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The Influence of Interleukin-6 on the Course of Ovarian Cancer

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ABSTRACT: In Poland, in 2015, according to the National Cancer Registry (NCR), cancer was diagnosed among 163 281 people, including 81 632 women and 81 649 men. Ovarian cancer in 2015 affected 3% of women who had cancer. Interleukin 6 is a glycoprotein that consists of 212 amino acids. The gene encoding interleukin 6 is located on chromosome 7 adjacent to the gene LOC541472 and RSP26P32 in 7p15.3. The sources of interleukin 6 include tumor cells and macrophages that are secreted by bone marrow cells as a result of a process in which monoblasts are transformed into the promonocyte in the bone marrow, and the next monocytes into the macrophage in the blood. Scientific evidence points to an increase of IL-6 in blood by about 10 pg/ml in relations to healthy people and the increased expression of the encoding gene IL-6 by 2.2 in cancer tissue in relation to healthy tissue. The authors of the studies carried out so far do not indicate a connection between the concentration of IL-6 in the blood and the size of the tumor according to the FIGO classification, and predict a shorter survival time for patients with an increased level of IL-6. Mutation in the encoding gene IL-6 174 G>C according to the previously collected research results does not affect the patients' expected life expectancy. There are no research results that would indicate that the mutation in the IL-6 gene affects its concentration in the blood or the level of gene expression that is responsible for its coding.

Keywords: Ovarian cancer; IL-6.

1. INTRODUCTION

Over 95% of malignant ovarian tumours have epithelial origin (cancer). Factors that increase the risk of disease are, among others, carrying the mutation of BRCA 1, BRCA 2 genes, hereditary cancer syndromes, childlessness. Reducing the risk of ovarian cancer is observed when using hormonal contraception, ovoid occlusion, uterine excision and breastfeeding [1]. Ovarian cancer is one of the most common causes of death in women worldwide. High mortality results from the diagnosis of the disease in its late stages [2]. This disease is characterized by a high rate of relapse, even when using the recommended therapies, i.e. surgery or chemotherapy [3]. The number of patients in 2015 according to the national cancer registry (NCR) was 163 821, including 81 632 women and 81 649 men. According to the NCR data, ovarian tumours accounted for 5% of cases. Data from 2013 tells us that ovarian cancer accounted for 5% of cancer cases. According to NCR data, the risk of becoming sick increases with age up to the middle of the seventh decade of life. After the age of 50, 80% of cases of ovarian cancer occur, of which 50% are diagnosed between 50 and 90 years of

age. Among women with ovarian cancer diagnosed in 2000-2002, the annual survival rate was 71.9%, while in 2003-2005 it was at the level of 70.8% [4]. In the early stages (25-30% of cases), the presence of a tumour is found in adnexa. In the case of women with advanced cancer (about 70% of patients), in addition to the presence of a tumour in the adnexa, there is still the presence of fluid in the abdominal or pleural cavity. The diagnosis of ovarian cancer is based on the pathomorphological assessment of the material obtained by biopsy of fluid from the peritoneal or pleural cavity or lymph nodes. In each case, the histological type and histological differentiation are determined. The degree of advancement in ovarian tumours is determined in surgical and morphological stages. The current classification of the International Federation of Gynaecology and Obstetrics of Ovarian Cancers was introduced in 2014. The I stage is limited to the ovaries. In the II stage, the pelvic structure is taken over. The III stage includes 1 or 2 ovaries with microscopic metastases to the peritoneum outside the pelvis, and/or metastases to regional lymph nodes. In the IV stage, distant metastases are formed [5]. Ovarian tumours can be divided into two types. Type I includes clinically less malignant ones diagnosed in the early stages of clinical advancement. They are serous, endometrial, mucosal, clear cell Brenner carcinomas. They are characterized by slow growth, less frequent relapses and a good prognosis (80% of 5-year survivals). Type I tumours are not sensitive to chemotherapy. Type II of ovarian cancers is responsible for 75% of cases and has a very unfavourable clinical course. Type II distinguishes the following tumours: serous, endometrial, undifferentiated and sarcoma. These tumours are characterized by high sensitivity to chemotherapy [6]. Some data indicate that one of the factors that can contribute to cancer is the involvement of inflammation, which occurs as a result of overexpression of genes that code cytokines [7]. According to literature data, cytokines are included in proteins that are responsible for the key role in cancer processes [8].

2. INTERLEUKIN-6

Interleukin-6 (IL-6) is immunoregulatory pro-inflammatory cytokine. IL-6 is a glycoprotein that consists of 212 amino acids [9]. Interleukin-6 includes, among others, tumor cells (ovarian cancer, multiple myeloma, prostate cancer, kidney cancer, melanoma, B-lymphoma, cervical cancer and others) and macrophages that are secreted by bone marrow cells as a result of the process in which the monoblast transforms into a promonocyte in the bone marrow, and then the monocyte into the macrophage in the blood. Heir number is not precisely determined in the research carried out so far [8, 10, 11]. In people, the gene coding interleukin 6 is located on chromosome 7 adjacent to the gene LOC541472 and RSP26P32 in 7p15.3 [12]. The reference ranges of interleukin-6 concentration are not precisely defined by most available standards.

3. THE ROLE OF INTERLEUKIN-6 IN THE COURSE OF OVARIAN CANCER

Interleukin 6 (IL-6) in numerous works is associated with inflammatory process, the increased occurrence of which is indicated in the pathogenesis of ovarian cancer [7]. The data indicate that IL-6 may be involved in the course of neoplastic diseases, i.e. multiple myeloma, endometrial cancer, lung, colon, breast and cervix cancer [13]. In the study by Dobrzycka et al. [14] 118 people suffering from ovarian cancer and 64 people in the control group participated. The average IL-6 concentration in the blood of patients with ovarian cancer was 11.5 pg/ml and in the control group 2.9 pg/ml. In the case of IL-8, it was 29.8 pg/ml in the group with ovarian cancer, and in the control group 9.3 pg/ml. In the group with ovarian cancer, the CRP level was 9.51 pg/ml and in the control group 1.2 pg/ml. The study group and the control group differed significantly between each other in the level of inflammatory mediators ($p<0.05$). In the study, a statistically significant difference was found in the level of IL-6 in groups of various malignancy and tumour size. Such a difference also occurred in the case of IL-8 and CRP, which point to inflammation [14]. In the study by Mądry et al. [15] among 20 patients in the years of 1990-1996, in the study group there were 3 patients with stage I cancer, 8

patients with state II cancer, 10 with stage III cancer, while the size of the cancer of the remaining patients was qualified as stage III and IV of malignancy. 13 patients died until the completion of the observations. At the end of the observation, 7 patients lived, 5 of whom were undergoing treatment and 2 under observation. Before the beginning of surgical treatment, the concentration of IL-6 was 25.51 pg/ml (min 2.02 pg/ml, max 134.25 pg/ml) and it decreased before the III course of chemotherapy on average to 4.80 pg/ml (min 0.82 pg/ml, max 30.36 pg/ml) in a statistically significant manner. There was no relationship between the size of the tumour and the clinical stage according to FIGO (International Federation of Gynaecology and Obstetrics) [15]. Evaluation of the level of IL-6 gene expression in a healthy and cancerous tissue by Masoumi-Moghaddam et al. among 98 people indicates its higher level in cancer tissue 3.35 ± 0.15 in relation to the healthy tissue 1.15 ± 0.15 [16]. In the study by Sanguinete et al. serum was collected from the test group composed of 26 people with ovarian cancer before surgery and the level of IL-6 was assessed. The study indicated two levels of IL-6 after data division according to the predicted survival duration < 60 months and > 60 months. A higher level was observed in women who were expected to have a shorter survival time [3]. In a study carried out by Kolomeyevskaya et al., the estimated survival time of patients with increased levels of IL-6 is shorter than in patients whose levels are within the upper normal limits, i.e. 12.5 pg/ml (according to [15, 17]). In the review paper and meta-analysis by Zhai et al., the effect of 174 G>C polymorphism in the IL-6 gene in the course of various cancers (including ovarian cancer) was assessed. Data based on predicted values do not indicate that polymorphism is associated with a shorter survival time for cancer patients [18].

4. CONCLUSIONS

The effects of IL-6 in ovarian cancer have not been fully understood. The results obtained so far show that the concentration of interleukin 6 may be higher in women with ovarian cancer in relation to healthy women and affect the predicted length of survival of patients with ovarian cancer. The authors of the studies carried out so far do not indicate a relation between the size of the tumour according to the FIGO classification and predict a shorter survival time for patients who had an increased level of IL-6. According to the previously collected research results, the mutation in the gene coding IL-6 174 G > C has no effect on the patients' expected life expectancy. There are no research results that could suggest that the mutation in the IL-6 gene affects its concentration in the blood or the level of gene expression that is responsible for its coding.

Conflict of Interest: The author declares no conflict of interest.

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