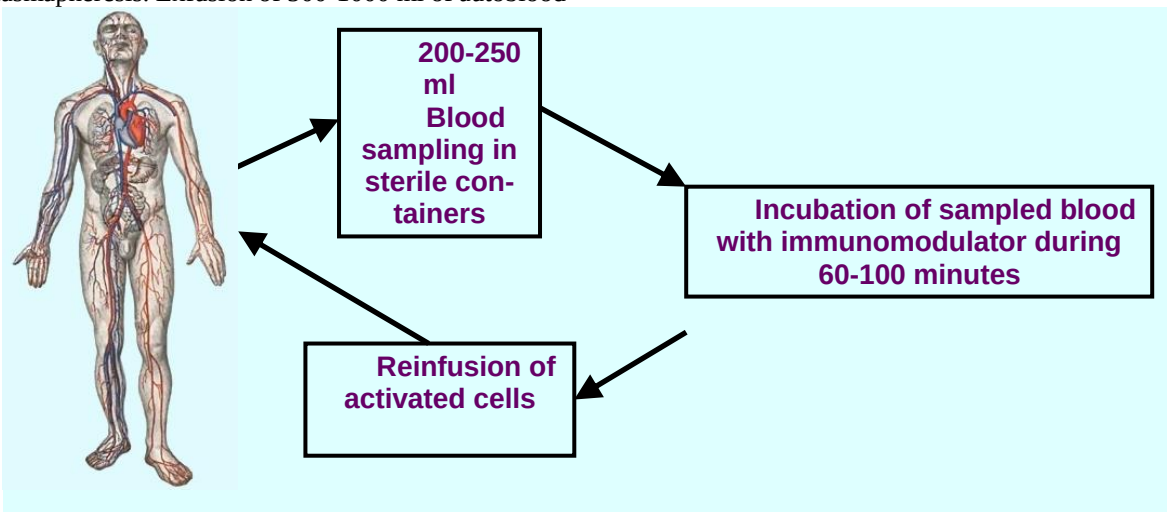
The groups of patients with cervical cancer and ovarian cancer

Methods of Immunotherapy	CC		OC	
	N	%	N	%
1. Control group (immunotherapy free)	95	40,4	78	39,4
2. EIFT	76	32,3	67	33,8
3. EIFT + Plasmapheresis	64	27,2	53	26,8
Total:	235	100	198	100

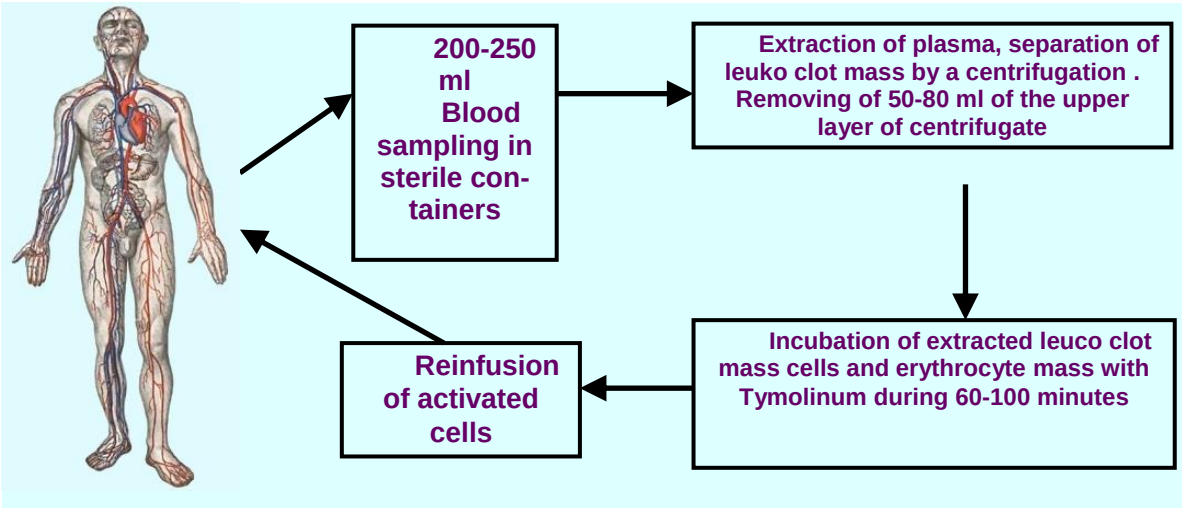
In the 1st group (control group) of patients immunotherapy was not performed.

In the 2nd group of patients with cervical and ovarian cancers EIFT was performed by exfusion of 200-250 ml autoblood into sterile containers "Gemakon" or "Terumo", with immunomodulator Thymalinum incubation in a total dose of 30 mg (during 3 procedures) at 37 ° C for 60-100 min with subsequent reinfusion of resulting conjugate (Figure 1).

In the 3rd group of patients EIFT method was used, which was an expansion of the capability of plasmapheresis. Exfusion of 500-1000 ml of autoblood into sterile containers "Gemakon" or "Terumo" was performed, and then it was centrifuged at 3000 rpm / min for 30 min. Afterwards, 50-80 ml of supernatant plasma containing antibodies, circulating immune complexes, cytokines, products of cellular metabolism was removed. The resulting leuko clot mass and erythrocyte mass were incubated with Thymalinum in a total dose of 30 mg (during 3 procedures) at 37C for 60-100 min, with subsequent return of the conjugate into the blood system of patients (Figure 2).



Puc.1. Methods of extracorporeal immunopharmacotherapy (EIFT) without plasmapheresis.



Puc.2. Methods of extracorporeal immunopharmacotherapy (EIFT) with intermittent plasmapheresis.

Age of examined patients with cervical cancer ranged from 21 to 74 years of age, mean 45,7±7,07 years. The age of patients with ovarian cancer was from 23 to 75 years of age, mean 42,6±6,5 years. Staging of the disease was done according to the International Clinical Classification TNM (7th edition, 2006). The study of medical charts revealed that the majority of patients with oncogynecological disease, a history made up from 1 to 3 months (in 47.3% of patients with cervical cancer, and in 43.8% of patients with ovarian cancer).

The results of the study. In prescribing the methods of extracorporeal immunotherapy to patients, we tried to take into consideration mostly the results of clinical and diagnostic tests. Morphological analysis of surgical specimens and biopsy results in patients with cervical cancer showed that the majority - 220 (93.6%) of examined patients had histologically diagnosed squamous cell cervical cancer, 15 (6.4%) of examined patients had clear-cell adenocarcinoma. 165 (83.3%) of the patients were diagnosed with cystadenocarcinoma, 33 patients (16.7%) of patients had other forms of ovarian cancer.

Examined patients who had chemotherapy experienced toxicity, among which leukopenia, lymphopenia, poor appetite, nausea, vomiting, taste disturbances and alopecia were most frequently observed. Radiation therapy in patients with cervical

cancer, usually was followed by the development of radiation reactions of the crucial pelvic organs - the bladder and rectum.

Methods of extracorporeal immunopharmacotherapy (EIFT) were designed primarily to reduce toxic manifestations after chemotherapy and radiation therapy, as well as improve the general condition of patients after major surgery.

Since the EIFT technique suggests blood sampling from the bloodstream of patients from 200 to 1,000 ml of blood with its special processing and subsequent return to the bloodstream, conservative therapeutic measures in the part of the patients were performed as the prevention of exacerbation of co-existing diseases. As a conservative treatment haemostatic, general health improving, cardiac, analgesic, anticoagulant, neurotropic, hepatotropic therapy in standard schemes was carried out. Immunopharmacotherapy with the use of extracorporeal methods was performed in the postoperative period. The best results after using the EIFT method were observed in the third group of patients, which was reflected in the improvement of blood count, reduced leukopenia and lymphopenia, as well as normalization of the B-lymphocytes, CD4+, CD8+ and NK findings. Less pronounced results were observed in the second group of patients.

The level of chemotherapy toxicity in patients with cervical cancer and ovarian cancer were determined with the score of CTC-NCIC. In the control group of patients, chemotherapy resulted in a clear manifestation of toxicity. Severity of side effects of chemotherapy, such as anemia, leukopenia, poor appetite, nausea and alopecia, in some of the patients was at the third level of toxicity (Table 2,3).

Table 2

Level of chemotherapy toxicity in groups of patients with cervical cancer according to the score of CTC-NCIC (n=235) (results of II и III level of toxicity %)

Indication	Groups of Patients					
	Control group, n=95		EIFT, n=76		Plasmapheresis + EIFT, n=64	
	Level of Toxicity					
	II	III	II	III	II	III
Anemia	25,0	16,4	23,7	0	13,3	0
Leukopenia	29,2	19,2	20,5	0	0	0
Llymphopenia	41,7	0	12,6	0	12,1	0
Poor appetite	26,7	8,4	18,2	0	0	0
Nausea	34,4	10,6	17,6	0	10,6	0
Vomiting	26,7	0	14,8	0	11,8	0
Taste disturbances	16,7	0	11,7	0	0	0
Alopecia	25,2	29,4	25,3	27,1	24,4	26,4

P<0,05

The data shows a decrease in toxicity of chemotherapeutic effects in this group of patients after EIFT. Performing EIFT with plasmapheresis contributed to even more pronounced decrease in side effects of the cytostatic treatment to the patients' health. It was successful in arresting main clinical manifestations of chemotherapy toxicity in half and even more cases in this group of patients.

Table 3

Level of chemotherapy toxicity in groups of patients with ovarian cancer accordingto the score of CTC-NCIC (n=235) (results of II и III level of toxicity %)

Indication	Groups of Patients					
	Control group, n=78		EIFT, n=67		Plasmapheresis + EIFT, n=53	
	Level of Toxicity					
	II	III	II	III	II	III
Anemia	24,2	18,3	26,8	0	12,6	0
Leukopenia	30,6	23,6	24,2	14,1	0	0
Lymphopenia	43,4	0	14,1	0	15,2	0
Poor appetite	28,4	7,7	15,2	12,6	0	0
Nausea	27,6	8,8	19,7	0	14,9	0
Vomiting	35,1	0	9,8	0	13,1	0
Taste disturbances	18,6	0	5,6	0	0	0
Alopecia	24,2	23,6	23,8	21,2	22,5	23,0

P<0,05

The quality of life in patients with cervical cancer and ovarian cancer after immunoregulatory measures was significantly higher than in the control group of patients without immunotherapy, which was reflected in the increase of both physical and mental components of health. The highest rates of physical health

component were observed in the third group, in which patients had EIFT with plasmapheresis.

Indicators of overall 5-year survival rate of patients with oncogynecological diseases after the treatment with the complex therapy in combination with immunotherapy were as follows: in the 1st control group of cervical cancer without performing immunotherapy - 58,7±5,8%; in the 2nd group of cervical cancer patients receiving EIFT without plasmapheresis - 69,3±6,2% (P=0.037), in the third group of patients with cervical cancer treated with EIFT and preliminary plasmapheresis - 74,3±7,1% (P=0.041). In patients with ovarian cancer this figure in the 1st control group of patients without immunotherapy was 62,5±6,1%; in the 2nd group of patients with ovarian cancer receiving EIFT without plasmapheresis - 71,5±6,7% (P=0.036) and in the third group of patients with ovarian cancer receiving EIFT with plasmapheresis - 76,5±6,3% (P=0.043).

Conclusion. Development, study and implementation into clinical practice various methods of immunotherapy is a current problem of modern oncology, since the use of these techniques can expand the therapeutic potential of the standard methods of treatment, and reduce their side effects, which will improve the quality of life in patients with malignant tumors. Our studies led to the conclusion that the most effective in treatment of patients with cervical cancer and ovarian cancer II-III stages is immunotherapy scheme, which includes intermittent plasmapheresis followed by EIFT, improves blood indicators, reduces leukopenia and lymphopenia, normalizes cellular, and humoral immunity, reduces major clinical manifestations of chemotherapy toxicity, improves the subjective state of patients and their quality of life.

Moreover, use of EIFT techniques in the treatment of oncogynecological diseases made it possible to increase the overall five-year survival rates of patients.

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