

EXPRESSION OF DRUG RESISTANCE PROTEINS IN TRIPLE-RECEPTOR-NEGATIVE TUMORS AS THE BASIS OF INDIVIDUALIZED THERAPY OF THE BREAST CANCER PATIENTS

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Aim: To evaluate the efficacy of the application of various chemotherapy schemes based on the immunohistochemical study of expression patterns of proteins associated with the drug resistance P-glycoprotein (P-gp), glutathione-S-transferase (GST), metallothioneins (MT) of breast cancer (BC) patients with the triple-receptor-negative (RE⁻, RP⁻, HER-2/neu⁻) cancer. **Methods and Results:** P-gp, GST and MT expression in BC-biopsy samples from 60 BC patients was evaluated by immunohistochemical analysis. The results of the clinical observations showed that 3-years relapse-free survival rate of the patients of with P-gp, GST and MT-positive tumors treated with taxoter + adriablastin / taxoter + cyclophosphamide (TA/TC), gemcitabine + carboplatin, or TC + bevacizumab was 61.5%, 78.6% and 81.2% respectively, vs 41.2% in the control group with P-gp, GST and MT-negative tumors treated with adriablastin + cyclophosphamide ($p < 0.05$), while overall survival rates were 84.4%, 92.6% and 93.8% respectively vs 70.6% in the control group ($p < 0.05$). **Conclusion:** The study points on the possibility to elevate the efficiency of polychemotherapy by its individualization based on the expression patterns of P-gp, GST and MT on tumor cells of the patients with the triple-receptor-negative BC.

Key Words: breast cancer; drug resistance; polychemotherapy.

The achievements of the modern genetics and molecular biology have significantly broadened the knowledge on the breast cancer (BC) [1]. Nowadays there are 5 types of this disease, one of which is estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu-negative BC, so-called triple-receptor-negative tumors. The results of the clinical observations prove that this type of BC is characterized by the negative forecast of the disease course, high risk of relapse and remote metastasis and by the low survival of the patients respectively [2]. As there are no receptors of steroid hormones and HER-2/neu, these tumors are irresponsive to hormonal and targeted therapy. Usually during the treatment of this type of the BC the polychemotherapy (PCT) scheme involving anthracyclines, more often — the AC ones (with further possible involvement of taxanes to the scheme), is applied [3, 4]. At the same time, there are data according to which a rather substantial percent of the tumors is irresponsive to the standard accepted chemotherapy schemes [5]. Due to this fact, the researches directed on individual chemotherapy with the patients with the triple-receptor-negative tumors are currently in spite of interest. It is known that the BC resistance to the anthracycline antibiotics, phytogetic alkaloids and taxanes is connected with the increased expression of P-glycoprotein (P-gp). Expression of glutathione-S-transferase (GST) and metallothioneins (MT) in the breast cancer cells characterizes the low responsiveness to cisplatin, chlorambucil and to other alkylating agents [6–9].

Thus, the aim of our research was the comparative study of the efficiency of the application of various schemes of antitumor therapy selected by immunohistochemical study of peculiar features of the expression

of proteins associated with the drug resistance (P-gp, GST and MT) of the patients with the triple-receptor-negative (RE⁻, RP⁻, HER-2/neu⁻) BC. Our research included 60 patients suffering from the BC with triple-receptor-negative tumors. All of these patients were in the pre-menopause condition and the disease stage corresponded to the criterion T₁₋₂N₀₋₂M₀.

Immunohistochemical studies of the expression of RE, RP, P-gp, GST and MT were carried out on the trepan-biopsy materials obtained prior to the beginning of the treatment with the application of the generally accepted method [10] with the use of specific MoAbs (Dako Cytomation, Denmark, and Chemicon International, Europe). At the beginning of the treatment all patients underwent a large fractional TγT and afterwards — a radical surgery. Statistical analysis was carried out with the help of the set of STATISTICA 6.0 software. Student's *t*-criterion was used for evaluation differences significance, $p < 0.05$ was considered significant.

Depending on the expression patterns of P-gp, GST and MT on BC cells, the BC patients were divided into 4 groups:

1) Control group (n = 17): the patients were treated according to the standard scheme adriablastin + cyclophosphamide (AC); BC cells were negative by P-gp, GST and MT expression.

2) The patients (n = 13) were treated according to the schemes taxoter + adriablastin (TA) (n = 7) and taxoter + cyclophosphamide (TC) (n = 6); BC cells express P-gp (40–80%), and GST and MT (0–50%).

3) The patients (n = 14) were treated according to the scheme gemcitabine + carboplatin; BC cells express P-gp (40–80%), GST (10–50%), and MT (0–20%).

4) The patients (n = 16) were treated according to the scheme TC + bevacizumab; BC cells express P-gp (40–80%), GST (5–20%) and MT (50–80%).

As a result of a comparative analysis, it was established that three-year survival of the patients of the

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Abbreviations used: BC – breast cancer; GST – glutathione-S-transferase; MT – metallothioneins; PCT – polychemotherapy; P-gp – P-glycoprotein.

2nd, 3rd and 4th group was significantly higher than that of the control group.

The results of the clinical observations showed that 3-years relapse-free survival rate of the patients of the 2nd, 3rd and 4th groups was 61.5%, 78.6% and 81.2% respectively, vs 41.2% in the control group ($p < 0.05$) (Table). Analysis of overall survival of the patients with the triple-receptor-negative BC has shown that in the 2nd, 3rd and 4th groups it reach 84.4%, 92.6% and 93.8% respectively, vs 70.6% in the control group ($p < 0.05$). It is necessary to note that the application of scheme TC + bevacizumab was found to be the most efficient one. Thus, our study has shown the possibility to elevate the efficiency of polychemotherapy by its individualization based on the expression patterns of P-gp, GST and MT on tumor cells of the patients with the triple-receptor-negative BC.

Table. Treatment schedules and survival rate of breast cancer patients

Group	PCT Scheme	3-year survival	
		Overall	Relapse-free
1 (control) (n = 17)	AC/CMF	70.6%	41.2%
2 (n = 13)	TA/TC	84.6%*	61.5%*
3 (n = 14)	Gemcitabine + carboplatin	92.6%*	78.6%*
4 (n = 16)	TC + bevacizumab	93.8%*	81.2%*

*Statistically significant compared to control group.

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