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RESULTS OF STUDY OF PARAMETERS OF BIOCHEMICAL AND ANTIOXIDANT STATUS IN PATIENTS WITH OVARIAN CANCER DURING POLYCHEMOTHERAPY

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The use of chemotherapeutic drugs causes an increase in the formation of free radicals and a change in antioxidant status. As a result, side effects are observed. On the basis of the Oncology Dispensary Ministry of Health of the Khabarovsk Territory (Komsomolsk-on-Amur) there was conducted a controlled randomized open study of parameters of biochemical and antioxidant status in patients with ovarian cancer: 30 patients received chemotherapy (a experimental group); the control group consisted of 20 healthy women, comparable in age. Biochemical status was evaluated by the levels of total protein, albumin, bilirubin and the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase in the blood of patients. Antioxidant status was evaluated by the levels of lipid hydroperoxides, conjugated dienes, and malondialdehyde and by the activity of the main components of the antioxidant system (ceruloplasmin, vitamin E) in the blood of patients. The administration of chemotherapeutic drugs to patients significantly increased the plasma levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, of lipid hydroperoxides by 50%, conjugated dienes by 51%, and malondialdehyde by 46% compared with the women in the control group. An analysis of the effect of chemotherapy on the activity of the antioxidant system components established that the blood concentrations of ceruloplasmin and vitamin E were 55 and 39%, respectively, lower than those in the control group. Thus, the incorporation of antioxidants into the treatment of patients with ovarian cancer should be considered pathogenetically justified, clinically reasonable, and promising.

Keywords: ovarian cancer, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lipid peroxidation, antioxidant system, patients.

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An urgent problem of modern gynecological oncology is an increase in the frequency of malignant ovarian tumors, the bulk of which are stage III-IV processes [2, 10]. Ovarian cancer is the most sensitive tumor to the therapeutic effect of cytotoxic drugs, however, the possibilities of specific therapy are limited due to toxic complications and pronounced metabolic dysfunctions at the level of the whole organism, which largely depend on the activation of lipid peroxidation (LP) [1, 15]. The action of peroxide products under these conditions is manifested in an increase in the membrane ion permeability, dissociation of oxidative phosphorylation, disruption of the structure and function of mitochondria, ribosomes, and a decrease in the activity of membrane-bound enzymes [9]. In addition, according to published data, platinum preparations, used mainly in the treatment regimen for patients with ovarian cancer, are antitumor agents that potentially cause the development of hepatotoxicity [3]. Therefore, there is a need to develop new science-based approaches and pathogenetically substantiated optimization of therapy in patients with ovarian cancer [14].

The purpose of the study was to study the parameters of biochemical and antioxidant status in patients with ovarian cancer during polychemotherapy (PCT).

Material and methods. A prospective, controlled, open, randomized trial was conducted in accordance with the “Rules for Qualitative Clinical Trials (GCP)” (OST No. 42–511–99 of December 29, 1998), with the provisions of the Helsinki Declaration and Guidelines for Good Clinical Practice developed at the International Conference on harmonization of technical requirements for the registration of pharmaceutical products intended for humans (ICH-GCP - International Conference on Harmonization of Technical Requirements for Human Use) and with the permission of the ethical committee of Amur State Medical Academy.

The control group consisted of 20 practically healthy women, comparable in age. The experimental group included 30 patients who are being treated in the oncology clinic of the Ministry of Health of the Khabarovsk Territory (Komsomolsk-on-Amur). Criteria for inclusion in the study: women over 18 years old; verified process (proven morphologically); stage III ovarian cancer; the absence of serious impaired renal, liver and hematopoietic function; adequate indicators of the cardiovascular and respiratory systems;

the absence of primary multiple, synchronous and metachron malignant tumors; voluntary informed consent. Criteria for exclusion from the study: acute infections, including hepatitis B and C, HIV; disease progression against the background of special treatment, identification of distant metastases according to the control clinical examination; history of uncontrolled convulsive disorder; previous neuropathy of any etiology, more than 1 degree of severity; clinically significant uncontrolled disorders: myocardial infarction, stroke, or transient ischemic attack, psychiatric illness / social circumstances that limit the patient's ability to fulfill the requirements of the study. All patients received PCT using platinum preparations: cisplatin, carboplatin (cytostatic antitumor chemotherapeutic drugs of the alkylating type containing divalent platinum (II) in the composition of the molecules according to the scheme: carboplatin AUC6-7 intravenously (iv) on the 1st day 21 -day course, or ATS (cisplatin 50 mg / m2 iv, doxorubicin 50 mg / m2 iv, cyclophosphamide 500 mg / m2 iv on the first day of the 21-day course).

Blood sampling was carried out before treatment and on the 5th day of treatment (in the process of PCT). We evaluated the level of total bilirubin, the concentration of total protein and albumin, aspartate aminotransferase (AcAT), alanine aminotransferase (AlAT), alkaline phosphatase (ALP) on a Clima MC-15 biochemical analyzer (China). The intensity of lipid peroxidation processes was evaluated by examining the content of lipid hydroperoxides, diene conjugates, malondialdehyde, and AOS components (ceruloplasmin, vitamin E) in the blood plasma of patients according to the methods described in our previously published works [8, 12, 17]. The following instruments were used in the work: KFK-2mp spectrophotometer, UNICO spectrophotometer, Solar PV 1251 C photoelectrocolorimeter. The results were statistically processed using Student's t test (t) using the Statistica v.6.0 program. The results were considered reliable at p <0.05.

Results and discussion. The algorithm of clinical and biochemical studies in cancer patients includes the mandatory determination of the content of total protein and albumin in the blood serum, since the development of malignant neoplasms is characterized, as a rule, by the state of severe hypoproteinemia due to a violation of the synthesizing function of the liver, the consumption of albumin as a plastic material for tumor tissue [4]. The results of our study showed a decrease in the concentration of total protein by 15% in the blood of patients with ovarian cancer at the first stage of the study (before treatment) in comparison with the same indicator in the group of healthy women (control), but the differences were not significant (Table 1). It is important to note that the content of total protein and albumin in patients at both I and II stage of the study (during PCT) was in the range of physiological norm, however, the normal concentration of albumin does not always provide adequate transport function of the protein, which may be associated with a violation secondary and / or tertiary structure. That is why T.V. Davydova et al. an opinion was expressed about the need to study in patients with ovarian cancer not only the concentration of serum albumin, but also the conformational transport characteristics of the latter [4]. The study of the total bilirubin content showed a significant decrease of this indicator by 42% in the blood of patients with ovarian cancer compared with the control and allowed us to state hypobilirubinemia (p <0.05). In the process of PCT (stage II treatment), the level of bilirubin in the experimental group tended to increase by 1.5 times, without leaving the range of the physiological norm, relative to the same parameter in stage I (p <0.05).

A study of the activity of hepatic transaminases in patients with stage III ovarian cancer upon admission to the Oncology Center (before treatment, stage I) made it possible to record the level of AlAT and AsAT within normal limits, which did not significantly differ from similar parameters in practically healthy women (control) (Table 2).

In the process of PCT in stage II, a significant increase in the activity of enzymes in the blood of patients was observed in comparison with indicators in stage I and relative to the upper limit of normal (ULN): the level of Alanine

Table 1

The concentration of total protein, albumin (g / l) and total bilirubin (μmol / l) of blood in healthy women and stage III ovarian cancer patients with chemotherapy (M ± m)

Indicator	Rate	Group		
		Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
			Stage I (before treatment)	II stage (5th day of treatment)
Total protein	65.0-85.0	82.5±4.4	70.7±5.6	69.8±6.0
Albumin	35.0-45.0	44.2±2.5	43.0±3.1	41.5±3.6
Total bilirubin	8.5-22.5	11.8±1.2	6.9±0.6*	11.0±0.8 **

Note. Here and in the Table 2 - 4: * - significance of differences in indicators compared with practically healthy women (control group) (p <0.05);
** - reliability of differences in indicators compared with patients at the first stage of the study (before treatment) (p <0.05).

Table 2

Enzymatic activity indices (e / l) in practically healthy women and stage III ovarian cancer patients with polychemotherapy (M ± m)

Indicator	Rate	Group		
		Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
			Stage I (before treatment)	II stage (5th day of treatment)
Alanine Aminotransferase	10-31	22.0±2.1	30.2±2.8	93.7±5.2***
Aspartate Aminotransferase	5-40	26.5±2.8	37.7±3.3	60.2±4.5***
Alkaline phosphatase	50-290	85.4±5.5	153.7±10.8*	258.9±21.1***

Aminotransferase exceeded ULN by 3 times and was 3.1 times higher than the same parameter in stage I (p <0.05), Aspartate Aminotransferase - 1.5 and 1.6 times, respectively (p <0.05), which indicates the development of hepatic cytolysis (or hepatic cell drug-induced liver injury (DILI) [3]) with the introduction of platinum preparations. The data obtained are consistent with the results of studies of E.V. Maximova, who established an increase in hepatic transaminases in 85.2% of cases in patients with ovarian cancer on the background of PCT [5]. The calculation of the de Ritis coefficient (Aspartate Aminotransferase / Alanine Aminotransferase) in patients at stage II made it possible to register a value of less than 1 (0.64), which indicates DILI with an inflammatory type of response [6]. PCT was accompanied by a significant increase in the level of alkaline phosphatase by 68.4% in the blood of patients with ovarian cancer in comparison with the activity of this enzyme at the first stage of research, which significantly exceeded the control by 3 times, but it is important to note that before the treatment and in the process of PCT, the values of alkaline phosphatase out of the range of physiological norms, which correlates with published data [14].

Thus, the study of biochemical status parameters in patients with stage III ovarian cancer indicated the formation of a hepatocellular type of liver injury during PCT, the main pathogenetic mechanisms of which are, firstly, the direct induction of apoptosis; secondly, the formation of toxic metabolites in phase I reactions (mediated by P-450 cytochromes), which leads to an increase in lipid peroxidation in hepatocytes and, as a consequence, a disruption in the structure of cell membranes and necrosis; thirdly, mitochondrial dysfunctions; fourthly, a violation of calcium metabolism in the cell, an increase in the intracellular concentration of Ca2 + ions, leading to injury to the cell wall and its lysis [3]. It is quite logical that under these conditions, the antioxidant system (AOS) experiences extreme stress and tension, since the activity of its components is aimed at stabilizing lipoperoxidation processes and inhibiting the cascade of LPO reactions that have a chain avalanche-like character. In addition, our previous preclinical studies on a model of toxic liver injury induced by the introduction of carbon tetrachloride showed a clear relationship between changes in the biochemical status and the state of the LPO / AOS system of the body [11, 13]. Therefore, it is advisable, in our opinion, to study the parameters of antioxidant status in ovarian cancer in the process of PCT, which is of fundamental importance for the purpose of further pharmacological correction of changes by the appointment of antioxidant agents [16].

Table 3

The content of lipid peroxidation products (nmol / ml) in practically healthy women and stage III ovarian cancer patients with polychemotherapy (M ± m)

Indicator	Group		
	Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
		Stage I (before treatment)	II stage (5th day of treatment)
Lipid hydroperoxides	30.8 ± 2.1	39.0 ± 1.5*	46.5 ± 1.8* **
Diene conjugates	36.0 ± 2.0	48.6 ± 2.2*	54.5 ± 2.0*
Malonic daldehyde	4.8 ± 0.2	5.7 ± 0.3	7.0 ± 0.3* **

Table 4

The content of antioxidant system components (μg / ml) in practically healthy women and patients with stage III ovarian cancer on the background of polychemotherapy (M ± m)

Indicator	Group		
	Control group (almost healthy), n=20	Experimental group (patients with ovarian cancer during polychemotherapy), n=30	
		Stage I (before treatment)	II stage (5th day of treatment)
Ceruloplasmin	32.6 ± 2.5	20.4 ± 1.8*	14.6 ± 1.0* **
Vitamin E	54.2 ± 3.0	42.5 ± 2.2*	33.2 ± 1.5* **

A study of the content of lipid peroxidation products in the blood plasma of patients with ovarian cancer showed (Table 3) that, against the background of the oncological process, a significant increase in the primary lipid peroxidation products was observed (lipid hydroperoxides were higher by 27%, diene conjugates by 35%, p <0.05) and unreliable - the secondary product of peroxidation of malondialdehyde (19%) in comparison with similar indicators in the group of healthy women. Analyzing the degree of accumulation of lipid peroxidation products in the dynamics of PCT, it is important to note a significant increase in lipid hydroperoxides by 19% (p <0.05), malondialdehyde by 23% (p <0.05) and diene conjugates by 12% on the 5th day of the study (II stage) in relation to these parameters in stage I, which in turn significantly exceeded the control by 50%, 46% and 51%, respectively (p <0.05). Our data are consistent with T.P. Gening et al., Indicating an increase in the level of secondary lipid peroxidation products in the blood plasma of patients with ovarian cancer in clinical stage III according to FIGO 3 days after the first course of PCT according to the CAP scheme and 3 days after the second course [7].

Analyzing the activity of the main components of the antioxidant system (Table 4), it is important to note that at the stage of patient admission to the Oncology Center (before treatment), there was a significant decrease in ceruloplasmin by 38% (p <0.05) and vitamin E by 22% (p < 0.05) compared with similar indicators in the group of healthy women (control), which indicates the tension of the antioxidant system in ovarian cancer. PCT with platinum drugs leads to a progression in the degree of AOS depletion, as indicated by a significant decrease in the concentration of ceruloplasmin (by 29%) and vitamin E (by 22%) in the blood plasma of patients relative to the indicators obtained at stage I of the study (p <0.05). On the 5th day of treatment, the content of ceruloplasmin was 55% lower than in the control group of women, vitamin E -

39% (p <0.05), which allows us to state the fact of a decrease in the activity of the main components of AOS against the background of an increase in the intensity of LPO processes in the conditions of PCT. Thus, the treatment of patients with ovarian cancer with the use of platinum preparations is accompanied by changes in the biochemical and antioxidant status of patients, which makes it necessary to include drugs with hepatoprotective and antioxidant effects in complex therapy.

Conclusions

1. Chemotherapy according to the ATS scheme in patients with stage III ovarian cancer promotes the development of hepatic cytolysis, inducing an increase in the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase.

2. Against the background of polychemotherapy of ovarian cancer with platinum preparations, changes in the antioxidant status of the body are observed, based on the accumulation of lipid peroxidation products and a significant decrease in the activity of the main components of the antioxidant system (ceruloplasmin, vitamin E).

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