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## Mechanisms of drug resistance in ovarian cancer

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### Abstract

Ovarian cancer is the fifth most common cancer affecting women and the most lethal cancer among the gynecological cancers. Because of the lack of specific symptoms and no special screening tools, it is recognised in an advanced stage. In addition, drug resistance in ovarian cancer is so frequent, that genes and cross-talks between some important pathways are still analysed. In this review, the major and recently identified molecular mechanisms of drug resistance, including platinum, taxane, bevacizumab and PARPi resistance mechanisms in ovarian cancer from relevant literature have been investigated.

**Key words:** platinum resistance; PARPi resistance; ovarian cancer; drug resistance

## Introduction

Ovarian cancer is the fifth (1) most common cancer affecting women and the eighth most common cause of cancer death. (2) Although it may occur at any age, especially women older than 50 years are suffering from this disease. There are no specific symptoms occurring in the beginning of the disease and also no special screening tools are used. Therefore, the disease is recognised in an advanced stage, which increases mortality and morbidity. (3) The risk factors such as family history of breast or ovarian cancer, high BMI, gonadotropic and steroid hormones, oncogenic and tumor suppressor genes, infertility increases the probability of this cancer. There are also factors like pregnancy, hysterectomy, tubal ligation and oral contraceptive, which reduce ovarian cancer risk. (1)

The most common type, which occurs in 70%, is epithelial type (4), actually serous carcinoma. In addition, the majority of high-grade serous ovarian cancers have recently been found to develop in the fallopian tube, not the ovary. From time to time, epithelial type can be associated with BRCA 1/2 mutation - they are present in approximately 14% of epithelial type cancer. (5)

Primary treatment of newly diagnosed ovarian cancer includes surgical treatment, whose main aim is the total cytoreduction of the tumor. Therefore the operation is extensive: obtaining fluid for cytological study, bilateral salpingo-oophorectomy, radical hysterectomy, excision of the greater omentum, pelvic and aortic lymphadenectomy and appendectomy are made. It is necessary for proper determination of the clinical stage. The primary treatment also includes standard protocol of chemotherapy, which includes 3 to 6 cycles of platinum (carboplatin or cisplatin) and taxoid (paclitaxel) in 21-day cycles. Unfortunately, the majority of patients are not sensitive to described first line treatment and the second-line chemotherapy protocol is needed.

The effect of first-line treatment defines the categories of patients:

- platinum sensitive - recurrence after 12 months since completion of first-line treatment (33.5% of patients),
- partly platinum sensitive - recurrence within 6-12 months after completion of first-line treatment (22.7% of patients),
- platinum resistant - recurrence within six months after completion of first-line treatment (22.7% of patients).
- platinum non-sensitive - tumor progression during first-line treatment (5.3% of patients). (6)

In the second-line treatment gemcitabine, doxorubicin and other combinations are used (6). but still the progression free survival and overall survival is not satisfying.

## Platinum resistance mechanisms

Resistance mechanisms of platinum are compound and multifaceted. Firstly, in the plasma membrane, exporters like ATP7A and ATP7B, which increased efflux of platinum are located. (7) Moreover, transporters like CTR1, QATP1B3 decrease platinum uptake. (8) There is some research, which describes the meaning of CYP1B1- the cytochrome, which is responsible for inactivation of the drug. Its expression is higher in the primary and metastatic loci of ovarian cells. (9)

Inside the cells, cisplatin can be also inactivated by detoxification or conversion to disabled conjugates by glutathione transferase  $\pi$  and  $\gamma$ -glutamylcysteine synthetase. (10) Some studies showed important role of ATP7B genes in ovarian carcinoma, which expression is higher in platinum-resistant cells compared with sensitive cells. ATP7B gene silencing resulted in an increased reduction of cisplatin levels and DNA adduct formation in cisplatin-resistant cells, which in vivo was connected with reduction in tumor growth, an increase of tumor cell apoptosis and an reduction of angiogenesis. (11)

Recently acquired knowledge has provided insight into the molecular mechanism of DNA repair pathways and their effect on response to chemotherapy. DNA mismatch repair (MMR) is associated with increased risk of developing several types of cancer. In the ovarian cancer it is not so important, because the incidence of germline MMR gene mutations is only 2%, but there are many mechanisms of seven main genes (MSH2, MSH3, MSH6, MLH1, MLH3, PMS1, PMS2) occurs in 29%. A number of in vitro studies suggested that MMR deficiency results in platinum resistance. (12) An impact on DNA, and in consequence platinum resistance, can be also caused by an increase in nucleotide excision repair (NER), especially when NER pathways repairs single strand DNA damage. (13) The higher expression of excision repair cross-complementing group 1 and 2 (ERCC1/2), a gene, which plays an important role in the NER pathway, was described in the group of platinum-resistant patients.

Although, BRCA1/2-deficient serous ovarian cancer is responsive to platinum, the resistance can develop. The most common mechanism is the reversion mutations, which restore DNA damage repair. (14,15)

### **Taxane resistance mechanisms**

Paclitaxel, which has shown biological activity in platinum-resistant ovarian cancer, can be used as a single-agent in second-line treatment. Unfortunately, most patients develop paclitaxel resistance as a result of the treatment.

In the paclitaxel resistance, one of the mechanisms is based on efflux pump P-gp. The expression of this pump is correlated with the resistance to taxanes and it is associated with decreased progression-free survival (16). The second mechanism of taxane resistance is modulation of apoptotic pathways, especially an impact on expression of several antiapoptotic proteins like Bcl-2, Bcl-XL, Mcl-1 and BIRC5 (<https://pubmed.ncbi.nlm.nih.gov/12363043/>). Moreover, a downregulation of proapoptotic factors, like Bax and caspases, has a consequence in chemoresistance (17).

### **Bevacizumab resistance mechanisms**

Bevacizumab is a recombinant humanized monoclonal antibody produced by recombinant DNA in Chinese hamster ovary cells. (18) It works by binding to vascular endothelial growth factor (VEGF), preventing it from attaching to receptors on the surface of endothelial cells. This reduces the vascularization of solid tumors and thus slows down their growth. (19) The effectiveness of bevacizumab has been proven for a number of different types of cancer: colorectal cancer (20), breast cancer (21), pancreatic cancer (22) and prostate cancer (23).

This drug is also used in the treatment of ovarian cancer. It is used as a maintenance treatment for high-grade serous ovarian cancer (HGSC). Despite the confirmed increased overall survival with such therapy, cases of tumor progression are frequently observed. The mechanism of drug resistance is not well understood in this case, but it is probably related to alterations in endothelial cell function (24) and VEGF pathway signaling. (25,26) One possible cause of resistance to bevacizumab is the presence of different varieties of VEGF proteins in ovarian cancer. A study by van der Bilt et al. Showed that in ovarian cancer we can find VEGF-A, VEGF-C and VEGF-D, which may be the reason for resistance of these changes to bevacizumab. (27) The possibilities of anti-VEGF therapy are also limited by proteins, the formation of which is induced by hypoxia. It has been shown that increasing the concentration of microseminoproteins, prostate associated (MSMP) (28) and hypoxia-inducible protein 2 (29) promotes the formation of new blood vessels in the tumor under hypoxic conditions. Additionally, it is stated that the level of MSMP is significantly elevated in patients with epithelial ovarian cancer who did not respond to bevacizumab treatment, which makes it possible to consider this protein as a potential biomarker of resistance to treatment with anti-VEGF therapy. (28)

### **Poly(adenosine diphosphate)-ribose polymerase inhibitor resistance mechanisms**

Currently, even 50% of patients around the world are treated with PARPi in standard therapy. Much of the resistance to PARPi is associated with platinum resistance and its mechanisms are overlapping, like BRCA1/2 reversion mutations. With PARPi, it was also described to damage TP53 binding protein 1 functions, like keeping cells from growing and dividing too fast or in an uncontrolled way. (30) Additionally, PARPi, especially niraparib, olaparib and rucaparib, play a role of P-glycoprotein substrates, which means increased drug efflux by those pumps and a decrease of the drug concentration inside cells. (31)

### **Summary**

The drug resistance mechanisms in ovarian cancer are getting more and more known and comprehensive. Ultimately, thanks to getting to know them, it will be possible to better select drugs for the patient, as well as implement possible changes in treatment. In addition, after evaluating the benefits and disadvantages of specific drugs, it may turn out that some drugs need to be replaced with others.

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