Molecular targeted therapy in epithelial ovarian cancer

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Abstract. Ovarian cancer is the most common cause of mortality of tumors from gynecologic origin and is often diagnosed after patients have already progressed to advanced disease stage. The current standard of care for treatment of epithelial ovarian cancer includes cytoreductive surgery followed by adjuvant chemotherapy. However, the development of resistance, disease recurrence and poor prognosis is still the most important problems. In spite of enhancements in tumor debulking surgery and combination regimens, the majority of patients with ovarian cancer not only experience adverse effects, but also eventually relapses. Therefore, additional therapeutic possibilities need to be explored to minimize adverse events and prolong progression-free survival and overall response rates in patients with ovarian cancer. Recent advances in the understanding of molecular mechanisms and genetics of epithelial ovarian cancer have led to the identification of new targets. In this review we focus on the molecular mechanisms and the clinical efficacy of molecular targeted therapy on epithelial ovarian cancer.

Key words: Angiogenesis, apoptosis, epithelial ovarian cancer, molecular targeted therapy, receptors

1. Introduction

Chemotherapeutic agents and radiotherapy used today for cancer treatment are not specific to cancer cells. Advancements in molecular biology made possible the studies identifying the important molecular targets related to different phases and pathways of carcinogenesis, better understanding of the biology and behavior of individual tumors and the improvement of individualized and molecular targeted therapies (1). It is necessary to identify the structures expressed differently from the normal epithelial cells in cancer cells for efficient targeted therapy. These targets can be molecules and cascades responsible from development, progression, invasion and metastasis of the cancer cells or inhibiting apoptosis. Ideally, the targets should not be the molecules/cascades taking a role in normal cell functions (2).

This review focused on the molecular mechanisms and clinical effects of the targeted therapy in epithelial ovarian cancer.

1.1. Ovarian cancer

Ovarian cancer is the most common cause of cancer death among gynecological tumors. Epithelial ovarian tumors comprise about 90% of all ovarian cancers. Most of the patients (70-80%) are generally diagnosed at the advanced stages of the disease after intra-peritoneal involvement. In spite of high clinical response reaching 80% with cytoreductive surgery followed by platinum and taxane based adjuvant chemotherapy, average 5-year survival rates are about 30% in the advanced stage disease (FIGO Stage III-IV) (3,4).

Today, development of resistance, disease recurrence and poor prognosis are most important problems in epithelial ovarian cancers up to now. Additionally, chemotherapeutic agents used during treatment cause severe side effects. In recent years, studies on targeted therapy with the purposes of being able to improve the course of the disease and to prevent drug resistance accelerated also in the ovarian cancers (1,2).

Ninety percent of epithelial ovarian cancers occur with clonal growth of a single cancer cell (monoclonal development) (5). Development of cancer cell from normal epithelial cell occurs in consequence of a series of genetic damage. These
Molecular target cells in cancer treatment are tumor cells and/or microenvironment of tumor, stromal cells, endothelial cells, endothelial precursor cells, pericytes and immune cells. Agents tried to be developed on this subject are targeting receptor and non-receptor tyrosine kinases, serin-treonin kinases, transferases, and the other enzymes and the pathways in cancer cells. While some of them are selective inhibitors, some of them are dual or multiple inhibitors (2,6,7).

The studies on targeted therapy in ovarian cancers can be summarized in the following topics (1,8,9).

1. Therapies targeting angiogenesis
2. Therapies targeting Epidermal Growth Factor Receptor (EGFR) family
3. Poly ADP-ribose polymerase (PARP) inhibitors
4. PI3K (Phosphatidylinositol 3-kinase)-Akt-mTOR (mammalian target of rapamycin) pathway inhibitors

1.1.1. Therapies targeting angiogenesis

Therapies targeting angiogenesis and especially vascular endothelial growth factor (VEGF) among targeted therapies in ovarian cancers became the most efficient therapies (8,9). Since it provides oxygen and nutrients necessary for tumor cells to maintain their biological functions, angiogenesis is important for tumor to maintain its growth and presence. VEGF pathway is the best studied pathway related to angiogenesis.

The VEGF protein family is made up of seven ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, Placental growth factor 1 and 2) and three receptors (VEGFR1, VEGFR2, VEGFR3) (10). Several mechanisms affect regulation of VEGF gene expression. Hypoxia is the most important one among these factors. Other factors are epidermal growth factors, transforming growth factors, insulin-like growth factor 1 (IGF-1), fibroblast growth factor, platelet-derived growth factor (PDGF) and many mutation or some oncogenes (10). Signaling occurring as a result of binding of VEGF to its receptors increases endothelial cell survival, proliferation, vascular permeability, migration and invasion.

VEGFRs are expressed often in ovarian cancer cells and associated with increased ascites production, metastatic disease and poor prognosis (11,12). In immunohistochemical studies, VEGF expression was shown more frequently in platinum-resistant ovarian cancer compared to platinum-sensitive ovarian cancer (13).

There are three methods targeting angiogenesis. These methods are enumerated as the treatments directly targeting VEGF, treatments targeting VEGF receptors and prevention of intracellular signal transduction as a result of inhibition of small molecule tyrosine kinase activity. Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody developed against all isoforms of VEGF-A which has a molecular weight of approximately 149 kD and a IgG1 structure. Bevacizumab inhibits the binding of VEGF to its receptors by binding to VEGF-A (1). In the studies performed for Bevacizumab, increased survival was shown in colorectal, breast and lung cancers (14-16) and its use in metastatic colorectal cancer, non-squamous, non-small cell lung cancer, glioblastoma and metastatic renal cell cancer was approved by FDA (17).

The studies regarding use of Bevacizumab in primary, persistent or recurrent ovarian cancer treatment are ongoing. In a case report, it was reported that an efficient response was obtained by using single-agent bevacizumab in a patient with recurrent and refractory serous ovarian cancer after failure of cytotoxic treatment (18). In their phase II study performed by using single-agent bevacizumab (15 mg/kg IV, once every 3 weeks) in 62 patients with persistent or recurrent epithelial ovarian cancer and received at least 1 or more cytotoxic therapy, Burger et al. (19) reported 21% clinical response. In another phase II study including 70 patients with recurrent ovarian cancer, oral cyclophosphamide 50 mg/day and IV bevacizumab 10 mg/kg once every 2 weeks were used as low-dose metronomic chemotherapy (20). Partial response was obtained in 24% of the patients. Probability of six-month survival and progression free disease was found to be 56%. Median progression free survival and median overall survival were determined to be 7,2 months and 16,9 months, respectively.

In another case control study including ten patients, it was reported that bevacizumab in combination with weekly taxane was well-tolerated in the women with advanced stage, recurrent and refractory epithelial ovarian cancer and this combination provided short-term but a considerable amount of improvement in the cancer-related symptoms (21). In the study, at
least 6 month progression free survival was shown in 25 (40.3%) patients. Median progression free survival and median overall survival were reported to be 4.7 months and 17 months, respectively. In a phase II study performed by Cannistra et al. (22) a clinical response at a rate of 15.9% was shown in the treatment of recurrent ovarian cancer or primary peritoneal cancer by using bevacizumab as a single-agent. However, gastrointestinal perforation was reported at a rate of 11% in this study after 3 or more bevacizumab treatment regimens.

Bevacizumab and (paclitaxel+carboplatin) combination in the first line chemotherapy of ovarian cancer showed a clinical response at a rate of 75-80% and a considerable toxicity (23,24).

Recently, 2 important phase III studies related to use of bevacizumab therapy in ovarian cancer were published (25,26). In the prospective randomized study was performed by Perren et al. (25) and including 1528 patients who had high-risk, early-stage disease (stage I or IIA and clear-cell or grade 3 tumors) or advanced (stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer. In their study, carboplatin and paclitaxel combination is compared with addition of bevacizumab to this combination and administration of bevacizumab following this combination. Progression free survival increased significantly in bevacizumab treatment group. In the randomized, double-blind, placebo-controlled study performed by Burger et al. (26) on 1873 patients with newly diagnosed stage III and IV epithelial ovarian, peritoneal and fallopian tubal cancer and undergone suboptimal surgery, the place of bevacizumab in primary treatment of ovarian cancer was investigated. Carboplatin and paclitaxel chemotherapy in conjunction with bevacizumab treatment for 10 months additionally prolonged the progression free survival 4 months compared to the standard treatment in advanced-stage ovarian cancer. First line chemotherapy and bevacizumab combination in ovarian cancer patients and maintenance treatment as single-agent increase the progression free survival but marked effect on overall survival is not observed. This treatment decreased the quality of life at low but clinically significant level compared to the standard treatment (27).

The most common adverse effects of bevacizumab treatment were hypertension, fatigue, proteinuria and nephrotic syndrome, gastrointestinal perforation and fistula. Arterial or venous thrombosis, ischemia in central nervous system, hemorrhage, pulmonary hypertension and wound healing problems are rarely seen (1,25-27).

VEGF Trap (Aflibercept) is a recombinant fusion protein. It exerts its affect by targeting VEGF receptor. It is a potent inhibitor of VEGF-A and placental growth factor (28). Although a reducing effect related to occurrence of symptomatic ascites was seen in advanced-stage ovarian cancer patients resistant to chemotherapy, the risk of fatal bowel perforation was found to be high.

Also small molecule tyrosine kinase inhibitors (TKI) exert their affects by targeting VEGF receptors. The studies regarding the use of small molecule TKI like pazopanib, cediranib (AZD2171; Recentin), sorafenib (Nexavar®) and vandetanib (Caprelsa®) in ovarian cancer are ongoing. They have advantages of oral route of administration. Sorafenib is inhibitor of VEGF receptor, platelet derived growth factor receptor (PDGFR) and c-Kit (stem cell factor receptor). Pazopanib (Votrient®) is inhibitor of VEGF receptor and PDGFR (10).

In a phase II study performed, the use of sorafenib and topotecan in ovarian cancer in combination showed high toxicity and a poor clinical efficacy (29). Again in a phase II study, it was determined that the use of vandetanib in monotherapy in recurrent ovarian cancers had no clinical efficacy (30).

A partial response (17.4%) was obtained to cediranib treatment in 46 patients with recurrent ovarian, fallopian tubal or peritoneal cancer (31). In this study, grade 3 hypertension was seen at a rate of 46%. Gastrointestinal perforation and fistula were not observed.

There are also studies performed with Vascular Disrupting Agents (VDA) targeting endothelial cells and pericytes (9). These agents cause ischemia and necrosis in the tumor. There are two types of VDA. First group is ligand-directed VDAs and second group is small-molecule VDAs. Also small-molecule VDAs are divided into two groups. Synthetic flavonoids taking place in the first group work through induction of local cytokine production. Tubulin binding agents taking place in the second group (combretastatin) exert synergistic effects in ovarian cancer xenografts with chemotherapy (32). The agents in this group are not promising since they are expensive, not specific and leading to severe toxicities (1).

1.1.2. Therapies targeting Epidermal Growth Factor Receptor family

Epidermal Growth Factor Receptor (EGFR) pathway plays an important role in growth,
maintenance therapy with erlotinib treatment are rash and diarrhea. It has been shown that cancer (42). The most common adverse effects chemotherapy-resistant and recurrent ovarian oral) in 34 cases with EGFR-positive administering Erlotinib treatment (150 mg/day (41). A partial response of 5.9% was obtained by considered to be effective in ovarian cancer yet of clinical responses and they have not been gefitinib or trastuzumab resulted in a wide range of ovarian cancers. It was shown that there was a strong correlation between EGFR expression in (2,7). EGFR expression is seen in 35% and 70% of ovarian cancers. It was shown that there was a survival, migration, invasion, angiogenesis, vasculogenesis and drug resistance of tumor cells (2,7). EGFR expression is seen in 35% and 70% of ovarian cancers. It was shown that there was a strong correlation between EGFR expression in the ovarian cancer cells and poor prognosis of the disease (34). Several low molecular weight inhibitors and antibodies inhibiting the ErbB receptors were developed. Some of ErbB ligands (EGF, HB-EGF, TGF α, amphiregulin and crypto) are expressed at high levels in ovarian cancers are associated with poor prognosis (35-37).

There are two groups of drugs developed against EGFR. First group includes monoclonal antibodies (Trastuzumab (Herceptin®), Pertuzumab (Perjeta®), Matuzumab, Cetuximab) developed against extracellular receptors and second group includes signal TKI (Gefinitib, Erlotinib (Tarceva®), Lapatinib, Canertinib) developed against intracellular receptors. Both group of drugs inhibit EGFR signaling by inhibiting phosphorylation or receptor activation (38,39). When pertzumab which was a monoclonal antibody against EGFR was combined with chemotherapy, it showed promising results (40). Clinical benefits can be seen in especially platinum-resistant ovarian cancer with low HER3 mRNA expression.

However, the other EGFR inhibitors like gefitinib or trastuzumab resulted in a wide range of clinical responses and they have not been considered to be effective in ovarian cancer yet (41). A partial response of 5.9% was obtained by administering Erlotinib treatment (150 mg/day oral) in 34 cases with EGFR-positive chemotherapy-resistant and recurrent ovarian cancer (42). The most common adverse effects are rash and diarrhea. It has been shown that maintenance therapy with erlotinib treatment following first line chemotherapy had no effect on progression free survival (43).

Expression and activation of the non-receptor tyrosine kinase Src leads to tumor cell growth, survival, and metastasis, and is an indicator of poor prognosis in ovarian tumors (41). Src kinase family has nine members: Src, Fyn, Yes, Lyn, Lck, Fgr, Blk, Hck and Yrk (41). It was shown that Src and Yes are produced and activated in the last phase of ovarian cancer and also these are key mediators of various receptor tyrosine kinases like EGFR, Met, VEGFR or HER2. Activation of Src promotes angiogenesis and invasion by supporting VEGF-A expression and by inhibiting anti-angiogenic factor expression through TGFβ1 (41). Activation of Src is also associated with platinum drug resistance. This result may have a therapeutic value by reducing the resistance development in the treatments with inhibition of Src combined with paclitaxel or anti-angiogenic agent (41). A phase II clinical study performed by using Src inhibitor saracatinib combined with paclitaxel in the patients with platinum-resistant ovarian cancer is ongoing.

1.1.3. Genomic instability and BRCA 1/BRCA 2

When a mutation occurs in tumor suppressor genes of BRCA1 or BRCA2, the probability of developing breast or ovarian cancer is higher. BRCA1 and BRCA2 encode proteins maintaining the integrity of the genome by mediating DNA-damage response and DNA repair. Although BRCA1 or BRCA2 mutations cause similar disorders, the proteins encoded by them have different functions. While BRCA1 takes place in both DNA-damage response and DNA repair, BRCA2 takes place only in DNA repair (44). Ovarian cancer patients with BRCA mutation are more sensitive to platinum based chemotherapy and give better results than the patients without BRCA mutation (45,46).

Poly ADP-ribose polymerase (PARP) is an enzyme implicated in base-excision pathway playing a role in the repair of single-strand breaks (38,39). When PARP is inhibited, single-strand breaks accumulate and progress to double-strand breaks and result in cell death (1). BRCA1 and BRCA2 proteins are involved in DNA repair pathway of normal cells. If somatic mutation or epigenetic effects cause inactivation in BRCA1 or BRCA2, alternative DNA repair pathways are engaged. Ultimately, chromosomal instability and cell death is seen. Use of PARP inhibitors in BRCA mutation carriers results in cell death. Olaparib is an oral small-molecule PARP inhibitor that was tested as single-agent therapy in phase II studies performed in recurrent ovarian cancer patients with and without BRCA mutation.
and it showed an efficient anti-tumor activity and an acceptable toxicity (47,48). In a current randomized phase II multicenter study, PARP inhibitor olaparib was compared with liposomal doxorubicin in the patients with BRCA1/2 mutation and recurrent ovarian cancers but significant difference was not reported (49).

In a randomized, double-blind, placebo-controlled phase II study, the efficacy of olaparib maintenance treatment was investigated in platinum-sensitive, recurrent, high grade serous ovarian, fallopian tubal or primary peritoneal cancer (50). One hundred and thirty-six patients were included in olaparib group, 129 patients were included in placebo group. Progression free survival in olaparib group was significantly longer compared to placebo group (8.4 months and 4.8 months, respectively). The studies regarding efficacy and tolerability of olaparib using together with paclitaxel and carboplatin in platinum-sensitive ovarian cancer are expected (11).

1.1.4. PI3K/AKT/mTOR cell signal pathway
Activation of phosphatidylinositol 3-kinase (PI3 K)/Akt pathway and increased mTOR (mammalian target of rapamycin) signaling are associated with drug resistance and poor prognosis in many cancer types (1). Activation of PI3 K and Akt was shown at a rate of 12-68% in ovarian cancer and it shows a close association with upregulation in mTOR signaling (11). Therefore, in treatment of ovarian cancer, mTOR pathway is targeted by using mTOR inhibitors.

Temsirolimus (Torisel®) is a synthetic, ester analog of rapamycin. It is indicated for the treatment of advanced renal cell carcinoma. In a phase II clinical study (GOG170I), a partial response was obtained in 5 of 54 cases (9.3%) with single-agent temsirolimus treatment in chemotherapy-resistant, recurrent ovarian or peritoneal cancers (51).

Phase I and II clinical studies related to the other mTOR inhibitors everolimus (Afinitor®) and sirolimus are ongoing (11). Future use will be for purposes of prevention of progression by combining these agents with chemotherapy and radiotherapy (1).

2. Conclusion
Since there is not a principle single oncogene in ovarian cancer, complete efficiency is not expected with targeted therapy. As it is in conventional chemotherapy regiments initiated as adjuvant to surgery in ovarian cancer treatments, it is considered that use of newly developed target therapy agents in combination with other molecular and cytotoxic regiments is more convenient approach compared to use alone.

In ovarian cancer treatment, many targeted therapies are developed. The studies are focused especially on angiogenesis inhibitors. Bevacizumab can be included among maintenance therapy agents in advanced-stage ovarian cancer. New studies related to TKI, PARP and mTOR inhibitors are required. Better understanding of molecular biology of ovarian tumor will show how better and how effective targeted therapy agents can be used in combination.

References


