REVIEW

RECENT PROGRESS IN OVARIAN CANCER THERAPY

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Abstract

Ovarian cancer (OC) represents the leading cause of gynecological cancer deaths in women. It has a high variety of histological origins, molecular pathways and genetic mutations (BRCA1 and BRCA2 somatic/germinal mutations, Lynch genes, RADS1C, RADS1D etc.) that play a key role in treatment response and prognosis (for example, clear cell carcinoma is less responsive to standard therapy). An important percentage of patients (80%) are diagnosed with metastatic disease, due to the lack of specific symptomatology and screening techniques leading to a dismal evolution. Standard treatment did not change drastically in decades consisting, nowadays, of cytoreductive surgery (debulking) and chemotherapy (a platinum-based agent, usually carboplatin and a taxane). Most patients experience complete response, but within a period of time, relapses occur and the cancerous cells may become platinum-resistant. This article depicts key clinical trials for many pharmacological agents including anti-angiogenesis drugs (bevacizumab, aflibercept, trebananib, pazopanib, sorafenib etc.), PARP-inhibitors (olaparib, niraparib), DNMT inhibitors (decitabine, azacytidine), various TKIs, DNA vaccines, oncolytic virus therapies and other agents.

Keywords: ovarian cancer, molecular agents, tyrosine kinase inhibitors.

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Introduction

Ovarian cancer (OC) is one of the most aggressive types of cancer in women, as early diagnosis is rarely performed, partly due to the lack of screening methods and to the apparently mild symptoms that can be easily confused with digestive problems (bloating, indigestion, constipation etc.).

Ovarian tumors present a high variety of histological origins and according to WHO, they can be classified in: surface epithelial (serous, mucinous, endometrioid, clear cell, transitional, epithelial-stromal) 65%, germ cell (15%), sex cord-stromal (10%), metastases such as Krukenberg tumors (5%), miscellaneous; 90% of the malignant neoplasms being surface epithelial. The histological origin affects the treatment response and the evolution. Clear cell carcinoma (CCC), for example, is less responsive to standard therapy and as a consequence has a worse prognosis.

The current standard of care consists of cytoreductive surgery (debulking) and chemotherapy (a platinum-based agent, usually carboplatin and a taxane, usually

paclitaxel intravenously). 80% of the patients have a complete response, but within a period of time most of them experience relapse after adjuvant chemotherapy. Furthermore, when the disease relapses, the cancerous cells become platinum-resistant. A recent study suggests that in high-grade serous cancer, stem cells (OCSC) – ALDH⁺ persist after the first line therapy and contribute to the relapse. IL-6 appears to influence the platinum-induced OCSC. Second-line therapy options are topotecan, lysosomal doxorubicin, gemcitabine etc. Bevacizumab (Avastin)—a monoclonal antibody that interferes with VEGF/VEGFR pathway and Olaparib - a PARP inhibitor are modern agents that are used along with chemotherapy or in palliative care. However, more than half of the patients die in less than 5 years(1). Many molecular pathways and genetic mutations have been studied and proven important in the course of the disease and play a key role in the potential treatment that can be implemented. Hereditary gene mutations account for 15-20% of cases (BRCA1 and BRCA2 somatic/germinal mutations – 75%, BRIP1, Lynch genes, RADS1C, RADS1D etc.), the remainders are considered sporadic. Gene mutations result in overexpression of certain proteins, expression of abnormal or nonfunctional proteins that promote proliferation, self-renewal, invasion and survival.

Epithelial OC is associated with the following molecular aberrations: TP53,

BRCA1 and 2, CDK12, RB1, NF1, PI3K/RAS/Notch/FOXM1 (in high-grade serous cancer); BRAF, NRAS, KRAS, ERBB2 (low-grade serous cancer); KRAS, HER2 (mucinous); ARID1A, PIK3CA, PTEN, CTNNB1, PPP2R1alfa (CCC); ARID1A, PIK3CA, PTEN, PPP2R1alfa, MMR deficiency (endometrioid). Nonepithelial OC is associated with FOXL2 (granulosa cell) and DICER1 (Sertoli-Leydig cell) aberrations.

Therapies

Monoclonal antibodies

Angiogenesis is an important factor in cancer growth and metastasis. Vascular endothelial growth factor VEGF –A activates VEGFR-2, a tyrosine kinase receptor, and induces angiogenesis and vascular permeability. It is the target of bevacizumab.

Anti VEGF antibodies

Bevacizumab (Avastin) is a humanized recombinant monoclonal antibody that interferes with VEGFR ligand binding. It is used in combination with chemotherapy or as monotherapy (15 mg/kg intravenously every 21 days). In recurrent epithelial OC it has a response rate of 16–21%. Bevacizumab significantly prolonged PFS in combination with carboplatin and paclitaxel, but with important gastrointestinal side effects (gastrointestinal perforation, bleeding). Up to date it is the most promising agent(2-4).

Aflibercept represents a decoy receptor fusion protein, that targets VEGF-A, VEGF-B and placental growth factor (PlGF) and thus inhibits angiogenesis. Aflibercept reduces proliferation and tumor volume in other types of cancer. It has been studied in advanced chemo resistant epithelial OC yielding promising results (response rate 54%). Alongside docetaxel, it has proven a satisfying therapeutic benefit(5, 6).

Anti CA125 antibodies

Oregovomab is a specific monoclonal antibody against CA125 that forms circulating immune complexes capable of inducing an immune response. Oregovomab was studied as an adjuvant immunotherapy for first line chemotherapy (paclitaxel and carboplatin). There have been noted minimal toxicity and no prolonged PFS(7).

Abagovomab is a murine anti-idiotypic antibody that mimics CA125 protein and induces an immune response. Results in phase I and II trials proved abagovomab to be safe and tolerable, although, in a phase III study, the agent was not labeled clinically effective in regards to survival. Another study suggested that the immune system status is of high importance in obtaining a clinical response. Further studies are necessary for this agent(8).

Catumaxomab is a trifunctional monoclonal antibody that targets EpCAM positive cells by activating T cells (CD3). It was studied as an ascites management agent in both platinum-resistant and -

refractory EOC. Intraperitoneal treatment was safe and with tolerable toxicity(9).

Volociximab is an integrin inhibitor mAb ($\alpha 5\beta 1$) that provides anti-angiogenic effects and may hinder cell proliferation. A phase II trial proved the tolerability of the agent, but further studies are needed(10).

Anti IGF-1R antibodies

AMG 479 (Ganitumab) represents a mAb against IGF-1R that affects cell proliferation through PI3K/Akt and MAP kinase pathways inhibition. It has been studied in combination with carboplatin and paclitaxel in vitro, showing a synergic interaction and with cisplatin, in vivo, increasing its effect. There are more studies that need to be performed in order to assess the potential effectiveness of AMG 479(11).

Other antibodies

AMG 386 (trebananib) is a recombinant peptide-Fc fusion protein, which reduces angiogenesis by binding angiotensin-1 and angiotensin-2 and, thus, preventing the association to Tie2 receptor. AMG 386 has been studied in combination with paclitaxel, topotecan and carboplatin. The administration of trebananib resulted in manageable side effects such as hypokalemia. PFS was improved by 2.8 months, but OS remained virtually unchanged. The results show potential efficacy(7-9).

Farletuzumab is a humanized monoclonal antibody (immunoglobulin G, subtype 1 kappa) which possesses high receptor affinity and, supposedly, induces

autophagy and inhibits Lyn kinase. Farletuzumab has been studied in phase I-III trials, alone or in association to paclitaxel and carboplatin, in patients with recurrent disease. The results showed an acceptable toxic profile with most of the symptoms linked to standard chemotherapy, but PFS was not significant(10, 11).

Tyrosine kinase inhibitors

EGFR inhibitors

Gefitinib, erlotinib and lapatinib are TKIs targeting EGFR and HER-2. Clinical trials investigated the response of a regimen composed of erlotinib in combination with conventional chemotherapeutic agents, rendering no improvements. A phase II trial assessed the effects of erlotinib and bevacizumab in patients with recurrent ovarian cancer. The results showed a high risk of severe gastrointestinal perforation(12).

A phase I trial evaluated lapatinib in patients with recurrent or persistent OC in combination with carboplatin and yielded poor results and severe toxicity. Despite the overexpression of EGFR, HER-2 and EGFR targeted therapies have poor response(13).

PDGFR and c-Kit inhibitors

Imatinib is a TK selective inhibitor of ABL kinase, BCR-ABL oncoprotein in CML, PDGFRs. It has been studied as monotherapy or in alongside docetaxel, paclitaxel, gemcitabine. The results showed no relevant response with no effect on PFS prolongation(14, 15).

Multikinase Inhibitors of angiogenesis

Pazopanib is an orally multi-targeting TKI(VEGFR, PDGFR, FGFR, c-KIT and RET) that exhibits an additional anti-tumorigenic effect. In a randomized, double-blind phase III study (AGO OVAR 16), pazopanib (800 mg orally) was administered to the carboplatin and paclitaxel scheme. Results showed an improved PFS of 5.6 months, but no effect on OS. As adverse effects, hypertension, neutropenia, liver toxicity and diarrhea were reported. Another study in combination to topotecan rendered a 1.7-fold drug exposure as opposed to monotherapy. This scheme would require future research(16).

Nintedanib is a triple angiokinase inhibitor (VEGFR, PDGFR, FGFR) which was part of a phase III clinical trial along with the administration of standard chemotherapy. Results showed a prolonged median PFS (from 16.6 to 17.3 months) and no effect on the OS. AEs prevailed in the hematologic and gastrointestinal sectors(17, 18).

Sorafenib is a multikinase inhibitor (VEGFR2, VEGFR3, PDGFR beta, Flt-3 and c-kit), having an inhibitory action on RAS/RAF/MEK/ERK signaling pathway. In a phase II study in combination with conventional chemotherapy, patients achieved partial responses (3.4%) and 34% experienced stable disease. Sorafenib in monotherapy confers modest activity and at the expense of notable toxicity. The most

common AEs were hand-foot skin reaction and rash(19, 20).

Dasatinib is a multitargeting TKI, including Src (implication in platinum-resistance), Lck, Bcr-Abl, c-Kit, PDGFR, FAK, EphA2. In recent studies, dasatinib along with paclitaxel, carboplatin, gefitinib, crizotinib had a synergic effect on regulating apoptosis, migration and invasion(21).

Inhibitors of the main signaling pathways

Rapamycin (mTOR) signaling pathway

PI3K/AKT/mTOR pathway mutations are present in clear cell ovarian cancer and endometroid adenocarcinoma accounting for proliferation and cell survival.

Temsirolimus and everolimus

Temsirolimus proved efficiency in endometrial cancer and has been included in clinical trials assessing its toxicity, safety and tolerability in OC. A phase II study showed modest results when it was used as monotherapy in persistent and relapsed disease. The noted adverse effects were fatigue, renal failure, pulmonary embolism, gastrointestinal symptoms. Temsirolimus was studied in a phase I clinical trial in combination with topotecan in advanced and recurrent OC. The study has been terminated because of increased toxicity (myelosuppression). Another phase I study included temsirolimus along with carboplatin and paclitaxel and was proven effective and well tolerated. A phase Ib clinical trial assessed temsirolimus in

combination with pegylated liposomal doxorubicin. The side effects were fatigue, mucositis and nausea. Temsirolimus was also studied in association to bevacizumab in advanced tumors and the most frequent adverse effects were thrombocytopenia and fatigue.

Everolimus was included in a phase I clinical trial consisting of a regimen composed of panitumumab and bevacizumab. The results showed a moderate activity. Adverse effects included hypertension, mucositis, electrolytic disorders(22).

Inhibitors of DNA-repairing mechanisms

Polyadenosine diphosphate-ribose polymerase inhibitors

PARP enzymes catalyze the addition of ADP-ribose units to DNA, being of outmost importance in single-strand DNA breaks repairing. If the mechanism is defective, single-strand DNA breaks quickly lead to double-strand DNA breaks. BRCA mutations are sensitizers to DNA breaks. PARPi lead to the accumulation of DNA breaks and so resulting in antitumor activity.

Olaparib is a PARP-1, -2, -3 inhibitor that received FDA approval and is currently used as 4th line treatment in patients with BRCA mutations.

Niraparib is a PARP-1, -2 inhibitor with affinity to PARP-2 that was also FDA approved for therapy in women with recurrent OC (regardless of BRCA type of mutation) who have previously been

treated with platinum-based chemotherapy. There were noted hematological (thrombocytopenia, anemia, neutropenia), respiratory and cardiovascular adverse effects(23).

DNA methylation inhibitors

DNA methylation (DNA methyltransferases) along with tumor suppressor genes inactivation can lead to oncogenesis. DNMT inhibitors (decitabine and azacytidine) have been evaluated in phase I/II trials as platinum-resistant OC sensitizer, displaying a promising response. A study including decitabine, paclitaxel, carboplatin with cytokine-induced killer cells resulted in a prolonged PFS in platinum-resistant patients. Further studies are needed(24).

Histone deacetylase removes acetyl groups and can offer chemotherapeutic resistance, thus combining HDAC inhibitors with chemotherapy may provide anticancer effects.

Vorinostat has been analyzed in combination to paclitaxel, carboplatin and gemcitabine in recurrent platinum-sensitive OC, but the adverse effects imposed the termination of the study(25).

Ubiquitin-proteasome pathway mutations are involved in a variety of neoplasms.

Bortezomib efficacy has been under the assessment of clinical trials as monotherapy or in combination with carboplatin, paclitaxel, gemcitabine. A recent study enhanced the synergic effects

of bortezomib and doxorubicin in OC by using nanocarriers in order to deliver the two agents(26).

Immunotherapy

DNA Vaccine

Follicle-stimulating hormone receptor (FSHR) is a transmembrane receptor expressed in healthy tissue (only in the granulosa cells of the selected follicle), 50% of OCs, endothelial cells of cancerous neoangiogenesis and metastasis. A new study designed a DNA vaccine to target FSHR and break immune tolerance starting from the principle that OC is an immunogenic disease. 2 types of vaccines were created using native or SynCon FSHR sequence. Both were capable of inducing a CD4 and CD8-dependent immune response, although CD8 T cells were the main players. There were observed important levels of IFN γ , TNF- α and IL-2. SynCon vaccine yielded superior immune response in comparison to native vaccine. The final results showed an increase in survival by up to 3 times in 25% of mice. As AEs only infertility would be expected.(27).

Oncolytic Virus Therapy

OVs (oncolytic virus) are potent combatants in cancer therapy, showing encouraging results in other types of cancers such as melanoma. It has been observed that systemic administration of OV results in an altered architecture of tumor vascularization implying furthermore a reduced perfusion with higher levels of

hypoxia. This phenomenon would render negative disease evolution such as metastasis. A recent study tackled this aspect by administering an agent (3TSR) that stabilizes the vascularization prior to the treatment with NDV (oncolytic Newcastle disease virus). 3TSR is an agent that not only normalizes the vascularization, but also promotes tumor cells apoptosis and increases the tumor infiltrating capacities of leukocytes with no apparent toxicity. In combination with the OV, primary tumor size has considerably decreased as well as secondary lesions and the action of other agents that require good perfusion and oxygen levels would probably improve. This new strategy holds great promise for future studies(28).

Conclusions

Ovarian cancer is the first cause of gynecologic cancer deaths and presents in 80% of patients as an end stage disease. Despite the advances in surgery and chemotherapy, treatment efficacy remains almost unchanged in decades, hence the need for more studies and therapeutic agents.

Conflict of interest

The authors declare no conflict of interest.

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