

The Significance of Immunohistochemical Markers in the Treatment of Breast Cancer

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Abstract: Breast cancer is a serious medical and social problem for most developed countries of the world. Immunohistochemical studies were performed on primary tumors of 70 breast cancer patients with different subtypes. An immunohistochemical study allows us to evaluate the indicators associated with the tumor cell cycle. Knowledge of immunohistochemical markers allows us to develop an optimal model for evaluating and choosing tactics for the treatment of breast cancer.

Keywords: immunohistochemical markers, breast cancer, tumor, receptor, treatment.

Relevance. Despite significant advances in understanding the biology and clinic of the disease, as well as radical changes in treatment approaches, the problem of breast cancer continues to be very relevant, especially in the Republic of Uzbekistan, where 75% of women already have stage 4 breast cancer with distant metastases at the initial detection. In Uzbekistan, there is an increase in the number of patients with primary breast cancer per 100,000 women, which in the whole Republic of Uzbekistan amounted to 6.6. In the regions of Uzbekistan, the greatest increase in the incidence was noted in the Republic of Karakalpakstan - 1.7 times, and in the city of Tashkent - 1.5 times. In 2018, 3,578 women with breast cancer were registered in Uzbekistan. Today, about 18,000 women have been diagnosed with breast cancer. The five-year survival rate is currently 45%, and the one-year mortality rate is 1.1% [5]. Breast cancer mortality also increased from 1985 to 2004, and this increase is greater in Bukhara and Surkhandarya.area - 3.9; 3.8 times, respectively. [9]

A recently published EBCTCG review (EarLyBreastCancerTrials' CollaborativeGroup)

indicates that the relative benefit of chemotherapy is identical in all subgroups, regardless of age, stage of the disease, histological degree of malignancy and the status of estrogen receptors (EBCTCG, 2012). This observation contradicts the results of individual studies in both adjuvant and neoadjuvant modes, as well as ideas about the biology of breast cancer. It is also necessary to take into account that many studies included in the EBCTCG review do not contain complete data on ER expression, in particular, quantitative assessment by the IHC method. Moreover, these studies included patients at higher risk than today's patients, and the endocrine therapy performed by today's standards can be considered suboptimal. However, all these contradictions can be discarded when taking into account the fact that with equal relative benefits, the absolute benefits obtained from the use of adjuvant chemotherapy vary significantly. Individual risk is determined by belonging to a biological subtype and the degree of prevalence of the disease. For example, the absolute benefit of the use of adjuvant chemotherapy in early breast cancer of luminal A-type is very small and should be balanced with the potential short-term and long-term undesirable effects of chemotherapy. Among the huge number of molecular biological studies related to the prediction of breast cancer and the search for factors predicting the sensitivity of the tumor to various treatment methods, it is necessary to include an integral assessment of a huge number of molecular biological characteristics of neoplasms, which are presented by the classification of breast cancer based on variations in the set of expressed genes and correlation. Many studies have provided evidence of the great prognostic value of such immunohistochemical markers as epidermal growth factor HER2-neu, tissue markers of proliferation and apoptosis. A breakthrough in the practical use of these

markers occurred after the appearance of the drug Herceptin, which is a humanized antibody to HER2-neu, one of the tyrosine kinase receptors of the ErbB family. This is one of the most important systems for regulating the transmission of the mitogenic signal. Blocking HER2-neu can significantly slow down or stop tumor growth, depending on such stimuli [1-5,9]. In accordance with the recommendations of St. Gallen 2015, it is indicated that for cases of ER-positive breast cancer with ambiguous indications for chemotherapeutic treatment, the decision on systemic adjuvant therapy should be based on the determination of the subtype (IHC-phenotype) of breast cancer. Indications for the inclusion of adjuvant cytotoxic chemotherapy for patients with luminal. Laboratory studies have shown that cells with the p53 mutation are resistant to radiation and chemotherapeutic agents that usually cause apoptosis. There are reports of a negative effect of p-53 on relapse-free and overall survival [6,7]. Ki-67 is a nuclear antigen expressed in the proliferative phase of the cell cycle. A correlation was established between the number of cells expressing Ki-67 and the degree of malignancy of the tumor, as well as the mitotic index [6,8,9]. With luminal B-subtype of breast cancer, experts recommend the inclusion of anthracyclines and taxanes if there are indications for chemotherapy. For the luminal A-subtype, "old" modes, such as AC and CMF, are recommended (Hart, 2015). Some experts believe that high-risk patients prefer dose-dense chemotherapy regimens with the support of granulocyte-colony stimulating factors (G-CSF).

2. Materials and methods

Immunohistochemical studies were performed on the primary tumors of 70 breast cancer patients. The immunohistochemistry (IHC) of the archival material was carried out in the private laboratory "PremiumDiagnostics LTD" on the equipment of DakoDenmark A / S, DaniaDakoproduktionsvej 42, DK-2600 GlostrupDenmark.

The evaluation of treatment results began with a statistical analysis of the prognostic values of signs that affect the outcome of the disease, based on three main types of conjugacy tables:

- The dependence of the progression of the disease and the negative reaction to the treatment on the severity of a separate prognostic factor;
- The dependence of the distribution of the degree of evidence of one sign on the degree of evidence of another sign

It was noted that the dependence of the disease progression in patients on the progression of breast cancer is high from a combination of several evidence-based factors. The expression level of HER2-neu corresponds to a low degree.

The evidence-based statistics were based on: differentiation and the III degree of malignancy of the tumor. Factor analysis with the determination of the specific weight of the combination of these morphological parameters in each trait that affects the outcome of the disease for a metastatic node in the lungs indicates that common factors are most aggressively distinguished; a nonparametric (rank) pool of tumor cells is involved in lung metastasis. In the correlation analysis using the Kendall (Rk) method for neoadjuvant polychemotherapy (6-8 courses of determining the relationship of indicators; the criterion of the standard scheme of taxana / platinum / gemcitabine of the Fisher angular transformation (F*), the criterion of drugs) at this stage of treatment of the primary tumor, compliance (consent) Pearson (χ^2), the criterion for changing the status of HER2neu were noted in 25% of cases and the relative risk (RR and 1 / RR) for detecting differences. The status did not change in 76% of cases [6]. Promoted. Four main levels of statistical significance were adopted so that the expression of HER2-neu was observed in 12.9% of the detected differences: high - $p < 0.001$, average $p < 0.01$, in patients and in 12.5% of cases, this indicator was reduced. low (marginal) $p < 0.05$, insignificant (unreliable) - $p > 0.05$. Changes in the expression of HER2-neu after neoadjuvant therapy. The main factors confirming the reliability of the differences were chemotherapy, which is uncertain and does not allow obtaining the results of multifunctional (universal) Fischer methods. a clinically significant conclusion. The IBM SPSS 18 program was used for statistical processing. Sections with a thickness of 4-5 microns

were made from each paraffin block of a breast cancer tumor using a Leica SM 2000R microtome (sliding microtome for everyday use), and then processed by standard methods. Antibodies to the receptors of estrogen, progesterone, androgens, oncoprotein, Her2/neu were used.

Results.

The incidence of tumors with HER2-neu overexpression was 58%, while tumors with a negative HER2-neu status were observed in 15% of cases. This correlates with the expression of estrogen receptors (ER) and progesterone receptors (PR). When assessing the hormonal status by the immunohistochemical method, positive expression of estrogen receptors was detected in 35% of cases: weak - in 57.9% of cases, moderate - in 28.7%, explicit - in 14.5% of cases.

The expression of progesterone receptors was noted in 45% of cases: explicit expression was detected in 22.8% of cases.

When comparing the expression of HER2-neu in the primary tumor, metastatic lymph node and in the pulmonary node, a moderate increase in expression was observed as the process progressed. As the tumor progressed, no changes were observed in the expression of HER2-neu; thus, the initially aggressive tumor cell retains its potential in both lymphogenic metastasis and hematogenous metastasis to the lungs. When assessing the marker of proliferative activity of Ki-67, positive expression was detected in 90% of cases: of these, weak expression was observed in 33.6% of cases, moderate - in 44.5% and pronounced - in 22.4% of cases. The expression of the apoptosis marker p-53 was noted in 80% of the observations: of these, explicit expression was detected in 38.0% of the observations, moderate - in 37.6% and weak - in 26% of the observations. The expression of HER2neu, the proliferation marker Ki-67, and the apoptosis marker P-53 is interrelated. An increase in the expression of these markers was noted as the tumor process progressed. A moderate increase in expression was observed when comparing the level of expression of markers in the primary tumor, metastatic lymph node and lung node as it progressed ($P < 0.05$).

Conclusion

Thus, when comparing the level of marker expression as the tumor progresses, an increase in the expression of the metastatic node in the lungs is observed compared to the expression of markers in the primary tumor. However, it is not possible to assess the role of these markers in breast cancer metastasis. When analyzing the prognosis of metastasis to the lungs and pleura,

it is necessary to take into account such indicators of the tumor as the morphological structure of the tumor, the degree of malignancy, the degree of differentiation of the tumor cell and, of course, its receptor status together with the immunohistochemical markers of progression.

The obtained data allow us, oncologists, to identify heterogeneous biological subtypes of a breast tumor, which is the main factor in modern oncology in choosing a treatment strategy.

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