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EXPERIMENTAL THERAPY OF BASAL-LIKE SUBTYPE BREAST CANCER

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Abstract
The cytotoxic activity of the drugs Ekdisten and Erexin was determined in relation to tumor tissue of breast cancer with a negative phenotype of receptor expression for estrogens and progesterone (ER(-)/PgR(-)). Drugs Ekdisten and Ereksin have significant cytotoxic activity against estrogen-negative breast cancer cells, while their effectiveness increases with the simultaneous use of drugs. The mechanism of such high cytotoxic activity of drugs lies in the possibilities of regulating the activity of the aromatase enzyme in cancer cells.

Keywords: Breast cancer, ekdisten, ereksin, estrogen-negative phenotype.

Histogenetically basal-like breast cancer (BC) relates to the basal epithelium, which consists an exterior layer adjacent to the basal membrane, lining the ducts and lobules in the healthy mammary gland. It is a morphologically and immunophenotypically heterogeneous population that has features of epithelial and smooth muscle cells, which is reflected in their name - myoepithelial. In addition to other markers, the expression of high molecular weight basal cytokeratins (CK5 / 6, CK14, CK17), EGFR (HER1), p-cadherin, CAV1 and CAV2 are typical for these cells. The expression of genes typical for basal/myoepithelial cells are also determined in basal-like BC cells. Many products of these genes perform a structural role, participate in the proliferation of cells, the inhibition of apoptosis, migration and / or invasion i.e. in processes peculiar to cancer [8]. At the same time, the expression of ER, ER-dependent and other genes characteristic for luminal epithelial cells of normal breast tissue as well as the genes of HER-2 amplicon in basal-like tumors are minimal. Thus, in a basis of aggressive phenotype of basal-like tumors lies the corresponding genotype, indicating the origin from the least differentiated (possibly even stem) cells [1, 2].

Endocrine therapy is indicated for most breast cancer patients with receptor-positive tumors (ER + / PR +) [3].

The ovarian production of steroids decreases with age, and postmenopausal estrogen production occurs mainly in peripheral tissues such as adipose tissue and adrenal glands, where the corticosteroid androstenedione converts firstly to estrone and then to estradiol [4, 5]. This peripheral conversion occurs with the help of aromatase (an enzyme complex consisting of cytochrome P450 and flavoproteins), which is a catalyst for the transfer of androgens to estrogens [6].

The treatment of basal-like BC with a negative phenotype of the expression of receptors for estrogens and progesterone (ER (-) / PgR (-)) is currently an urgent problem in oncology.

As natural aromatase inhibitors, we propose to use two preparations which are obtained from the natural raw materials of Uzbekistan: Ekdisten and Ereksin.

We conducted a determination of the cytotoxic activity of the preparations Ekdisten and Ereksin in relation to the tumor tissue of breast cancer with the negative phenotype of the expression of receptors for estrogen and progesterone (ER (-) / PgR (-)).

Material and methods. For the study, samples of tumor tissue of breast cancer were selected in patients who underwent surgery for the treatment of this disease at the Republican Cancer Research Center in Tashkent, Uzbekistan. Criteria for selection were a verified diagnosis of breast cancer and surgical intervention in this reason.

All patients were undergone routine clinical studies (biochemical status, clinical characteristics of the tumor, histological, ultrasound, radiographic examination, computer tomography).

Determination of the expression of receptors for estrogens and progesterone was carried out using commercial kits for the immunohistochemical study of DAKO.The cytotoxic activity was determined according to the method [7].

Results. The results of the determination of the cytotoxic activity of the studied preparations in relation to tumor tissue of breast cancer with a negative (ER (-) / PgR (-)) phenotype of receptor expression for estrogens and progesterone are presented in Table 1.

The study of the cytotoxic activity of the preparations Ekdisten and Ereksin in relation to estrogen-negative breast cancer cells showed that in doses 200 μg/10^6 cells, Ekdysten suppresses the viability of cancer cells by 63.0% (54.0±4.98% was necrotic and 9,0±2.86% apoptotic cell death). In doses 4.0 mg/ 10^6 cells, ereksin induces the death of 47.0% of cancer cells (37.0±4.82% was necrotic and 10.0±3.0% apoptotic cell death).

The most significant cytotoxic effect on estrogen-negative breast cancer cells was observed with the combined use of drugs Ekdisten and Ereksin: in doses 200 μg/10^6 + 4 mg/10^6 cells, the viability of cancer cells was 71.0±4.53%.

The study of background states of aromatase activity in samples of estrogen-negative and estrogen-positive forms of breast cancer

Table 1

The cytotoxic activity of the preparations Ekdisten and Ereksin in relation to estrogen-negative breast cancer cells

Groups and influencing doses of preparations	Dead, %	Alive, %	Apoptosis, %
Ekdisten			
1-group 200 μg/10^6	54.0±4.98	37.0±4.82	9.0±2.86
2-group 100 μg/10^6	19.0±3.92	67.0±4.70	14.0±3.46
3-group 50 μg/10^6	24.0±4.27	60.0±4.89	16.0±3.66
4-group 25 μg/10^6	40.0±4.89	62.0±4.85	8.0±2.71
Ereksin			
1- group 4 mg/10^6	37.0±4.82	53.0±4,99	10.0±3.0
2-group 2 mg/10^6	12.0±3.24	74.0±4.38	14.0±3.46
3-group 800 μg/10^6	28.0±4.48	71.0±4.53	1.0±0.99
4-group 400 μg/10^6	27.0±4.43	71.0±4.53	2.0±1.4
Ekdisten+ Ereksin			
1-group 200 μg/10^6 + 4 mg/10^6	71.0±4.53	29.0±4.53	0
2-group 100 μg/10^6 + 2 мг/10^6	52.0±4.99	41.0±4.91	7.0±2.55
3-group 50 μg/10^6+800 μg/10^6	33,0±4,70	61.0±4.87	6.0±2.37
4- group 25 μg/10^6 + 800 μg/10^6	28.0±4.48	68.0±4.66	4.0±1.95
control	**18.0±3.84**	**82.0±3.84**	**0**

showed high enzyme activity in cells in the case of the negative phenotype. Under influence of preparations Ekdisten and Ereksin, it has been determined that the inhibition of aromatase activity by Ereksin in breast cancer cells exceeds analogous indicators of Ekdisten 2.4 times.

Conclusion. Preparations Ekdisten and Ereksin have significant cytotoxic activity against estrogen-negative breast cancer cells, while their effectiveness increases with the combined use of preparations. The mechanism of such a high cytotoxic activity of preparations lies in possibilities of regulation of the activity of the aromatase enzyme in cancer cells.

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