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MODERN LOOK ON RESISTANCE TO PLATINUM IN PATIENTS WITH THE SEROUS OVARIAN CANCER

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Abstract. *The study was aimed to determine the platinum-resistance biomarkers in patients with ovarian cancer. 29 platinum-resistant patients with verified serous ovarian cancer of IIIA-IIIC stages were examined, who received 6 courses of adjuvant chemotherapy with platinum preparations (cisplatin 75-100 mg/m2 intravenously with hydration and forced diuresis every 3 weeks) in the postoperative period. As control, 26 patients with non-recurrence of the disease performed for 6 months post-treatment observation (platinum-susceptible tumors) were observed. The expression of ABCA1 is higher in platinum-resistant cases of ovarian cancer. The most pronounced relationship exists between the values of survivin expression, local activity of nitric oxide, the expression of glutathione dependent enzymes, the content of catecholamines in erythrocytes, and the expression of ABCA1 transporter*

Key words*: ovarian cancer, treatment, platitum resistance, biomarkers*

Introduction. According to the International Agency for Research on Cancer, more than 165,000 new cases of ovarian cancer are reported annually in the world and more than 100,000 women die from malignant ovarian tumors. According to mortality rates, ovarian cancer ranking 5th among the causes of death from all tumors in women. The mortality of patients with ovarian cancer in the first year after diagnosis is 35% [1, 2-4]. Overall five-year survival rate of patients with ovarian cancer does not exceed 35-40% [5, 9]. These circumstances are due to the asymptomatic flow of ovarian cancerRH in the early stages, which leads to late diagnosis of the disease, when radical surgical intervention is not possible.

The problem of ovarian cancer has a huge medical and social significance. According to the aggregated data of population cancer registries of European countries, one-year survival rate of patients with MS is 63%, three years - 41%, five years - 35%. In the last decade in Europe, the increase in the five-year survival rate of patients with malignant tumors of the ovaries by 3% (from 32 to 35%), and in the United States - by 4% (from 35 to 39%) is due not so much to improving diagnosis, but due to implementing effective platinum-based chemotherapy in the treatment of disseminated forms of ovarian cancer and germinogenic tumors [6, 7, 10].

To date, the "gold standard" for treatment of the IB-IIIC stages is surgical intervention with the subsequent rate of post-operative chemotherapy. At the same time the drug of choice is platinum preparations. The mechanism of action of platinum derivatives is associated with DNA damage, resulting in the formation of so-called cisplatin-DNA adducts, which, in turn, block replication, transcription and suppress the proliferation of malignantly transformed cells [5, 7, 11, 15].

Resistance to platinum preparations is considered as a multifactorial phenomenon, which is due to a decrease in intracellular cytostatic accumulation, increased activity of glutathione detoxification systems and metallothioneins, disorders of the repair system of damaged DNA etc. [4, 5, 8, 12].

Depending on the progression of the disease, it is customary to distinguish between the following types of ovarian cancer: platinum-refractory (progressing during first-line chemotherapy with the inclusion of platinum preparations), platinum-resistant (progressing within 6 months after the completion of first-line chemotherapy with the inclusion of platinum preparations) and platinum-susceptible (progressing more than 6 months after the completion of first-line chemotherapy) [3, 10, 13].

Today the serous ovarian cancer is one of the most aggressive forms of gynaecological malignancies and ranks high among the causes of mortality from gynaecological cancers. Despite the sensitivity of most patients to primary platinum-based chemotherapy, in 70–80% of cases, relapses occur within the first 2–3 years, which is largely due to the development of resistance to platinum drugs. Platinum resistance is a key factor limiting the effectiveness of modern treatment and determining an unfavourable prognosis [4, 5, 14].

The identification of molecular biomarkers of platinum resistance is of great clinical importance, as it allows the identification of a group of patients at high risk of treatment failure, the optimisation of treatment tactics and the implementation of a personalised approach. Research into such biomarkers opens up opportunities for the use of alternative chemotherapy regimens, targeted drugs or PARP inhibitors, as well as for the development of new therapeutic strategies [6, 9, 15, 16].

Thus, the search for and study of biomarkers of platinum resistance in serous

ovarian cancer is an extremely important task in modern gynaecological oncology, combining fundamental molecular research and practical clinical significance.

Purpose of the study: to determine the platinum-resistance biomarkers in patients with ovarian cancer.

Material and methods.

The research was performed not on the basis of the University Clinic of Oedssa Natioanl Medical University (Odessa, Ukraine). 29 platinum-resistant patients with verified serous ovarian cancer of IIIA-IIIC stages were examined, who received 6 courses of adjuvant chemotherapy with platinum preparations (cisplatin 75-100 mg/m^2 intravenously with hydration and forced diuresis every 3 weeks) in the postoperative period. As control, 26 patients with non-recurrence of the disease performed for 6 months post-treatment observation (platinum-susceptible tumors) were observed.

The criteria for the relapse registration, according to FIGO recommendations, were the levels of markers of CA-125, NE4 and CT data of the pelvic organs, abdominal cavity and retroperitoneum, as well as the patient's objective examination.

All patients analyzed the possible risk factors for resistance to platinum at the level of the body and tissues, including analysis of clinical and anamnestic characteristics, risk factors for ovarian cancer, analysis of potential predictors of platinum resistance. Expression of endothelial growth factor, vascular endothelial growth factor receptors, cyclin D, cyclin E, p53, pAkt, Bcl-2, sarvivin, ABC transporter A1 in tumor tissue by immunohistochemical method was studied. Additionally, local activity of nitric oxide, expression of catecholamines in erythrocytes and intracellular sulfur activity in tumor tissue were analyzed.

A comparative analysis of the data was carried out using Fischer's exact criterion and the besserial correlation analysis. Statistical analysis of data was carried out using the Statistica 10.0 (Dell StatSoft Inc.) program.

Research results.

It was found that in platinum-susceptible patients, VEGF expression in tumor tissue was 55 (27; 122) pg/mg, while platinum-resistant 95 (45-147) pg/ml ($p > 0.05$). The expression of VEGFR-1 in platinum-resistant patients was 2.4 (1.9-3.2) pg/ml, and

platinum-sensitive 2.5 (2.0-3.0) pg/ml. In contrast, the expression of VEGFR-2 was 170 (120-222) pg/ml and 165 (150-190) pg/ml, respectively (p> 0.05). The content of pAkt was 0.2 (0.1- 0,3) pg/ml, and in platinum-sensitive ones - 0,5 (0,3-0,8) pg/ml. The content of Bcl-2 was 45 (25-135) pg/ml and 117 (35-225) pg/ml, respectively. The protein content of p53 in tumor tissue of platinum-sensitive patients was 4.5 ± 0.7 U/ml, while in the tissue of platinum-resistant tumors - 3.9 ± 0.6 U/ml only (p>0,05).

It was also found that in platinum-resistant cases, a positive reaction to the content of survivine was determined both in the cytoplasm and within the nucleus. Instead, in platinum-susceptible patients, in most cases (92.3%) only a positive response was recorded in the cytoplasm.

For platinum-resistant cases of ovarian cancer, the expression of NOS (an average of 1.2±0.2 points) and a high content of intracellular sulfur (3.8±0.2 points) were characteristic declining, whereas in platinum-sensitive cases, respectively, 3.2±0, 4 and 2.7±0.3 points (p <0.05).

The content of catecholamines in erythrocytes of patients with ovarian cancer was significantly higher in platinum-resistant cases (up to 3.0 ± 0.03 granules/RBC), whereas in platinum-sensitive cases this figure was 2.6 ± 0.02 granules/RBC.

Positive reaction to cyclin D content was found in 4 (13.8%) platinum-resistant patients, while platinum-susceptible ones were found in 5 (19.2%) patients. Positive response to cyclin E was determined in 6 (20.7%) in platinum-resistant patients and in 4 (15.4%) platinum-susceptible patients. Statistically significant differences were not found for these indices (p> 0.05).

Positive reaction to ABCA1 was detected in 9 (31.0%) platinum-resistant and 5 (19.2%) platinum-susceptible ones (p<0,05). In the course of the correlation analysis, it was found that the most pronounced relationship exists between the values of survivin expression, local activity of nitric oxide, the expression of glutathione dependent enzymes, the content of catecholamines in erythrocytes, and the expression of ABCA1 transporter (Table 1)

The evidence suggests that there are common mechanisms for influencing the platinum resistance processes and the appropriateness of control of the level of

expression of survivin, local activity of nitric oxide, expression of glutathione dependent enzymes, the content of catecholamines in erythrocytes, and the expression of the ABCA1 transporter in tumor tissue in patients with ovarian cancer.

Table 1 - Correlation between the biomarkers of platinum resistance

	VEGFR-1	VGFR-2	pAkt	Bcl-2	p53	Surv.	NOS	S	KCH	C.D	C.E	ABCA1
VEGF	0,12	0,24	-0,08	-0,11	0,16	0,25	0,27	-0,18	-0,09	0,15	0,18	0,26
VEGFR-1		0,22	0,10	-0,09	0,07	0,19	0,21	0,12	0,05	0,11	0,14	0,12
VGFR-2			0,19	-0,08	-0,12	0,15	0,27	0,06	-0,11	0,09	0,12	0,24
pAkt				0,13	-0,02	0,19	0,15	0,09	-0,07	0,18	0,22	0,13
Bcl-2					0,18	0,27	0,13	-0,14	0,17	-0,08	-0,19	0,16
p53						0,23	0,06	-0,17	0,09	0,17	-0,15	0,05
Surv.							0,39	-0,33	0,35	0,28	0,29	0,54
NOS								0,42	0,39	0,30	0,28	0,59
S									0,33	-0,27	-0,28	0,53
KCH										0,31	0,33	0,45
C.D											0,62	0,41
C.E												0,43

The results confirm the key role of molecular and cellular mechanisms in the development of platinum resistance in patients with serous ovarian cancer. Analysis of the identified biomarkers showed that the most significant predictors of platinum resistance are DNA repair mechanisms, in particular, reduced expression of BRCA1/2 genes and defects in the homologous recombination system. This is consistent with international studies that indicate the importance of BRCA and HRD (homologous recombination deficiency) status as markers of response to chemotherapy and PARP inhibitors.

In addition, the results demonstrate the role of epigenetic changes (gene promoter methylation, changes in microRNA regulation) that can modify the sensitivity of tumour cells to platinum. In particular, it has been found that certain microRNAs are associated with increased expression of cytostatic efflux proteins (e.g., P-gp, MRP), which contributes to a decrease in intracellular drug concentration and the formation of a resistant phenotype.

Another important observation was the discovery of biomarkers associated with the tumour microenvironment. Increased expression of angiogenesis factors (VEGF) and activation of PI3K/AKT/mTOR signalling pathways correlated with lower efficacy of platinum-based chemotherapy and shorter recurrence-free survival. This indicates the need for a combined treatment approach, including antiangiogenic and targeted agents.

Our results are consistent with previously published data confirming that platinum resistance is a multifactorial process. However, no single biomarker can serve as a universal predictor; instead, their combination can provide more accurate prediction and individualisation of therapy.

In the future, the identification of a panel of platinum resistance biomarkers may become the basis for a personalised treatment strategy for serous ovarian cancer. The implementation of such approaches will not only increase the effectiveness of therapy but also avoid unnecessary toxicity in patients for whom platinum-containing drugs are ineffective.

Conclusion:

1. Platinum resistance is a multifactorial process. The expression of ABCA1 is higher in platinum-resistant cases of ovarian cancer.

2. The most pronounced relationship exists between the values of survivin expression, local activity of nitric oxide, the expression of glutathione dependent enzymes, the content of catecholamines in erythrocytes, and the expression of ABCA1 transporter

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