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REVIEW ARTICLE

Treatment of ovarian cancer beyond chemotherapy: Are we hitting the target?

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Abstract Ovarian cancer (OC) is the sixth most common cancer worldwide among women, and, in developed countries, it is the leading cause of mortality among gynecological malignancies. With an overall cure rate of <40 % across all stages, it comprises a variety of tumors with different histopathological features and biological behavior. Nowadays, OC is considered a general term that designates a group of molecularly and etiologically distinct diseases that share an anatomical location. Approximately 70–80 % of patients with OC will relapse after first-line chemotherapy, and the majority of them will eventually die of chemotherapy-resistant disease. Until now, the management of relapsed OC remains an unmet medical need. Therapy rather depends on tumor stage and grade than on histological type, but there is growing evidence that, as epithelial OC is a heterogeneous disease, it needs a tailored approach based on the underlying molecular genetic changes. Several phase III studies investigating targeted therapies are underway, and a more individual approach for treating OC will be selected in the future. The purpose of this paper was to review the literature in order to highlight available data emerging from trials and to evaluate efficacy and safety of molecularly targeted drugs in OC.

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Introduction

Ovarian cancer (OC) is the sixth most common cancer worldwide among women, and, in developed countries, it is the leading cause of mortality among gynecological malignancies [1, 2]. Patients with OC have high mortality rate due to the fact that the majority present at an advanced stage disease with wide peritoneal metastasis [3]—approximately 75 % stages III or IV [4, 5]. This mode of spread is explained by the fact that OC mainly disseminates by direct extension, through seeding or exfoliation of tumor cells from ovarian/fallopian tubes to the peritoneal cavity, and it is less likely to disperse through vasculature, even though lymph nodes can be involved, which makes OC a very aggressive disease [3]. OC has an overall cure rate of <40 % across all stages [1].

OC comprises a variety of tumors with different histopathological features and biological behavior [6]. About 90 % of primary malignant ovarian tumors are epithelial carcinomas and are further divided into numerous histologic subtypes: serous, endometrioid, clear-cell, mucinous, transitional cell, and squamous cell carcinomas with serous being the most common subtype, representing 70–80 % of all cases. Major risk factors for OC include advancing age, number of ovulatory cycles, and a positive family history of ovarian, breast, uterine, or colon cancer related to mutations of *BRCA1*, *BRCA2*, mismatch repair genes, or *TP53* in the germline cells [7].

Nowadays, OC is considered a general term that designates a group of molecularly and etiologically distinct diseases that share an anatomical location [6].

Biology and origin of ovarian cancer

Although the origin of epithelial OC is still a subject of debate, three anatomical sites—fallopian tube, mesothelial cells covering the peritoneum, and surface ovarian epithelium—have been suggested to be the potential sites of origin for ovarian serous adenocarcinomas. Traditionally, OCs have been thought to arise from ovarian surface epithelial cells into cancers that resemble epithelium of the fallopian tube (serous), endometrium (endometrioid), mucin-secreting endocervical glands (mucinous) and glycogen-filled vaginal rests (clear cell) [1]. Evidences suggest that a subset of epithelial OCs may instead originate in the fallopian tube fimbria, subsequently spreading to the ovary or peritoneal cavity. In contrast to many other cancers, malignant transformation triggers the program of normal differentiation [1, 7]. Approximately 15 % of OCs are familial and 85 % sporadic.

Two major pathways for developing OC have been proposed.

Type I OC involves low-grade serous carcinoma, mucinous, low-grade endometrioid, Brenner tumors and clear-cell histotype [1].

The tumorigenic pathway in type I carcinomas is characterized by the development through atypically proliferating or borderline tumors. They follow a progression model, which has been defined as a progression from serous borderline tumor (low malignant potential) in 60 % of cases [8] to low-grade carcinoma. With papillary architecture, these sorts of carcinomas present in younger women and occur at early stage disease (I or II—mostly at stage I) and show a favorable prognosis even at advanced stages [6]. Despite of having indolent behavior, they are relatively resistant (not refractory) to standard carboplatin and paclitaxel chemotherapy, but may respond to hormonal treatment [1, 6]. Low-grade type I cancers appear to be driven by activating mutations on a background of a relatively normal karyotype. The genetic pathway in low-grade serous carcinoma involves *BRAF* (2–35 %), *KRAS* (19–54 %) [9], *ERBB2* or *PTEN* mutations, microsatellite instability (MSI), and expression of IGF receptor. Low-grade serous cancers tend to have wild-type *TP53* and *BRCA1/2* [1, 6].

KRAS is frequently mutated in mucinous cancers [1, 10] and is associated with borderline tumors [1, 11]. Inactivating mutations of *ARID1A*, a chromatin-remodeling gene, have been found in 49 % of ovarian clear-cell carcinomas and 30 % of endometrioid ovarian cancers [1, 12, 13]. Low-grade endometrioid cancers exhibit frequent inactivating mutations and epigenetic silencing of *PTEN* and activating mutations of *PIK3CA* that up-regulate phosphatidylinositol-3-kinase (PI3K) signaling [1].

Progression into type II carcinomas seems to occur only in a small subset of type I carcinomas, in particular low-grade serous and endometrioid carcinomas. *TP53* mutations may occur during progression into type II carcinomas [6].

The second pathway is the de novo model consisting of high-grade serous carcinomas, which present in older women, typically detected as very advanced stage disease (III–IV). These tumors grow aggressively, respond to conventional chemotherapy but less often to hormonal manipulation, and have a high mortality rate. High-grade endometrioid, undifferentiated carcinomas, as well as malignant mixed mesodermal tumors also count among type II [6]. The most frequent and constant genetic change in high-grade serous carcinoma is *TP53* mutations—occurs in 50–96 % of cases [1].

High-grade type II cancers are driven by copy number abnormalities and marked genomic instability. Amplification and overexpression of genes in the *PI3K* family occur in more than 40 % of type II cancers, conferring PI3Kness, or activation of the PI3K pathway. When OCs occur in carriers of *BRCA1* or *BRCA2* germline mutations, they are generally type II high-grade tumors. Somatic mutations of *BRCA1* and *BRCA2* can also occur, *BRCA1* can be silenced, and upstream mutations can down-regulate BRCA function, producing BRCAness, or homologous DNA repair deficiency in more than 40 % of type II OCs [1].

Less than 1 % of type II cancers have mutations in *BRAF*, *PI3KCA*, *KRAS*, or *NRAS*, which are important drivers of high-grade serous cancers. Despite the low prevalence of *Rb* mutations, dysfunction of the Rb pathway has been found in 67 % of high-grade serous cancers [1, 14]. Also, the chromatin-remodeling gene *Rsf-1* has been recently demonstrated in high-grade ovarian serous carcinomas. Abundant Rsf-1 expression can contribute to genomic instability, which favors tumor growth and has anti-apoptotic effects, which is typical for type II OCs [6, 15].

The *BRCA1* and *BRCA2* genes are located on chromosomes 17q21 and 13q12, respectively. In *BRCA1* mutation carriers, the cumulative lifetime risk for OC is 40 % and, in *BRCA2* mutation carriers, 10 % [6, 16]. In *BRCA1* and *2* germline mutation carriers, somatic inactivation of the remaining wild-type allele is required, which means that a somatic mutation has to be dominant [6, 17].

BRCA1 and *BRCA2* seem to be involved in the repair of DNA double-strand breaks and in the regulation of transcription [6, 18]. In particular, *BRCA1* repairs DNA breaks by homologous recombination. *BRCA1* moves to the locus of DNA break site, recruited there by the histone protein H2AX [6, 19]. *BRCA1* also acts in the alternative nonhomologous end-joining (NHEJ) pathway, while *BRCA2* only works in the repair process of double-strand breaks using homologous recombination [6]. It seems that cells which lack functioning *BRCA1* or *BRCA2* are more likely to accumulate chromosomal abnormalities [6, 20].

Table 1 Clinical trials with target therapy in ovarian cancer

Drug	Class	Phase	Number of patients	Response
Cetuximab monotherapy [67]	EGFR MAb	II	25	PR: 4 % SD: 36 % PFS: 2.1 m
Cetuximab combination therapy (carboplatin) [68]	EGFR MAb	II	28	CR: 10.7 % PR: 21.4 % SD: 28.6 % PFS: 9.4 m
Erlotinib monotherapy [69]	TKI	II	34	PR: 6 % SD: 44 % PFS: 8 m
Erlotinib combination therapy (carboplatin and docetaxel) [2]	TKI	Ib	23	CR 21.7 % PR: 30.4 %
Gefitinib monotherapy [72]	TKI	II	27	PR: 3.7 % PFS > 6 m: 14.8 %
Gefitinib monotherapy [2]	TKI	II	24	OR 0 %
Gefitinib combination therapy (carboplatin and paclitaxel) [74]	TKI	II	68	Platinum-sensitive: OR: 61.9 %; PFS: 9.2 m; OS: 25.7 m. Platinum-resistant: OR: 19.2 %; PFS: 6.1 m; OS: 16.9 m
Lapatinib combination therapy (topotecan) [75]	TKI	II	39	RP: 14 %
Lapatinib monotherapy [76]	TKI	II	28	OR: 0 %
Farletuzumab combination therapy (carboplatin and paclitaxel/docetaxel) [55]	FR-alpha MAb	III	1,100	Median PFS: 9.0 (placebo), 9.5 (FAR 1.25 mg/kg), and 9.7 (FAR 2.5 mg/kg) months hazard ratio = 0.86 [0.70, 1.06] for 2.5 versus placebo
Vintafolide plus pegylated liposomal doxorubicin (PLD) versus PLD alone [60]	Folate–desacetylvinblastine monohydrazide (DAVLBH) conjugate	II	161	Median PFS for vintafolide plus PLD: 5.0 months PLD alone: 2.7 months
Niraparib [39, 40]	PARP inhibitor	I	39	Prolonged PR: 3 patients
Olaparib monotherapy [24, 28]	PARP inhibitor	I	50	OR: 28 %
Iniparib combination therapy (carboplatin and gemcitabine) [23, 34]	PARP inhibitor	II	41	OR: 65 % PFS: 9.5 m
Rucaparib [40]	PARP inhibitor	II	41	ORR: 5 % SD: 26 % for 4 months
Temsirolimus, bevacizumab, and liposomal doxorubicin; single-agent temsirolimus; temsirolimus and bevacizumab; sirolimus and docetaxel; and PX866 [42]	mTOR inhibitors/PI3K	I	23	RR: 30 %
Temsirolimus [46, 48]	mTOR inhibitors	II	60	PR: 9.3 % PFS ≥ 6 months: 24.1 %
Rilotumumab [3]	Monoclonal antibody HGF-target (MET receptor ligand)	II	30	CR: 3.2 %; PFS: 6.5 %

Table 1 continued

Drug	Class	Phase	Number of patients	Response
Oregovomab (monoimmunotherapy) [79]	IgG1 monoclonal antibody—anti-CA125	III	375	TTR: 10.3 months (95 % CI 9.7–13.0 months) for oregovomab and 12.9 months (95 % CI 10.1–17.4 months) for placebo ($p = 0.29$)
Abagovomab (monoimmunotherapy) [77]	IgG1 anti-idiotypic vaccine; anti-CA125	III	888	HR of RFS: 1.099 (95 % CI 0.919–1.315; $p = 0.301$) HR of OS: 1.15 (95 % CI 0.872–1.518; $p = 0.322$)

The somatic loss of the functional *BRCA* gene product was also observed in sporadic OCs. Loss of heterozygosity of the *BRCA1* gene was found in 50–70 % of sporadic OCs, and loss of heterozygosity of *BRCA2* was found in 30–50 % [6, 21].

Endometrioid and clear-cell carcinomas arise within endometriosis, which typically results from implantation of endometrial tissue into the ovaries. It has been further proposed that based on preliminary data, mucinous and transitional (Brenner) tumors may arise from transitional-type epithelial nests at the tubal–mesothelial junction by a process of metaplasia [6].

The Integrated Genomic Analyses of serous OC performed by the Cancer Genome Atlas Project provided key molecular insights into OC classification, which may have a direct effect on treatment recommendations for patients and provides opportunities for genome-guided clinical trials and drug development. Overall, the mutational spectrum was simple with mutations in *TP53* occurring in at least 96 % of samples, in *BRCA1* and *BRCA2* in 22 % of tumors, owing to a combination of germline and somatic mutations. In 2–6 % of cases, seven other significantly mutated genes were identified. Furthermore, the marked molecular differences between endometrioid, clear-cell, mucinous, and serous tumors suggest that histological subtypes warrant separate clinical trials to develop the independent treatment paradigms that have improved outcomes in other tumor types [14]. Until now, there are no validated molecular diagnostic tests for OC.

The standard treatment for advanced stage disease is staging laparotomy with tumor debulking followed by platinum–taxane-based chemotherapy. Approximately 70–80 % of patients with OC will relapse after first-line chemotherapy, and the management of relapsed OC remains an unmet medical need. Most patients will eventually die of chemotherapy-resistant disease. Currently, therapy can be expected to be a more individual approach for treating OC since several phase III studies investigating targeted therapies are underway [6]. To date, however, individual targeted agents have had only a modest impact on recurrent OC in unselected patients.

Angiogenesis is a critical and essential process for tumor growth, invasion, and metastasis. The VEGF family and their receptors (VEGFR) are the most studied pathway related to tumor neovascularization. All members of the VEGF ligands family stimulate cellular response by binding to tyrosine kinase receptors on the cell surface, causing dimerization and activation. Neovascularization also involves another growth factors and cytokines, such as fibroblast growth factors, angiopoietin, platelet-derived growth factors (PDGF), tumor necrosis factor-alpha, and interleukin 6 and 8 receptor pathways [22].

The aim of this paper was to review the literature in order to synthesize available data emerging from trials and evaluate the efficacy and safety of molecularly targeted drugs in OC. Although angiogenesis is a promising target for OC treatment, this subject is not in the scope of this article, as there are many recent papers published exploring it.

PARP1 inhibitors

Poly-ADP-ribose polymerase inhibitors (PARP inhibitors) belong to a family of multifunctional enzymes with promising effects in OCs featuring *BRCA1* or *2* mutations. These drugs block base excision repair and lead to the accumulation of DNA single-strand breaks (SSB). The latter subsequently cause DNA double-strand breaks at replication forks [6, 23]. In normal cells, these double-strand breaks (DSB) are repaired in the presence of the tumor suppressor proteins BRCA1 and 2. In the absence of these proteins, the lesions cannot be repaired, resulting in cell death [6]. Poly (ADP-ribose) polymerase (PARP) is a family of nuclear proteins with enzymatic properties and recruiting ability for DNA repair proteins. The most important member of the PARP family is PARP1, which is involved in the base excision repair system that repairs DNA damage induced by radiation and alkylating agents [24].

The concept of synthetic lethality was the rationale for developing PARP inhibitors for the treatment of tumors deficient in BRCA1 or BRCA2. Synthetic lethality is a phenomenon in which the individual deletion of two independent genes does not cause cell death, but the combined deletion is cytotoxic [24, 25]. Initial observations showed that PARP1 inhibitors had cytotoxic effects on BRCA1- or BRCA2-deficient cells and human tumors. This was caused by the lack of repair of SSB due to PARP1 inhibition and the lack of DSB repair because of homologous recombination (HR) dysfunction due to *BRCA* mutations. The advantages of synthetic lethality are the possible avoidance of the toxic effects of chemotherapy and its selectivity [24]. BRCAness is a phenotype that some sporadic tumors share with familial BRCA cancers (such as improved response and survival with exposure to platinum agents in OC) [24, 26]. These features are due to specific DNA repair defects [24, 27]. The overall frequency of the BRCAness phenotype and HR dysfunction in OC is estimated to be present in up to 50 % of high-grade serous ovarian [24, 26].

In the initial proof-of-concept study with the PARP1 inhibitor olaparib in *BRCA* mutation carriers, 28 % of patients with OC achieved an objective response of a median duration of 7 months [24, 28]. The important finding was the objective antitumor activity in platinum-resistant patients at dosages below the recommended/maximum tolerated doses (MTD). These promising results were confirmed in the expansion cohort study, in which a total of 50 *BRCA1/BRCA2*-mutated patients (13 platinum-sensitive, 24 platinum-resistant, and 13 platinum-refractory) were treated with olaparib 200 mg twice a day continuously [24, 29]. Objective response rates were 46, 33, and 0 %, respectively, confirming the activity of olaparib in patients with platinum-resistant disease [24].

Three phase II studies with the PARP inhibitors olaparib and iniparib have demonstrated activity in platinum-sensitive OC [6, 24, 30, 31]. A preliminary study has demonstrated that OC patients with *BRCA1* or *2* mutations respond better to olaparib than those without mutations [6, 32]. Olaparib seems to be associated with improved progression-free survival (PFS) after conventional chemotherapy (median, 8.4 vs. 4.8 months from randomization on completion of chemotherapy; hazard ratio for progression or death, 0.35; 95 % confidence interval [CI] 0.25–0.49; $p < 0.001$) [6, 31] and therapeutic response in both platinum-resistant and platinum-refractory disease (overall clinical benefit rate of 46 %—95 % CI 32–61 %), with a median response duration of 28 weeks) [6, 29].

The rationale for developing PARP inhibitors in combination with chemotherapy is the potentiation of the DNA-damaging effects of the cytotoxic compounds (usually platinum agents and topotecan) [24, 33]. So far, the most promising combination is iniparib with gemcitabine/carboplatin [24, 34]. The antitumor activity of iniparib (5–6 mg/kg, days 1, 4, 8, and 11 every 3 weeks) with gemcitabine (1,000 mg/m^2, days 1 and 8) and carboplatin (AUC 4, day 1) was 65 % (60 % in mutated and 71 % in wild-type *BRCA*), with a PFS of 9.5 months [24, 35]. Toxicity was remarkable, with 42 % grade 3–4 thrombocytopenia and 59 % grade 3–4 neutropenia [24, 36].

The efficacy of olaparib as maintenance in patients with platinum-sensitive high-grade serous OC has been assessed in a randomized double-blind placebo-controlled phase II study [24, 37]. The primary analysis showed that treatment with olaparib was associated with a significantly longer PFS (8.3 vs. 3.7 months), irrespective of *BRCA* status. Objective responses were seen in 12 % and 4 % of patients receiving olaparib and placebo, respectively. Ledermann et al. updated the results of this study. The number of patients with a known *BRCA* mutation increased to 95 % of the study population, at least 50 % showing a deleterious *BRCA* mutation. In this subset of patients, was seen an increase in PFS from 4.3 to 11.2 months (HR 0.18, $p = 0.0001$). In the subset of patients with wild-type *BRCA*, they found no difference PFS (5.5 months in both arms). The conclusions were that maintenance with a PARP inhibitor did not improve OS in the overall patient population (final analysis will be performed with 85 % maturity), and the use of olaparib maintenance therapy led to the greatest

clinical benefit, compared to placebo, in patients with *BRCA* mutation [38].

Niraparib (MK4827), an oral PARP inhibitor, was evaluated in a phase I study, in a cohort of 39 patients treated at 7 successive dose levels; 11 of these patients were *BRCA* mutation carriers. The results reported that three patients with serous OC had prolonged partial response (PR) (1 sporadic platinum-sensitive, 2 *BRCA*-deficient OC). Disease stabilization was observed for more than 44 weeks in the sporadic serous OC patient and for more than 16 weeks in the two patients with *BRCA*-deficient disease [39, 40].

A phase II study with the rucaparib (AG-014699/PF-0136738) enrolled 41 patients with either breast or OC and known BRCA deficiencies. They received rucaparib as monotherapy and were followed for overall response rate (ORR). Preliminary findings included a clinical benefit rate of 32 %, but an ORR of 5 % (2/38). However, 26 % (10/38) achieved stable disease (SD) for 4 months and 3 patients remained on study for more than 54 weeks [40].

Recently, it was presented at ASCO 2014 meeting, a phase II multicenter, open-label study evaluating patients with recurrent platinum-sensitive, high-grade serous, or *BRCA*-related OC. In this trial, patients were randomly assigned to receive olaparib 400 mg twice daily (46 patients) or a combination of olaparib 400 mg twice daily with the antiangiogenic agent cediranib 30 mg once daily (44 patients) until disease progression. With a median follow-up of 16.6 months, PFS was 17.7 months for patients who received the combination therapy versus 9 month for patients who received olaparib alone (HR 0.42, 95 % CI 0.23, 0.76; $p = 0.005$). The objective RR was 80 % for patients on the combination arm compared with 48 % for patients on olaparib alone ($p = 0.002$). CR were seen in 5 patients who received combination therapy, and PR in 30 patients from the same population; for patients who received olaparib alone, CR were seen in 2 patients and PR in 20 patients. These data support additional clinical evaluation of the olaparib and cediranib combination in OC, which may herald the beginning of treatments that avoid chemotherapy in some patients with recurrent OC [41] (Table 1).

PI3K inhibitors

Mutations in the p110 subunit of *PI3K*, called *PIK3CA*, are often responsible for activation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and have been reported in various human cancers. PIK3CA mutations can cause neoplastic transformation and promote cancer progression [42, 43]. The PI3K/AKT/mTOR pathway is often deregulated in gynecologic and breast cancers, and *PIK3CA* mutations have been reported in approximately 12 % of OCs [42, 44].

Preclinical studies suggested that *PIK3CA* mutations could predict response to PI3K and mTOR inhibitors, although mutations in the mitogen-activated protein kinase (MAPK) pathway (KRAS, NRAS, BRAF) might mediate resistance [43, 45].

Mutations in the MAPK pathway are more frequent in patients with *PIK3CA* mutations compared with patients with wild-type *PIK3CA* (35 vs. 11 %, respectively; $p = 0.04$). *PIK3CA* mutations occur in a significant proportion of patients with advanced OCs and that, even in a patient population that has experienced failure with standard therapies, they are associated with response to treatments that include PI3K/AKT/mTOR inhibitors. In a study conducted by Janku e *cols*, 23 *PIK3CA*-mutant patients with breast and gynecologic cancers who experienced treatment failure with standard therapies had a response rate (RR) of 30 %. Responses lasting longer than 8 months were observed in 70 %, and all responses were observed with combined therapy (44 vs. 0 %; $p = 0.06$) [42].

mTOR inhibitors

The mammalian target of rapamycin (mTOR) signaling is a serine/threonine kinase complex that regulates cell metabolism, growth, autophagy, and protein translation [46]. mTOR mediates and is regulated by many of the molecular products of the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway. mTOR exists in two distinct multiprotein complexes: mTOR complexes 1 and 2 (mTORC1 and mTORC2). mTORC1 signaling can be activated by amino acids and growth factors. Hypoxia stimulates expression of hypoxia-inducible transcription factor (HIF) and other growth factors, such as angiopoietins 1 and 2 (ANG 1, ANG 2); basic fibroblast growth factor (bFGF); tumor growth factor-β (TGFβ); and platelet-derived growth factor (PDGF). All of them can activate the PI3K/AKT/mTOR in endothelial cells, pericytes, and cancer cells [46]. Inhibition of mTOR can block angiogenesis by inhibition of HIF1α transcription as well as by intercepting the PDGF/PDGFR and/or VEGF/VEGFR signaling cascade [47].

Various mTOR inhibitors available for use in clinical trials include the prototype rapamycin (sirolimus) and three rapamycin derivatives: temsirolimus, everolimus, and ridaforolimus. Each of these inhibitors forms a complex with the intracellular immunophilin FKBP12; subsequent inhibition of phosphorylation of S6K1 and 4EBP1 prevents cyclin-dependent kinase (CDK) activation, which results in cell cycle arrest at G1/S phase and subsequent cell death by autophagy or apoptosis [46, 47].

A GOG phase II trial of the mTOR inhibitor temsirolimus (25 mg/week) in patients with persistent or recurrent epithelial OC and primary peritoneal cancer was

published in 2011. It enrolled 60 patients, and 54 were eligible for evaluation with PR in 9.3 % and PFS ≥6 months in only 24.1 %. Those results did not allow a phase III study [46, 48].

GOG 1701, another phase II clinical trial evaluating temsirolimus, enrolled 54 patients. Five of them (5.3 %) presented PR to temsirolimus monotherapy for refractory, recurrent OC or primary peritoneal cancers [49].

The roles of the mTOR inhibitors are still unclear, especially in the context of combination therapy, which may be antagonistic or a chemoresistant promoter. Phase I and II trials in recurrence or refractory OC have shown a modest response, but the presence of confounding factors suggests that further investigation is needed. Recently, combinations of mTOR inhibitors with other treatment modalities such as hormonal therapy, chemotherapy, or targeted therapies are underway, and initial results are encouraging, demonstrating clinical benefit without significant additional toxicity [48].

Folate receptor antibodies

Folate, a basic component of cell metabolism, DNA synthesis and repair, is an essential vitamin required by both normal and tumor cells [5]. Three isoforms of folate receptors have been identified [5, 50]. The isoform alpha is the most widely studied and has restricted expression in normal cells, but is highly expressed in various non-mucinous tumors of epithelial origin, including OC [5, 51]. Folate receptor alpha (FR) binds folic acid with high affinity and transports folate by receptor-mediated endocytosis. FR-alpha is distinct from the bulk folate carrier and is not in the pathway of cellular metabolism of folic acid [5, 52].

FR is overexpressed in virtually all epithelial OC, including primary peritoneal and fallopian tube malignancies but largely absent from normal tissue making it an attractive therapeutic target [5]. The increasing levels of tissue FR were noted, when the tumor progressed from early to advanced stages [5, 52]. Additionally, expression of FR is maintained in metastatic foci and recurrent tumors, and the degree of FR expression has been associated with aggressiveness and staging of tumor [5, 53]. Cells which express FR have been shown to grow in presence of low folate concentrations and have growth advantages in vivo and in vitro when compared with cells without FR. Furthermore, intracellular expression of single-chain antibodies (intrabody) to down-modulate membrane expression of FR result in inhibition of cell growth. Restricted distribution of FR in normal tissues and its high expression in epithelial OC, along with its putative role in tumor cell transformation, make this antigen a suitable target for antigen-specific, monoclonal antibody-based immunotherapy [5].

FR: an immunologic target

Farletuzumab, initially identified as MORAb-003, is a humanized, IgG monoclonal antibody with high affinity for FR that is overexpressed in about 90 % of OC [6, 54]. A phase II efficacy and safety study using a combination of farletuzumab with carboplatin and taxane in patients with platinum-sensitive OC showed improved RRs [complete response (CR): 7 %, PR: 63 %] and a longer time-to-progression (21 % had second remission longer than their first one). The combination of farletuzumab, carboplatin, and pegylated liposomal doxorubicin (PLD) has a good safety profile, according to a study with platinum-sensitive OC patients following first or second relapse [5, 6].

A multinational, randomized, placebo-controlled trial study of weekly paclitaxel with and without farletuzumab in platinum-resistant recurrent OC patients was closed prematurely. An interim analysis indicated that it was unlikely to produce a statistically significant difference in the two arms [5].

Vergote et al. has recently published at 2013 ESGO Congress, the results of a phase III double-blind, placebo-controlled study of weekly farletuzumab with carboplatin/taxane in patients with platinum-sensitive OC at first relapse. Median PFS was 9.0 (placebo), 9.5 (Farletuzumab 1.25 mg/kg), and 9.7 (Farletuzumab 2.5 mg/kg) months with no statistically significant difference between arms (hazard ratio = 0.86, 95 % CI 0.70–1.06 for 2.5 mg/kg vs. placebo). Neither 1.25 mg/kg of farletuzumab nor 2.5 mg/kg met the study's primary PFS endpoint [55].

Vintafolide: combined therapy

Vintafolide (EC145), a folate–desacetylvinblastine monohydrazide (DAVLBH) conjugate [56], is a construction of folic acid conjugated to the microtubule-destabilizing agent DAVLBH via a self-immolative disulfide-based linker system. DAVLBH is a vinca alkaloid that can prevent microtubule formation during mitosis of the cell. In this model, EC145 is endocytosed in the tumoral cell after binding to the FRα with high affinity and then releases free drugs thanks to biologically relevant pH (in the endocyte) via sulfhydryl-assisted cleavage of the disulfide linker [57], leading to liberation of DAVLBH in the cytoplasm of the tumor cell, which allows it to move quickly to the nucleus where it can play its role. It cannot enter cells through RFC, so it is highly specific for tumor cells.

A phase I study was conducted [58] in order to determine the MTD of vintafolide in patients with solid refractory tumors. The MTD was determined to be 2.5 mg, either for a bolus or for 1-h infusion, as no dose-limited toxicity was encountered. Pharmacokinetic parameters for EC145 were also investigated and reported, revealing levels of

EC145 consistent with those necessary for cytotoxicity, through targeting of FR. Vintafolide was characterized by a short half-life, which indicates quick uptake by FR-expressing tissue [59].

Recently, Naumann et al. reported the results of PRECEDENT trial. This was a phase II international trial for patients with platinum-resistant OC, in which EC145 was added to standard therapy with pegylated liposomal doxorubicin (PLD). Median PFS for participants receiving vintafolide plus PLD was 5.0 months compared with 2.7 months for PLD alone (hazard ratio = 0.63, 95 % CI 0.41–0.96; $p = 0.031$). It was also examined the utility of an FR-target imaging, 99mTc-etarfolatide (EC20). The greatest benefit was observed in the subgroup of patients with 100 % of lesions expressing the folate receptor, with a median PFS of 5.5 months in the combination therapy and 1.5 months in the single-drug PLD (hazard ratio = 0.38, 95 % CI 0.17–0.85; $p = 0.013$) [60].

Recently, it was announced that the prospective randomized double-blind phase III trial with vintafolide—the PROCEED study would be closed for futility after an interim analysis. Vintafolide did not demonstrate improvement in PFS, in patients with platinum-resistant OC [61].

MET blockade

c-MET protooncogene is located at 7q31 locus of chromosome 7 [3]. MET is a membrane receptor that is essential for embryonic development and wound healing; it has an extracellular α-subunit and transmembrane β-subunit. While the extracellular portion is responsible for binding to hepatocyte growth factor (the only known ligand for MET receptor), the intracellular portion is responsible for signal transduction. The binding of hepatocyte growth factor (HGF) scatter factor to MET receptor leads to c-Met phosphorylation and its activation. Once activated, c-Met will interact either directly or indirectly with numerous intracellular substrates such as RAS and Gab1. c-Met engagement activates multiple transduction oncogenic pathways such as RAS, PI3K, STAT, β-catenin, and Notch pathway (important in controlling and the regulation of multiple cell differentiation processes during embryonic and adult life) [3, 62].

MET gene mutation is not a frequent initiating event in most common human cancers, but it was more frequently associated with tumor progression. There is compelling evidence on the involvement of HGF/MET pathway in ovarian carcinogenesis [3].

MET was expressed in normal ovarian epithelium as well as in benign tumors, and it was over-expressed in a subset (30–40 %) of epithelial OC. Even though this overexpression was seen regardless of the histologic subtypes, it was still most frequently expressed in papillary serous carcinoma and in clear-cell carcinoma [3].

In OC, overexpression of MET was associated with poor prognosis where tumors with overexpression of MET protein had lower survival rate in comparison to those with low MET expression (17 vs. 32 months) [3, 63]. Because of its ubiquitous role in cancer, the MET axis makes it an attractive target for cancer therapy [3, 64]. Several MET pathway inhibitors are currently being studied:

1. antibodies that compete and block the binding of HGF to MET and therefore blocking downstream activation of the pathway, that is, rilotumumab and ficlatuzumab;
2. monoclonal antibodies that block the activation of MET receptor. By binding to the receptor, these antibodies resulted to its degradation and subsequently to its inactivation (onartuzumab);
3. selective MET kinase inhibitors that inhibit MET receptor activation such as tivantinib (ARQ 197) and PF04217903 and nonselective MET kinase inhibitors such as crizotinib (PF02341066), cabozantinib (XL 184), and foretinib.

Rilotumumab is the first agent targeting the MET pathway tested in women with epithelial OC. Rilotumumab was evaluated in a phase II trial for treatment of persistent or recurrent epithelial OC. In the study, patients should have received previously platinum-based therapy with a progression-free interval of 12 months or a second recurrence. Patients received rilotumumab 20 mg/kg intravenously every 14 days until unacceptable toxicity or disease progression. One patient achieved CR (3.2 %; 90 % CI 0.2–14 %), and two women had 6 months PFS (6.5 %; 90 % CI 1.1–19 %). The study was stopped after the first stage of accrual, as rilotumumab had limited activity. This level of activity does not warrant further evaluation of rilotumumab as a single agent in patients with OC [3].

Knowing that OC is a disease with very limited therapeutic options, MET inhibitors compounds seem to be very promising therapeutic intervention for patients with OC [3].

EGFR blockade

The EGFR receptor is overexpressed in 30–98 % of epithelial OC; it has a pivotal role in tumorigenesis; and its expression strongly affects the outcomes of cancer patients in clinic. The family of EGFRs (ERBBs) consists of four receptor tyrosine kinases: EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2; ErbB2), HER3 (ErbB3), and HER4 (ErbB4). Binding of extra-cellular ligands to the ligand-binding domain of the receptor leads to formation of active homo- or heterodimers, inducing C-terminal autophosphorylation of EGFR and activation of docking proteins, such as GRB2 or SHC1, tyrosine

auto-phosphorylation, and ultimate initiation of cascade of intracellular signaling events [2, 65]. The major signaling pathways activated by EGFR dimerization intracellularly are the RAS/RAF/MAPK pathway, the signal transducer and activator of transcription proteins pathway (STAT pathway), the PI3K/Akt pathway, and the Src kinase pathway [2, 66].

EGFR has been found to act as a strong prognostic indicator in OC, with increased expression being associated with reduced recurrence-free or OS rates [2]. Inhibition of EGFR activation or downstream pathways appears to be a promising strategy in epithelial OC therapy, and two kinds of approach are conceivable. Extracellularly, the EGFR ligand-binding site can be blocked by monoclonal antibodies (MAbs), leading to internalization and degradation of the receptor. Intracellularly, another promising approach is the tyrosine kinase inhibitors (TKIs), a separate drug classes with distinct mechanisms of action and pharmacodynamics, which inactivate downstream signaling cascades, thereby blocking signal transduction to the cell nucleus and following gene transcription and protein translation [2].

Cetuximab is a chimeric antibody of IgG1 isotype. Single-agent cetuximab studies in unselected epithelial OC populations only show minimal activity [2, 67]. In a phase II clinical trial of cetuximab and carboplatin combination in 28 patients with recurrent platinum-sensitive OC, 35 % (9/28) develop an objective response and 31 % (8/28) have SD and the median time-to-progression was 9.4 months (range 0.9–22.2) [2, 68]. The other EGFR MAb is panitumumab, a recombinant human IgG2 monoclonal antibody. So far, no studies of panitumumab application in OCs have been reported [2].

Tyrosine kinase inhibitors are low molecular weight compounds which compete with ATP for binding to the receptor's intracellular tyrosine kinase (TK) domain, thereby inhibiting TK activity [2]. The most advanced reversible EGFR-specific TKIs in clinical development are erlotinib and gefitinib.

In a single-agent erlotinib phase II study of patients with platinum-resistant, EGFR-positive OC, a 6 % response rate was noted with 2/34 partial responders and 15/34 (44 %) SD patients, and median OS of 8 months with survival being significantly longer in women who developed a rash [2, 69].

In a phase II study of an unselected population with OC, the treatment included paclitaxel (175 mg/m^2) and carboplatin (AUC 6) every 3 weeks for up to 6 cycles, plus oral erlotinib 150 mg/day, and the results indicated that erlotinib plus carboplatin–paclitaxel did not improve pathological complete response (pCR) compared with carboplatin–paclitaxel alone [2, 70]. Hirte et al. investigated the effect of addition of erlotinib (150 mg/day) to salvage carboplatin chemotherapy (AUC 5 every 21 days) for 50 OC patients who previously received platinum-based drugs, with 33 in the platinum-sensitive arm and 17 in the platinum-resistant arm. In the platinum-sensitive arm, there were 3 (10 %) CRs and 14 (47 %) PRs, for an ORR of 57 %. In the platinum-resistant arm, there were no CRs and 1 PR, for an ORR of 7 %. Besides, for platinum-sensitive patients with EGFR-positive tumors, there were 12 responses (60 % ORR), and in the platinum-resistant arm, the only one responding patient was EGFR-positive. Hirte's study with selected OC population indicates that EGFR-positive expression presents benefits to ORR in platinum-sensitive patients receiving combination therapy of erlotinib and carboplatin [2, 71].

In a recent phase III trial published by Vergote et al., erlotinib was added as maintenance therapy for 2 years in patients with no evidence of disease progression after first-line platinum-based chemotherapy for OC. The study did not meet its primary endpoint with no improvement in PFS (12 months in both arms) or OS. Treatment with erlotinib was also more toxic (25 % stopped the drug due to side effects). Other analyses were carried out, such as mutation, immunohistochemistry, FISH for EGFR, and the relationship between the development of rash and RR. Unfortunately, none of them showed any relation with better outcomes in the erlotinib arm [65].

In the trial conducted by Schilder et al., 27 evaluable patients were treated with gefitinib (500 mg/day), of whom 11 confirmed to be EGFR-positive and 17 platinum-resistant. Four patients, each of whom were both EGFR-positive and platinum-resistant, experienced prolonged PFS (>9 months) above the median PFS (2.2 months). The RR for patients with EGFR-positive tumors was 9 % (1/11), and this patient was the only responder confirmed to have EGFR protein expression as well as an *EGFR* mutation. Although well tolerated, gefitinib only shows minimal activity in unscreened patients with recurrent OC [2, 72].

Gefitinib and tamoxifen combination therapy was investigated by Wagner et al. in patients with OC refractory or resistant to platinum- and taxane-based therapy. Fifty-six patients with epithelial OC or cancer of the fallopian tube or peritoneum received oral gefitinib 500 mg/day and tamoxifen 40 mg/day until progression or unacceptable toxicity. In the unselected population of patients, there were no tumor responses, but 16 patients had SD, with median time-to-progression of 58 days (95 % CI 55–71 days) and median survival of 253 days (95 % CI 137–355 days). Gefitinib plus tamoxifen combination appears to be inefficacious in the treatment of patients with refractory/resistant OC [2, 73].

In another phase II study of gefitinib in combination with paclitaxel and carboplatin conducted by Pautier et al., patients were stratified as either resistant ($n = 21$) or sensitive ($n = 42$) and received 6–8 cycles of gefitinib (500 mg/

day), paclitaxel (175 mg/m^2), and carboplatin (AUC 5) every 3 weeks, followed by gefitinib alone. ORRs and disease control rates were 19.2 and 69.2 % for resistant/refractory and 61.9 and 81.0 % for sensitive disease. However, the good clinical response seemed to be more related with regimen of carboplatin and paclitaxel than with gefitinib [2, 74].

Comparing the TKIs with traditional chemotherapy, the RR to single-agent erlotinib or gefitinib in platinum-pretreated OC is overall very low, 0–5.9 %, slightly higher in patients characterized as EGFR-positive 5.9–9 %. These responses rates are much lower than that of single-agent paclitaxel or oxaliplatin in platinum-resistant cancers, 8 and 22 %, respectively. The RRs of erlotinib or gefitinib combination therapy in OC are considerably higher, 7.1–19.2 % in the platinum-refractory/resistant cohorts and 56.7–61.9 % in the platinum-sensitive cohorts [2].

Lapatinib, a tyrosine kinase inhibitor targeting EGFR and HER2 was evaluated in a phase II trial, combined with topotecan, for recurrent OC. In this study, patients that had relapsed within 6 months ($n = 20$) or between 6 and 12 months ($n = 19$) received weekly topotecan (3.2 mg/m^2 given intravenously on days 1, 8, and 15) and daily oral lapatinib (1,250 mg). An objective (partial) response was observed in 5 patients (14 %), all with late relapse. The rates of overall benefits, including responses and stabilizations, were 37 and 62 % in patients having relapsed within or after 6 months, respectively, and median time-to-progression were 58 and 94 days. The study failed to demonstrate a clinical benefit of lapatinib–topotecan compared to previously described activity with topotecan alone in the context of low levels of EGFR and HER2 expressions [75].

Another phase II trial evaluated lapatinib alone in the treatment of persistent or recurrent OC and up to 2 prior chemotherapy regimens for recurrent disease. Patients were treated with lapatinib 1,500 mg/day. Twenty-five of 28 patients were eligible and evaluable for analysis of efficacy and toxicity. No objective responses were observed [76].

To date, studies using EGFR antagonists in OC have shown limited clinical benefits [2].

Immunotherapy

Various data collectively suggest that the immune system has a protective role against OC, therefore building a rationale supporting the role for immunotherapy. Regarding potential targets, CA-125 is a high-molecular weight mucin-like glycoprotein (MUC16) over-expressed on the surface of OC cells. It is expressed by 80 % of nonmucinous epithelial OC, and constant increase in its value is generally associated with recurrence and/or progression of disease. MUC16 expression has been directly correlated with platinum resistance and tumor invasiveness [77].

Oregovomab (B43.13, OvRex) is a murine monoclonal antibody of IgG1 subclass with high affinity for CA125. It does not directly inhibit tumor growth nor induces complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity (ADCC). In fact it elicits tumor-specific T-cell responses [78].

A trial with 184 OC (FIGO I–IV) patients showed that treatment with oregovomab generates humoral and anti-CA125 responses. Forty-three percent (26/60) had a greater than threefold increase in anti-CA125 antibody levels, and the levels of increase correlated with the amount of circulating CA125 at the time of injection. Responders had a longer survival compared with nonresponders (22.9 vs. 13.5 months; $p = 0.0089$), and patients that also presented an increase in T-cell proliferation in response to CA125, 53 % (9/17), had a significantly longer survival time than nonresponders (>21 vs. 13.2 months; $p = 0.0202$). Another phase II trial confirmed this finding [79].

Berek et al. conducted a phase III trial that analyzed the role of oregovomab as a monoimmunotherapy after front-line platinum-based chemotherapy. Although oregovomab demonstrated bioactivity, the strategy of monoimmunotherapy was not effective [80]. Abagovomab (ACA-126) is an anti-idiotypic antibody produced by a mouse hybridoma and generated against OC125. The murine monoclonal antibody recognizes the tumor-associated antigen CA-125 [81].

Phase I studies demonstrated that abagovomab was safe and effective drug, capable to induce a satisfactory immune response in patients with chemotherapy-resistant OC. A phase Ib/II with 119 patients showed that 68.1 % of the patients that received abagovomab developed Ab3 responses and these patients had a significantly longer OS (23.4 months) compared with Ab3 nonresponders (4.9 months) [81].

Due to these promising results, a phase III trial (MIMOSA) involving 888 patients with FIGO stage III/IV OC in complete clinical remission after primary surgery and platinum-based chemotherapy was conducted. Patients were randomly assigned to abagovomab or placebo. However, there was no benefit in recurrence-free survival (RFS) and OS when administered as a maintenance therapy, even though it induced a measurable immune response [77].

The absence of RFS and OS benefits with abagovomab parallels the data reported with oregovomab, when used as monoimmunotherapy. Much interest remains in considering CA-125 as one viable target. Recently, trials have examined the combination of anti-CA125 drugs with conventional chemotherapies, carboplatin, and paclitaxel. A phase II study aimed to compare the magnitude of antibody and cellular response to CA125 evoked by administration of oregovomab simultaneously or 1-week after chemotherapy treatment. The authors observed that this combination triggered stronger immune responses than those

measured in monoimmunotherapy protocols [82]. Perhaps, the true potential of these drugs lies within being administered in combination with chemotherapy. Future studies are still needed in order to confirm the clinical benefit of chemoimmunotherapy.

Results of clinical trials investigating antibody-based immunotherapies are inconsistent; hence, it is too early to conclude if these drugs will be incorporated into treatment regimens against OC. New targets are being explored for immunotherapy in OC, as well as other effectors and the combination of these approaches with immunomodulatory therapies directed toward CTLA4 and/or PDL1 [78].

Conclusion

Different histological types of OC features specific signaling characteristics that may be used to mark molecular targets and provide an individualized therapy. There is growing evidence that epithelial OC is a heterogeneous disease that needs a tailored approach based on the underlying molecular characteristics, while understanding the pathogenesis is crucial for a successful implementation of novel therapies.

Conflict of interest None.

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