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INTEGRAL ASSESSMENT OF FACTORS AFFECTING THE EFFECTIVENESS OF ACCOMPANYING IMMUNOTHERAPY IN ONCOGYNECOLOGICAL PATIENTS

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ABSTRACT

According to our data, the overall 5-year survival rates in patients with cervical cancer II-III stages after complex therapy in combination with immunotherapy were as follows: in the group of patients receiving EIPT without plasmapheresis - 68.3 ± 5.4% (P = 0.037), in the group of patients receiving EIPHT with preliminary plasmapheresis - 72.3 ± 5.1% (P = 0.041) and in the control group without immunotherapy - 59.2 ± 4.2%. The parameters of the overall 5-year survival in patients with stage II-III ovarian cancer were: in the group receiving EIPHT without plasmapheresis - 72.1 ± 4.9% (P = 0.036), in the group receiving EIPHT with plasmapheresis - 73.5 ± 5.32% (P = 0.043) and in the control group without immunotherapy - 62.6 ± 5.0%. The analysis of the correlation of the tumor markers level and 5-year survival of patients allows to conclude that the positive level of p53, VEGF and Ki-67 in patients with cervical cancer and ovarian cancer, along with high proliferative activity of the tumor, may serve as a basis for this the category of patients accompanying immunotherapy with EIPHT, which can significantly increase the effectiveness of standard antitumor treatment regimens. At a positive level of oncomarkers, along with high proliferative activity of the tumor, it is possible to recommend carrying out accompanying immunotherapy with EIPHT with plasmapheresis.

KEYWORDS: Oncogynecological diseases, ovarian cancer, cervical cancer, molecular-biological markers, proliferation.

INTRODUCTION

It is known from literature sources that cervical cancer, adverse factors of prognosis affecting tumor survival and recurrence include high prevalence of the process, lymph node metastases, large tumor size, tumor infiltration of the parameter, low-grade cancer, light and small-celled cervical cancer . When conducting combined radiation treatment, adverse factors are anemia, thrombocytopenia.[1,5,8,10] Increased attention to the problem of growth of oncological morbidity is one of the characteristic features of the modern healthcare system of all developed countries. This is due, above all, to a steady trend of increasing malignant neoplasm among the population, which has reached fairly high rates and will increase in the foreseeable future. Annually, cancer affects 12 million people worldwide, and the number of cancer cases in the world has increased by twenty percent over the past ten years. This is the second cause of death after cardiovascular disease in developed countries, and the general cause of 10% of all deaths in the world, which is about 6 million deaths per year.[3,6,11,13,15] In recent years, progress has been made in the study of immunology and immunotherapy of cancer, including malignant tumors in the female reproductive system. The data are received that the majority of malignant tumors develop on the basis of pronounced disorders of the immune system that arise even with precancerous diseases, are determined by the prevalence of the tumor process and are exacerbated by the applied therapeutic effect. These data, as well as information on a more favorable course of the disease with preserved immunity, encourage many researchers to further study the state of the immune system and the development on this basis of more effective regimens for treatment of patients with malignant tumors with the inclusion of immunotherapy methods.[7,11,13,15,16] Ovarian cancer (OC) is currently the fourth leading cause of cancer death among women and continues to be the most fatal of gynecological tumors.[2,5,9,10] Cervical cancer (CC) is also one of the most common malignant tumors of the female genitalia. The incidence rate worldwide varies from 10 to 40 per 100,000 female population, with almost half of the patients dying within the first year due to late diagnosis of the disease.[5,8] The recurrence rate of patients with OC is approximately 75%, which is equivalent to approximately 2500 patients per year. Relapse therapy is the most controversial section of oncogynecology and is mainly palliative in nature, and with this in mind, its main goal is to prolong life and improve its quality.[8,10] Five-year survival with cervical

cancer according to the data of different authors in the presence of III-IV stage of the disease is 17-22%. The main cause of death is also cancer recurrence, which range from 37% to 50% of all treated patients.[7,11,14,15] In this regard, the improvement of methods of drug therapy to prolong and improve the quality of life of patients is a very urgent problem of clinical oncology. At present, the main tasks of immunotherapy in oncology have been formulated: basic immunotherapy of tumors with the aim of obtaining a direct antitumor effect, reducing the side effects of traditional antitumor therapy (treatment of myelosuppression and immunosuppression, correction of general toxicity, antioxidant effect), prevention of tumor recurrence and the emergence of new other tumors, prevention and treatment of concomitant infectious complications (viral, bacterial and fungal infections).[1,3,4,8] Development, study and introduction of various methods of immunotherapy into clinical practice is an actual problem of modern oncology, as the application of these techniques can expand the therapeutic possibilities of standard methods of treatment, as well as reduce their side effects, which will improve the quality of life of patients with malignant neoplasms. Therefore, the aim of the study was to study the factors affecting the effectiveness of accompanying immunotherapy in oncogynecological patients.

The aim of the study was an integral assessment of the factors affecting the effectiveness of accompanying immunotherapy in patients with cancer.

MATERIAL AND METHODS

The prediction of individual risk factors affecting the long-term results of treatment of oncogynecological patients was carried out on the basis of integrated data evaluation. For this purpose, the method of likelihood ratio was used, which allows not only to take into account the degree of probability of consequences from the influence of the factor, but also to identify the most significant risks. This method was used to compare mortality rates for 5-year follow-up in groups of cancer patients with cervical cancer and ovarian cancer with immunotherapy compared with the control group.

RESULTS AND DISCUSSION

Prediction of individual risk factors affecting long-term results of treatment of patients with cervical cancer was carried out based on integrated data evaluation. For this, the likelihood ratio method was used, which allows not only to take into account the degree of probability of consequences from the influence of the factor, but also to identify the most significant risks. With the help of this method, mortality rates over the 5-year follow-up period in the groups of patients with cervical cancer with immunotherapy and in the control group were compared (Table 1).

Table 1: Predictive table of risk factors in patients with cervical cancer.

Factors		Gradation Factor	Likelihood ratio
Age, years		21-40	0,75
		41-60	0,64
		61-80	0,61
Tumor volume, cm		From 10	0,67
		From 10 to 15	0,82
		From 15 to 20	**1,16**
Degree of differentiation of the tumor		High-	0,64
		Moderately-	0,82
		Low-	**1,18**
Oncomarkers	p53	+	**1,25**
		-	0,70
	VEGF	+	**1,21**
		-	0,65
	Ki-67	+	**1,27**
		-	0,76
	Bcl-2	+	0,86
		-	0,67
	EGFR	+	0,77
		-	0,54
Proliferative activity of the tumor		High	**1,25**
		low	0,68

The likelihood values were found from the formula: P1 = pi / n - EIPHT group; P2 = pi / n - group with EIPHT + PPh; P3 = pi / n is a control group without immunotherapy. Further, the likelihood ratio R = (P1 + P2) / P3 was found.

In the future, those factors were excluded where the maximum risk did not exceed a significant figure of 1. To such factors, in which the difference between the studied groups did not exceed 1, and which accordingly did not influence the survival of patients, the age, Bcl- 2

and EGFR. The significant factors from all of the studies reviewed in our studies that reflect the difference in the results of the 5-year survival of patients with cervical cancer between the groups with immunotherapy and control group were: tumor volume, tumor differentiation level, p53, VEGF, Ki-67, proliferative activity of the tumor. Based on our studies, we proposed an algorithm for the conditions for the use of immunotherapy in the combined treatment of patients with cervical cancer IIA-IIIC stages (Table 2). To unfavorable prognostic factors in OC affecting survival and recurrence of the tumor, according to the literature, include: the stage of the disease according to the FIGO clinical classification, the histological type and differentiation of the tumor, as well as the volume of unremoved tumor masses in cytoreductive operations. For early stages of the disease, such factors include a clear-cell histostructure, high mitotic activity, aneuploidy. Similarly, predictions of individual risk factors affecting long-term results of treatment of patients with ovarian cancer were carried out. Using the likelihood ratio method, mortality rates were compared for a 5-year follow-up period in groups of patients with OC with immunotherapy and in the control group (Table 2).

Table 2: Algorithm for choosing the method of accompanying immunotherapy in the complex treatment of patients with cervical cancer IIA-IIIB stages.

Risk factors	Type of immunotherapy
Tumor volume from 15 to 20 cm	EIPHT + plasmapheresis
Low grade	
differentiation of the tumor	
Positive level of oncomarkers p53, VEGF, Ki-67	
High proliferative activity of the tumor	
High level of LP by DK	
Tumor volume from 10 to 15 cm	
Moderate degree of differentiation of the tumor	
Positive level of oncomarkers p53, VEGF, Ki-67	
High proliferative activity of the tumor	
High level of LP by DK	EIPHT
Tumor volume up to 10 cm	
High degree	
differentiation of the tumor	
Negative level of oncomarkers p53, VEGF, Ki-67	

The likelihood values were found from the formula: P1 = pi / n - EIPHT group; P2 = pi / n - group with EIPHT + PPh; P3 = pi / n is a control group without immunotherapy. Further, the likelihood ratio R = (P1 + P2) / P3 was found. In the future, those factors were excluded where the maximum risk did not exceed a significant figure of 1. To such factors, in which the difference between the study groups did not exceed 1, and which accordingly did not influence the survival of patients, the age, Her- 2 / neu and EGFR, LPO level by MDA.

Table 3: Prognostic table of risk factors in patients with ovarian cancer.

Factors		Factor gradations	Likelihood ratio
Age, years		21-40	0,71
		41-60	0,64
		61-80	0,57
Tumor volume, cm		to 10	0,73
		more than 10	**1,18**
Degree of differentiation of the tumor		High-	0,70
		Moderately-	0,84
		Low-	**1,20**
Oncomarkers	p53	+	**1,21**
		-	0,76
	VEGF	+	**1,19**
		-	0,73
	Ki-67	+	**1,24**
		-	0,67
	Her-2/neu	+	0,87
		-	0,65
	EGFR	+	0,82
		-	0,59
Proliferative activity of the tumor		High	**1,23**
		Low-	0,71

The significant factors of all those examined in our studies that reflect the difference in the results of 5-year survival of patients with OC between groups with immunotherapy and control group were: tumor volume, degree of tumor differentiation, level of oncomarkers p53, VEGF, Ki-67, proliferative activity of the tumor, level of indicators. Based on the conducted studies, we proposed an algorithm for the conditions of application of immunotherapy in combined treatment of patients with OA IIA-IIIC stages (Table 4).

Table 4: Algorithm for choosing the method of accompanying immunotherapy in the complex treatment of patients with ovarian cancer IIA-IIIC stages.

Risk factors	Type of immunotherapy
The tumor volume is more than 10 cm	EIPHT + plasmapheresis
Low grade differentiation of the tumor	
Positive level of oncomarkers p53, VEGF, Ki-67	
High proliferative activity of the tumor	
High level of LPO by DK	
The tumor volume is more than 10 cm	
Moderate degree differentiation of the tumor	
Positive level of oncomarkers p53, VEGF, Ki-67	
High proliferative	EIPHT
tumor activity	
High level of LPO by DK	
Tumor volume up to 10 cm	
High degree	

CONCLUSION

According to our data, the overall 5-year survival rates in patients with cervical cancer II-III stages after complex therapy in combination with immunotherapy were as follows: in the group of patients receiving EIPHT without plasmapheresis - 68.3 ± 5.4% (P = 0.037), in the group of patients receiving EIPHT with preliminary plasmapheresis - 72.3 ± 5.1% (P = 0.041) and in the control group without immunotherapy - 59.2 ± 4.2%. The parameters of the overall 5-year survival in patients with stage II-III ovarian cancer were: in the group receiving EIPHT without plasmapheresis - 72.1 ± 4.9% (P = 0.036), in the group receiving EIPHT with plasmapheresis - 73.5 ± 5.32% (P = 0.043) and in the control group without immunotherapy - 62.6 ± 5.0%. The analysis of the correlation of the tumor markers level and 5-year survival of patients allows to conclude that the positive level of p53, VEGF and Ki-67 in patients with cervical cancer and ovarian cancer, along with high proliferative activity of the tumor, may serve as a basis for this the category of patients accompanying immunotherapy with EIPHT, which can significantly increase the effectiveness of standard antitumor treatment regimens. At a positive level of oncomarkers, along with high proliferative activity of the tumor, it is possible to recommend carrying out accompanying immunotherapy with EIPHT with plasmapheresis.

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