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Triple negative endometrial cancer

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Endometrial cancer (EC) is the most common malignancy of the female genital tract in the developed countries [1]. In Poland, EC incidence increased from 3.496 to 5.251 between 2000 and 2011, with 5.251 new cases were diagnosed in 2011 alone [2], and this upward trend is expected to continue [3]. There are two types of endometrial cancer: estrogen-related type I (approximately 80% of the cases) and unrelated to estrogen type II. Type I includes *adenocarcinomas* which grow slowly, have better prognosis, superficially infiltrate the *myometrium*, originate from endometrial hyperplasia without atypia, and occur before and after menopause. The most common type I mutations include *PTEN, KRAS* and microsatellite instability. Type II is represented by serous, mucinous, clear-cell carcinomas, with aggressive behavior associated with poor prognosis, high risk of distant metastases at diagnosis, deeper infiltration of the uterine muscle, often to serosa, originating from the atrophic endometrium, and typically presenting after menopause. The most common type II mutations include *TP53*, *HER-2* and *P16* [1].

Prognostic factors in EC include the presence of estrogen receptors (ER) and progesterone receptors (PR), as well as HER2 overexpression. PR and ER are markers of good prognosis [4, 5]. Their absence indicates poorer prognosis, an unfavorable histological type (such as clear-cell or serous carcinoma), higher histological grade, more frequent metastasis to the lymph nodes, and higher clinical staging at diagnosis [6, 7]. HER2 overexpression implies poor prognosis, higher histological grade and clinical staging, and shorter survival [8, 9, 10]. Similarly shorter survival was observed in patients with breast cancer with HER2 overexpression [11, 12]. Endometrial carcinoma with simultaneous absence of ER and PR expression as well as HER2 is marked as triple negative type (ER-, PR-, HER-2 -).

Numerous authors have described the relation between ER, PR and HER-2 expression and clinico-pathological factors, as well as prognosis in endometrial cancer. However, to the best of our knowledge, only 4 papers have dealt with triple negative EC [13–16].

The triple negative phenotype was first described in breast cancer. Triple negative carcinoma is associated with a higher risk of metastasis and poor prognosis [17]. Similarly to 12–17% of triple negative breast cancer cases, the triple negative phenotype is observed in approximately 15–20.7% of EC patients [13, 14]. It is related to more frequent metastases to the lymph nodes, deeper myometrial invasion, unfavorable histological type, higher histological grade and clinical staging, and shorter survival [14]. Due to poor prognosis, the search for new treatment options for EC continues [13].

The triple negative phenotype is also found in 15.5% of ovarian cancers [18]. Interestingly, the percentage of triple negative ovarian, endometrial and breast cancers is similar, which may indicate similar pathogenesis.

In the group of triple negative breast cancers, the *BRCA-1* mutation occurs in 10% of the cases [17]. On the other hand, 90% of BRCA-dependent tumors are triple negative. Moreover, similarly to the *BRCA-1* mutation, the *PTEN* mutation, detected in 30–80% of EC cases, sensitizes cancer cells to the therapy with PARP-1 inhibitors [19–21]. High activity of PARP-1 is observed at the time of genome instability [22]. A high level of the PARP-1 expression was observed in BRCA-1-dependent breast cancers. Cancer cells which are constitutively deprived of one DNA repair mechanism have been found to reveal overexpression of PARP-1[23], which has become a rationale for clinical studies on the PARP-1 inhibitor in BRCA-dependent breast cancers [24, 25].

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PTEN is a suppressor gene located on the long arm of chromosome 10 (*locus* 10q23.31) which encodes phosphatidylinositol-3 ,4, 5-trisphosphate phosphatase, a protein taking part in the regulation of the phosphatidylinositol 3-kinase (PI3-K)/AKT pathway. The activation of this pathway impacts cell growth and survival. Mutation in the *PTEN* gene, which is usually caused by the mutation of both its alleles, leads to the loss of the suppressing effect of an encoded protein on the PI3-K/AKT pathway, thus disturbing the cell-division cycle and preventing abnormal cell apoptosis [26]. The PTEN protein is of a considerable diagnostic value in EC prognosis [27]. The *PTEN* gene mutation is associated with positive prognostic factors such as a favorable histological type, lower histological grade, absence of myometrial invasion, and lower clinical staging [28]. *PTEN* mutations are related to tumor response to chemotherapy. Apart from its direct cancer-fighting property due to the HER-2 receptor inhibition, trastuzumab acts indirectly through activation of the *PTEN* protein, thus restraining the PI3-K/AKT pathway and causing apoptosis. The mutation of *PTEN* which prevents the expression of the protein can provoke the resistance of HER-positive cells to trastuzumab [29]. Abnormal *PTEN* expression leads to an increased activity of the mTOR protein kinase, thus improving the sensitivity of these cells to chemotherapy with mTOR inhibitors [30].

Clinical trials are aimed at individualizing therapy. The purpose of a targeted therapy is to reduce the adverse effects of cancer-fighting drugs by destroying tumor cells directly, while saving the healthy ones. Therefore, advanced clinical studies are conducted on PARP-1 inhibitors and on drugs which can block the mTOR and PI3K/AKT pathways. The PARP-1 expression in breast cancers indicates its varied activity in individual histological types of this cancer [23]. Noteworthy, PARP inhibitors are present in the treatment of all types of triple negative tumors. Considering their similar pathogenesis and the equal role of DNA repair pathways, we can expect similar effects in their treatment. What is also important is an equal role of the *PARP* mutation in breast and ovarian cancers, as well as of the *PTEN* mutation in endometrial cancer. The drugs expected to be used in the therapy of triple negative carcinomas are responsible for inhibiting the PARP protein or the mTOR and PI3K-AKT pathways. The latest research has found that the activity of PI3K/AKT pathway is absent in triple negative endometrial cancers [31].

Data on the expression levels of receptors which are prognostic factors in triple negative endometrial cancers are limited. The existing studies have reported significantly higher CD151 expression in triple negative endometrial cancer as compared to other histological types. Increased CD151 expression is the basis for worse prognosis [15]. Likewise, higher CD151 expression in triple negative breast cancer is associated with shorter survival time and poorer prognosis [32].

A study examined the relation between tumor-related macrophages and the triple negative phenomenon in the endometrial cancer. In comparison to tumors which are not burdened with this phenomenon, a considerably higher percentage of tumor-related macrophages were found in triple negative cancer. Also, a relation between EGFR expression and triple negative endometrial cancer was observed [13]. The results of research on the role of individual receptor expression in triple negative ovarian cancer have not been published yet. Noteworthy, triple negative cervical cancer has not been described in the literature so far.

Studies on the triple negative phenomenon continue to be conducted. Due to their aggressive character and poor prognosis, triple negative cancers are important objects of research and may serve as individualized treatment targets.

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