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REVIEW

Clinical utility of targeted treatments in the management of epithelial ovarian cancer

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Abstract: Epithelial ovarian cancer is typically found in its advanced stages, where a combination of surgical debulking and platinum/taxane-based chemotherapy is recommended. Although over 70%–80% of patients achieve remission, a significant proportion develop recurrence of their disease. Additional cytotoxic chemotherapy, as well as surgery, is typically used to manage disease recurrence. Therapies that target specific pathways in cancer cells are rapidly developing in the laboratory and are increasingly being studied in patients with ovarian cancer. We review the current status of novel therapies in the management of epithelial ovarian cancer.

Keywords: angiogenesis, polyadenosine ribose pathway inhibitors, epidermal growth factor receptor, folate inhibitors

Introduction

In the United States, approximately 21,000 women are newly diagnosed with ovarian cancer each year. There are also 14,600 reported deaths from ovarian cancer each year, making it the fifth most common cause of death from cancer and the most common cause of death due to gynecologic cancer.[1] Globally each year, there are approximately 200,000 new diagnoses of ovarian cancer and 125,000 deaths due to the disease.[2,3] Mortality rates for ovarian cancer are high because patients often present with clinically advanced disease. Unfortunately, to date, we lack adequate screening tests for early detection of epithelial ovarian cancer (EOC).

Management of newly diagnosed EOC typically involves surgical exploration for histological confirmation, staging, and maximal cytoreductive effort if gross metastatic disease is present. The goal is to achieve complete resection or at least optimal tumor debulking, defined as residual tumor of less than 1 cm in diameter.[4] Patients undergoing optimal tumor debulking have higher overall survival rates than those with suboptimal tumor debulking.[5] For the majority of EOC patients, surgery is followed by chemotherapy with a combination of a regimen containing platinum and taxane, which leads to a 70%–80% complete response rate.[6] Patients who have significant risks for surgery or are not surgical candidates for upfront debulking will often undergo neoadjuvant chemotherapy for 3–4 cycles and then proceed to interval debulking surgery followed by additional chemotherapy. In a Phase III trial by the European Gynecological Cancer group, this approach was shown to reduce mortality rates and adverse postoperative complications.[7] However, the overall survival rate was considerably lower compared with other Phase III trials involving advanced EOC.[7,8] Despite an excellent complete response rate after primary therapy, 70%–80% of patients will develop recurrence

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within a median of 18 months.[8] The responsiveness of the cancer to subsequent treatment generally decreases and those that recur 6 months or less from initial treatment (platinum-resistant disease) or have persistent disease despite primary upfront therapy have a poor prognosis. Clearly, novel approaches to the treatment of ovarian cancer are needed. Extensive research has led to improved understanding of the mechanisms involved in the pathogenesis of EOC. This has led to the rapid development of new agents that target pathways critical to ovarian cancer.

EOC has a unique pattern of metastases. Patients often have peritoneal disease that involves the surfaces of the bowel and other viscera within the intra-abdominal/pelvic cavity. Ovarian cancers are also heterogeneous in nature, making cure for these patients difficult. Multiple pathways in EOC have been determined to contribute to the pathogenesis and have recently been reviewed in detail.[9] Table 1 lists key pathways of interest, where targeted agents have been developed. These pathways are important in driving ovarian cancer cell survival, proliferation, and metastasis. In addition, angiogenesis is thought to be critical in the development of ovarian cancer. This review will examine how the current clinical trials involving these pathways impact the management and treatment of patients with EOC.

Targeted therapy in recurrent ovarian cancer

We begin our discussion with patients having recurrent ovarian cancer, given that the development of new agents generally starts with women who have measurable recurrent disease. Despite a 70%–80% remission rate after upfront treatment of EOC, 70%–80% of patients develop recurrence and ultimately succumb to their disease. With numerous agents now available to treat patients with recurrent ovarian cancer, overall survival has steadily improved. However, clinicians/researchers continue to strive to find effective therapies while trying to minimize potential side effects to patients. Thus targeted therapies may become increasingly important to help maintain quality of life while still improving patient survival. Numerous Phase II trials have examined the effectiveness of various targeted therapies in both platinum-sensitive and platinum-resistant patients, and Phase III trials are increasingly incorporating quality of life measures.

Angiogenesis inhibitors

Angiogenesis has been an area of active research in EOC. Angiogenesis is the growth and development of new blood vessels, which is driven by vascular endothelial growth factor (VEGF). As tumors enlarge, they begin to outgrow their blood supply. Hypoxia develops, which in turn stimulates an increase in VEGF production by tumors. VEGF acts upon endothelial cells, which leads to complex changes and the increase of blood vessels. There is a family of receptors that has been identified on endothelial cells, and the major VEGF receptor involved in angiogenesis is VEGFR-2. VEGF receptors on tumor cells may also be critical to tumor growth. Angiogenesis involves a complex interaction between tumor cells, endothelial cells, and stromal cells.

Bevacizumab was one of the earliest angiogenesis inhibitors examined. Bevacizumab is a humanized monoclonal antibody directed against VEGF. Burger et al reported a Phase II Gynecologic Oncology Group study (GOG170D) which examined single-agent bevacizumab (15 mg/kg intravenously every 3 weeks) in patients with recurrent EOC.[10] A 21% response rate was noted and 40.3% had a 6-month progression-free survival. However, another Phase II study of bevacizumab in patients with recurrent platinum-resistant EOC was stopped early due to increased rates of bowel perforation (11.4%).[11] Despite this, patients experienced a 16% response rate, and the median progression-free survival duration was 4.4 months. These studies indicated that

Table 1 Key pathways involved in the pathogenesis of epithelial ovarian cancer

Pathway	Function
Angiogenesis	Formation of new blood vessels to support cancer growth and metastasis; involved in vascular permeability and vasodilation.
Epidermal growth factor receptor	Membrane receptors that dimerize and activate tyrosine kinase activity, leading to activation of MAPK and PI3K/AKT pathways. This leads to increased cell growth and decreased apoptosis.
Folate pathway	Essential for purine biosynthesis; folate transporter overexpression increases folate to cancer cells, leading to DNA replication and tumor growth.
Polyadenosine diphosphate-ribose polymerase	Enzyme that repairs DNA single-strand breaks via base excision repair pathway. Inhibition of pathway leads to increased single-strand breaks, and thus DNA double-strand breaks. BRCA mutations lead to defective double-strand break repairs, resulting in chromosome instability and cell death.
PI3K-AKT-mTOR pathway	Regulates apoptosis, metabolism, cell proliferation, angiogenesis, and cell growth.

Abbreviations: PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; MAPK, mitogen activated protein kinase.

bevacizumab itself was active in the treatment of recurrent EOC, which was unique from other cancer types where bevacizumab activity was only noted in combination with other cytotoxic agents.

Bevacizumab has also been studied in combination with other agents. Garcia et al reported on the combination of bevacizumab and cytoxan administered in a metronomic fashion and found significant clinical activity (24% response rate, 56% progression-free survival at 6 months). However, the combination of bevacizumab and erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, failed to demonstrate improved clinical activity (15% overall response rate).[12]

The first and only Phase III placebo-controlled study of bevacizumab in patients with recurrent ovarian cancer was recently completed, ie, OCEANS (study of carboplatin and gemcitabine plus bevacizumab in patients with ovary, peritoneal, or fallopian tube carcinoma). This study was reported at the 2011 American Society of Clinical Oncology meeting.[13] The results show a significant improvement in median progression-free survival in the bevacizumab arm (12.4 months) compared with the placebo arm (8.4 months). Currently the Gynecologic Oncology Group is studying carboplatin and paclitaxel combined with placebo versus bevacizumab in patients with platinum-sensitive first-line recurrent disease (GOG213). Patients are initially determined if they are appropriate surgical candidates, and if so, are randomized to secondary cytoreduction or to no surgery. Patients who are not surgical candidates or have completed the surgical arm of the trial are then randomized to either carboplatin-paclitaxel or carboplatin-paclitaxel plus bevacizumab followed by maintenance bevacizumab.

Given the significant serious toxicities (eg, bowel perforation, fistula formation, thrombosis) noted in the trials, further studies are needed to improve the selection of patients who will respond to therapy and avoid unnecessary exposure and risk to bevacizumab. It is also interesting that there may be a rebound effect of worsening survival upon discontinuing bevacizumab treatments based on recent laboratory findings.[14,15] Further studies are needed to determine whether continuing bevacizumab or other antiangiogenic agents should be considered in patients.

Although bevacizumab has been the most studied anti-angiogenesis agent, numerous other angiogenesis inhibitors have also been examined and are mostly in Phase II trials. Aflibercept (or VEGF Trap) is a protein that contains portions of the VEGFR-1 and VEGFR-2 extracellular domains that are fused to the Fc portion of IgG. Aflibercept binds VEGFA and VEGFB and placental growth factor. Tew et al reported on the preliminary results of a randomized Phase II trial of aflibercept at the 2007 American Society of Clinical Oncology meeting.[16] Patients with heavily pretreated recurrent ovarian cancer were randomized to receive either 2 mg/kg or 4 mg/kg dosing. Five partial responses (11%) were noted, along with significant grade 3–4 toxicities, including hypertension, proteinuria, encephalopathy, and renal failure. Of note, there were two bowel perforations reported. Aflibercept has also been used to treat symptomatic malignant ascites in patients with recurrent ovarian cancer.[17] The mean time to repeat paracentesis was longer when patients were treated with aflibercept (55 days) as compared with placebo (22 days). However, three fatal gastrointestinal perforations were noted in patients treated with aflibercept.

The small-molecule tyrosine kinase inhibitors that target the VEGF receptor have also been examined. Sorafenib is a kinase inhibitor that targets the VEGF receptor and also targets Raf, platelet-derived growth factor (PDGF) receptor, Flt3, and c-kit. In a Phase II study by the Gynecologic Oncology Group, patients with recurrent ovarian cancer treated with sorafenib showed only a 3.4% partial response, while 34% had stable disease and 24% were progression-free at 6 months.[18] Sorafenib has also been combined with cytotoxic agents (gemcitabine) and the results have been similarly poor (4.7% objective response rate).[19] Another multitargeted kinase inhibitor, sunitinib, has also been examined, and only one of 30 patients demonstrated a partial response (3.3%), while 53% had stable disease.[20] Although the results have not been more encouraging, additional studies are needed to determine whether novel combinations of these agents with either cytotoxic or other targeted agents can improve patient outcomes.

Cediranib is a potent VEGF inhibitor with activity against VEGFR-1, VEGFR-2, and VEGFR-3, and has shown some promise in initial studies. A Phase II study using single-agent oral cediranib in recurrent EOC showed a 17% partial response rate, with stable disease noted in 13%. Median progression-free survival was 5.2 months.[21] Cediranib is currently being tested in the International Collaboration for Ovarian Neoplasia (ICON) trial, in which patients are randomized to three arms, ie, platinum-based chemotherapy with placebo maintenance, platinum-based chemotherapy plus cediranib with placebo maintenance, or platinum-based chemotherapy plus cediranib with cediranib maintenance. Cediranib so far has shown no significant toxicities in this double-blind study, allowing expansion into the second phase of this trial.[22]

Additional drugs have been developed to novel targets in the angiogenesis pathway and are in early clinical development (Table 2). These include AMG 386, which targets the angiopoietin pathway and leads to inhibition of tumor endothelial cell proliferation and growth,[23] and BIBF 1120, which is a triple angiokinase inhibitor that blocks the VEGF, PDGF, and fibroblast growth factor receptors.[24] In contrast with blocking the formation of new vessels, drugs that target the existing tumor vasculature (vascular disrupting agents) are in early research (Table 2).

Epidermal growth factor receptor

The EGFR is part of a family of tyrosine kinase receptors known as ErbB. This family also includes ErbB-2 (HER-2), ErbB-3, and ErbB-4. Ligand binding to these receptors leads to homodimerization and heterodimerization, which in turn leads to activation of the signal transduction pathway and ultimately promotes cell proliferation, angiogenesis, metastasis, and inhibition of apoptosis.[25] EGFR has been found to be overexpressed in 35%–70% of ovarian cancers.[25] Numerous EGFR inhibitors have been developed and tested in patients with ovarian cancer. These inhibitors include small molecules that block the tyrosine kinase activity of the receptor and monoclonal antibodies that target the extracellular domain.

Erlotinib and gefitinib, both small-molecule inhibitors, have been examined in patients with recurrent ovarian cancer. Single-agent Phase II studies of both drugs have been disappointing, with poor response rates noted (6% for erlotinib[26]; 0%–4% for gefitinib[27,28]). Even when patients had detectable levels of target EGFR and phospho-EGFR, which were decreased with gefitinib therapy, there was no clinically associated benefit.[29] Phase II studies combining erlotinib or gefitinib with cytotoxic chemotherapies did demonstrate significant clinical response. Patients with recurrent ovarian cancer and up to two prior lines of chemotherapy who were treated with erlotinib and carboplatin demonstrated a 57% overall response rate in platinum-sensitive disease, while a 7% overall response rate was noted in platinum-resistant disease.[30] A Phase II study of gefitinib with paclitaxel and carboplatin as second-line treatment for ovarian cancer demonstrated a 62% overall response rate in platinum-sensitive patients compared with a 19.2% overall response rate in platinum-resistant patients.[31] However, the extent of contribution of the EGFR inhibitor in these combinations is unclear.

Monoclonal antibodies directed towards EGFR have been developed. Cetuximab, a chimeric monoclonal antibody that blocks the binding of epidermal growth factor to its receptor, was examined in a Phase II study of patients with persistent or recurrent ovarian cancer. However, there was minimal activity noted, with only one of 25 patients noted to have a partial response and nine having stable disease.[32] In a Gynecologic Oncology Group Phase II study, when cetuximab was combined with carboplatin in patients who were EGFR-positive, nine of 28 patients had an objective response, with eight noted to have stable disease.[33] Despite this, further evaluation of this combination in a second stage of accrual was halted due to the response rate not meeting the study criteria.[33] EMD72000 (matuzumab), a humanized anti-EGFR monoclonal antibody, was also tested in a heavily pretreated group of patients with platinum-resistant ovarian cancer. No responses were noted in this Phase II trial.[34]

Similarly poor response rates have been also noted for anti-HER2 antibodies. Patients with recurrent ovarian cancer treated with trastuzumab had an overall response rate of 7.3%. Interestingly, only 11.4% of patients screened for this study demonstrated 2+/3+ immunohistochemical levels of HER2, which were required for treatment. Another antibody, pertuzumab, that blocks HER2 dimerization, showed only a 4.3% response rate.[35] When combined with gemcitabine in platinum-resistant ovarian cancer, a randomized Phase II study noted that the overall response rate and hazard ratio were improved compared with the placebo arm (overall response rate 13.8 versus 4.6; progression-free survival hazards ratio 0.32).[36] Current studies involve panitumumab, a fully human monoclonal antibody to EGFR (Table 2).

Other tyrosine kinase inhibitors

PDGF and KIT represent novel targets in ovarian cancers. Henriksen et al found that PDGF and its receptor PDGFR-α, are present in 73% and 36% of malignant ovarian tumors, respectively.[37] This may lead to autocrine stimulation of ovarian cancer cells.[38] Recently, PDGF-B has been shown to be important in recruiting pericytes to the endothelium.[39] Pericytes help to stabilize and maintain function of the microvasculature. Preclinical data suggest that inhibition of pericyte function may improve antiangiogenic therapies.[40,41] KIT is a transmembrane glycoprotein and a member of the tyrosine kinase family.[42] Found in numerous malignancies, KIT is activated by its ligand, stem cell factor, and also by mutations in the c-kit gene, both of which lead to downstream activation of signaling pathways.[42]

Thus far, inhibitors of the PDGF and KIT pathways have been disappointing. Sunitinib, a multikinase inhibitor, the targets of which include VEGF receptors 1–3 and PDGF α

Table 2 Summary of current clinical trials of targeted therapies for recurrent ovarian cancer*

Class	Drug	Intervention	Phase	Protocol ID
Angiogenesis inhibitors	Bevacizumab	Paclitaxel-topotecan-doxorubicin Paclitaxel-topotecan-doxorubicin, bevacizumab	III	MO22224, 2009-011400-33, NCT00976911
	Bevacizumab	Carboplatin, paclitaxel, bevacizumab	III	MO22923, 2010-019525-34, NCT01239732
	Bevacizumab	Carboplatin, bevacizumab	II	2008-000878-20, S-20080033, 2612-3754, NCT00744718
	Bevacizumab	Bevacizumab, gemcitabine	II	AVF4314S, NCT01131039
	Bevacizumab, sorafenib (VEGF inhibitor)	Bevacizumab, sorafenib	II	070058, 07-C-0058, NCI-07-C-0058, NCI-P6840, 7358, NCT00436215
	Sorafenib	Sorafenib and topotecan	II	TRIAS 2009, NCT01047891
	AMG 386	Paclitaxel plus AMG 386 Paclitaxel plus placebo	III	TRINOVA1: 20090508, NCT01204749
	AMG 386	Doxorubicin or topotecan and AMG 386	I	20070182, NCT00770536
	BIBF 1120	Carboplatin, doxorubicin, BIBF 1120 in dose escalation	I	1199.119, 2010-022523-30, NCT01314105
	BIBF 1120	Doxorubicin, BIBF 1120 in dose escalation	I, II	GYN10-149, NCT01485874
	BIBF 1120	Carboplatin, doxorubicin, BIBF 1120	I	11990117, NCT01329549
	Pazopanib	Paclitaxel, pazopanib Paclitaxel, placebo	II	GOG-0186J, NCT01468909
	Pazopanib	Pazopanib	II	GEICO-1002, 2010-020439-38, NCT01262014
	Pazopanib	Doxorubicin, pazopanib in dose escalation	I, II	SCRI GYN 26, NCT01035658
	Pazopanib	Pazopanib and cyclophosphamide	I, II	3107000, NCT01238770
	Pazopanib	Carboplatin, paclitaxel, pazopanib in dose escalation	I, II	CDR0000703686, EORTC-55092, EU-21119, EUDRACT-2010-024077-39, NCT01402271
	Cediranib Olaparib	Cediranib and olaparib Olaparib only	I, II	DFCI 09-293, U01CA062490-16S2, NCI 8348, NCT01116648
Vascular disrupting agents	Ombrabulin	Ombrabulin Placebo	II	EFC10260, 2010-024631-16, U1111-1118-5437, NCT01332656
	Fosbretabulin	Bevacizumab, fosbretabulin Bevacizumab alone	II	GOG-01861, NCT01305213
	EP-100	1EP-100, paclitaxel Paclitaxel alone	II	ACT12601, U1111-1124-2062, NCT01485848
PARP inhibitors	AZD2281	Carboplatin AZD2281 in dose escalation	I	080092, 08-C-0092, NCT01445418
	Veliparib	Carboplatin, doxorubicin, veliparib in dose escalation	I	GOG-9927, NCT01459380
	Veliparib	Doxorubicin, veliparib in dose escalation	I	CDR0000674917, AECM-000248, 00-0248, 8475, NCT01145430
	Veliparib (ABT-888)	ABT-888 in dose escalation	I	UPCI 08-121, 8282, NCT00892736, CINJ-050810
	Veliparib (ABT-888)	Cyclophosphamide, ABT-888	II	110080, 11-C-0080, NCT01306032
	Veliparib	Veliparib	I, II	Veli-BRCA, NCT01472783
	Veliparib (ABT-888)	Topotecan and ABT-888 in dose escalation	I, II	MAYO-MC0861, MC0861, 8329, NCT01012817
	Iniparib (BSI-201)	Carboplatin, gemcitabine, iniparib	II	TCD11504, 20090208, NCT01033292
P13K/AKT/mTOR inhibitors	MK-2206	MK-2206	II	10-402, NCT01283035

(*Continued*)

Table 2 (*Continued*)

Class	Drug	Intervention	Phase	Protocol ID
	MM-121	Paclitaxel, MM-121 Paclitaxel alone	II	MM-121-04-02-08 (ARD11586), NCT01447706
	Temsirolimus	Temsirolimus and bevacizumab	II	MAYO-MC0845, MC0845, 8233, NCT01010126
	Everolimus	Carboplatin, doxorubicin, everolimus in dose escalation	I	IRB 10-019, NCI-2011-00055, NCT01281514
	Everolimus RAD001	RAD001 and bevacizumab	II	09-01-RAD001BEV, NCT01031381
	Everolimus	Bevacizumab Everolimus, bevacizumab	II	GOG-0186G, NCT00886691
Folate pathway inhibitors	Pralatrexate	Carboplatin and pralatrexate in dose escalation	I, II	10-113, NCT01188876
	Pemetrexed	Pemetrexed and carboplatin	II	MMC-08-04-097, NCT01001910
	Farletuzumab MORAb-003	Carboplatin, taxane, farletuzumab Carboplatin, taxane only	III	MORAb003-004, NCT00849667
EGFR inhibitor	Panitumumab	Carboplatin, doxorubicin, panitumumab Carboplatin, doxorubicin	II	GMIHO-008/2009_AG56, 2010-018849-59, AG56, NCT01388621
	Panitumumab	Panitumumab and gemcitabine	II	WIH 20050782, NCT01296035

Note: *Data for table obtained from http://www.cancer.gov/clinicaltrials and was accessed on February 9, 2012.
Abbreviations: VEGF, vascular endothelial growth factor; PARP, polyadenosine ribose pathway.

and β, was shown to have modest activity in patients with recurrent ovarian cancer (3.3% partial response and 53% stable disease).[20] Imatinib is a tyrosine kinase inhibitor that targets KIT and PDGF receptor α and β. Like the small-molecule EGFR inhibitors, single-agent imatinib has minimal activity alone, with an overall response rate of 0%–2%.[27,43–45] Combination therapy of imatinib with cytotoxic chemotherapy did not demonstrate a striking improvement in response. Imatinib was combined with docetaxel in heavily pretreated platinum-resistant ovarian cancer patients, and a 21.7% overall response rate was noted.[46] Imatinib with weekly paclitaxel yielded a 25% overall response rate.[47]

Polyadenosine ribose pathway inhibitors

The polyadenosine ribose pathway (PARP) pathway is an exciting new target that is gaining momentum in clinical trials. The concept of targeting PARP has been recently reviewed by Javle and Curtin.[48] PARP is a nuclear enzyme that functions to repair DNA damage (specifically single-strand breaks) in cells. Inhibition of PARP leads to more single-strand breaks. Persistent single-strand breaks lead to collapse of the replication fork, which then leads to replication-associated double-strand DNA breaks. Typically, double-strand breaks are repaired by homologous recombination, which is mediated in part by BRCA1 and BRCA2 proteins. Mutations in BRCA1 and BRCA2 occur in about 10% of all EOC patients, and predispose women to increased risk of breast and ovarian cancer. More recently, inactivation of BRCA1 may be a common event in the pathogenesis of sporadic cases of EOC. This is thought to occur via various mechanisms, such as loss of heterozygosity, hypermethylation, and haploinsufficiency.[49]

Importantly, when PARP is inhibited and the homologous recombination pathway is defective (eg, due to BRCA1 or 2 mutation), this leads to increased double-strand breaks which are lethal if they persist or lead to genomic instability due to utilization of alternative, error-prone repair pathways.

Several studies involving PARP inhibitors have been recently completed in ovarian cancer patients. Fong et al reported a Phase I trial which involved patients with BRCA1 or BRCA2 mutations, with 35% of patients having ovarian cancer. Olaparib (AZD2281) was examined and found to be generally well tolerated.[50] The cohort of BRCA-mutated patients with ovarian, fallopian tube, and primary peritoneal cancers were expanded and examined for response to olaparib.[51] Twenty of 50 patients had a complete or partial response. Despite decreased response to olaparib in platinum-refractory or platinum-resistant disease, a significant response to treatment was still noted, with a 41.7% response rate in platinum-resistant disease by RECIST (Response Evaluation Criteria In Solid Tumors) criteria. There were no responders in the platinum-refractory group by RECIST criteria, but a 15.4% response rate was noted by Gynecologic Cancer Intergroup criteria, which utilizes CA125 for determination of response. Treatments were well tolerated, with mild gastrointestinal symptoms and fatigue being the most common toxicities reported.

Olaparib was examined in a Phase II study involving women with BRCA1 or BRCA2 mutations and recurrent

ovarian cancers.[52] Audeh et al examined two cohorts which involved two different dosing schedules for olaparib (cohort 1, 400 mg twice daily; cohort 2, 100 mg twice daily), with objective tumor response by RECIST criteria being the primary endpoint of the study. A 33% and 13% response rate was noted for cohort 1 and 2, respectively. Again, the treatments were well tolerated, with nausea and fatigue being the most common adverse events reported. There were two deaths reported in cohort 1, one from intestinal perforation and disease progression, and the other due to development of acute myeloid leukemia. Studies of other PARP inhibitors (AZD2281, BSI-201, ABT-888) are currently ongoing (see Table 2).

Folate inhibitors

Targeting of the folate pathways has been utilized in the past for other types of cancers, such as leukemias. As our understanding of the pathway has evolved, new inhibitors have been generated. Two such inhibitors, pemetrexed and farletuzumab, have been examined in the clinical setting. Pemetrexed is a multitargeting antifolate drug that inhibits multiple DNA synthesis pathway enzymes and gains access into the cell by a reduced folate carrier.[53] Folate receptor alpha, which transports folate across the cell membrane, has been found to be upregulated in ovarian cancer cells.[54,55] A humanized monoclonal antibody, farletuzumab, has been recently developed and binds to folate receptor alpha.[56]

There are two Phase II studies that have reported on single-agent pemetrexed in patients with platinum-resistant ovarian cancer, and significant activity was reported in both trials.[57–58] Miller et al noted a 21% response rate, with 35% of patients having stable disease.[57] Vergote et al compared two different doses of pemetrexed (500 mg/m^2 versus 900 mg/m^2).[58] The response rate was about the same (9%–10%) at either dose. In addition, progression-free survival and overall survival were essentially similar. Bone marrow toxicities were similarly noted. Pemetrexed has also been combined with carboplatin in platinum-sensitive recurrent ovarian cancers. The overall response rate was 51.1% with 31.1% with stable disease.[59] The combination was generally well tolerated. Recently, farletuzumab has been examined in a Phase I study.[60] It was well tolerated and appears acceptable to advance to Phase II studies. Current studies involving inhibition of the folate pathway are noted in Table 2.

Other targeted agents in recurrent ovarian cancer

The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase involved in the regulation of cell growth. mTOR is a downstream target of the AKT/PI3K signaling pathway. Inhibitors have been developed against mTOR and are showing activity in ovarian cancer.

Enzastaurin is an oral protein kinase C inhibitor (specifically protein kinase C beta) and an inhibitor of the PI3K/AKT signaling pathway. A Phase II study by the Gynecologic Oncology Group in patients with recurrent ovarian or primary peritoneal cancers treated with enzastaurin showed an 11% progression-free survival of ≥6 months, with a 7% partial response rate noted.[61] There appeared to be low activity noted. However, the treatment was well tolerated, with no grade 4 adverse events reported.

Recently, Behbakht et al reported a Phase II trial of the mTOR inhibitor, temsirolimus. There was clinically significant activity noted, with 24% of patients describing a ≥6-month progression-free survival.[62] However, the study did not meet Gynecologic Oncology Group criteria to continue studying the drug in a Phase III trial. Additional mTOR inhibitors are currently undergoing investigation (everolimus, MK-2206, MM-121, Table 2). MK-2206 is an allosteric AKT inhibitor that has been found in preclinical studies to enhance the effectiveness of cytotoxic chemotherapies.[63] MM-121 is an antibody directed against ErbB3, which activates PI3K signaling in EGFR.[64] Both of these novel PI3K/AKT pathway inhibitors are currently under investigation (Table 2).

Management of newly diagnosed EOC

Current standard chemotherapy includes treatment with intravenous carboplatin and paclitaxel every three weeks. Several studies have tried to alter this regimen slightly by either changing the mode of administration of the drug or changing the dose rate. One study performed by the Japanese Gynecologic Oncology Group changed the dose of paclitaxel given over one hour from 180 mg/m^2 intravenously every 3 weeks to a dose-dense regimen of 80 mg/m^2 intravenously once a week.[65] Both groups received a mean of six cycles of treatment.[65] The main toxicity was hematologic, causing a delay in or discontinuation of treatment, especially in the dose-dense group. The main adverse event was neutropenia, which was found in both the dose-dense and conventional dose groups. The study found a significantly longer progression-free survival and higher rate of overall survival at 3 years in patients treated with the dose-dense regimen.[65] The Japanese group is also working on a dose-dense protocol using intraperitoneal chemotherapy in which they propose to demonstrate that intraperitoneal chemotherapy is superior to conventional intravenous administration.[66]

Other trials have already demonstrated benefit from changing the route of administration of chemotherapy from intravenous to intraperitoneal. The Phase III trial led by Armstrong for the Gynecologic Oncology Group showed a significant increase in median progression-free survival by 5 months for patients who received intraperitoneal cisplatin and paclitaxel compared with those who received intravenous chemotherapy after optimal debulking. In addition, median overall survival was increased by approximately 15 months in the intraperitoneal group, with a 25% decrease in risk of death. Although significantly more patients in the intraperitoneal group experienced serious adverse events, including gastrointestinal, pulmonary, cardiovascular or renal events, most of these did not lead to discontinuation of treatment. Quality of life was also similar between the groups after one year of treatment.[67]

Other studies have tried to improve upon standard chemotherapy for ovarian cancer by addition of a third chemotherapeutic drug to the regimen. A large multicenter, multiarm trial proposed by the Gynecologic Oncology Group in conjunction with the ICON group (GOG182-ICON5) launched in 2001, compared the addition of gemcitabine, methoxypolyethylene glycosylated liposomal doxorubicin, or topotecan to carboplatin and paclitaxel.[68] To date, the study has not shown a significant improvement in progression-free survival or overall survival in patients to suggest a change from standard intravenous carboplatin and paclitaxel.[68]

Targeted agents in front-line therapy for EOC

Angiogenesis inhibitors, in particular, bevacizumab, are one of the most well studied target agents in cancer treatment. The formation of new vasculature is a key component to the spread and proliferation of cancer. Angiogenesis may be mediated along several different pathways, including VEGF, PDGF, EGFR, and tyrosine kinase inhibitors. Promising studies have added bevacizumab, a VEGF inhibitor, to standard treatment regimens with carboplatin and paclitaxel.

One study by the Gynecologic Oncology Group (GOG218) randomized patients with advanced EOC after debulking surgery into one of three treatment groups: standard paclitaxel, carboplatin, and placebo; paclitaxel, carboplatin and bevacizumab added on cycle 2 with placebo maintenance; or paclitaxel, carboplatin, and bevacizumab, followed by 15 months of maintenance bevacizumab.[69] Arm 3 showed an improvement of 4 months in progression-free survival compared with arm 1, and demonstrated that the addition of bevacizumab showed benefit over conventional chemotherapy. Although the results may be statistically different, their clinical relevance may be tempered by the potential high costs related to bevacizumab therapy.[70] In addition, there was no significant difference in overall survival between the three arms, but it should be noted that the study was not powered for overall survival.[69]

Another Phase III trial has also supported the use of bevacizumab in the upfront setting. A Phase III trial by the Gynecologic Cancer Intergroup (ICON7) randomized patients with stage II–IV EOC to carboplatin, paclitaxel and placebo, or to carboplatin, paclitaxel, and bevacizumab, with additional maintenance bevacizumab after primary therapy.[71] This study found a 1.5-month improvement in progression-free survival in patients treated with bevacizumab compared with the control arm (hazard ratio for progression or death 0.81; 95% confidence interval: 0.70–0.94; $P = 0.004$). Overall survival data were not mature at the time of reporting.

In both GOG218 and ICON7, bevacizumab was well tolerated and the rates of bowel perforation were not statistically different between the controls and bevacizumab-containing arms. It was interesting to note that the progression-free survival curves for both studies seem to converge after bevacizumab was discontinued and suggests that prolonged bevacizumab maintenance therapy may benefit patients. Further studies are needed to address this finding. An additional question that remains is whether the routes of administration of chemotherapy (ie, intravenous versus intraperitoneal) matter. Studies already show the benefits of the intraperitoneal route, though its toxicity remains higher than with conventional intravenous administration. Some researchers have analyzed the cost-effectiveness of intraperitoneal chemotherapy because of potential longer-term hospital stays for serious toxicity.[72] Others argue that if overall survival is increased with intraperitoneal administration, then it may prove to be a good value.[73] A recently closed Gynecologic Oncology Group study (GOG-252) was designed to compare intravenous carboplatin with intraperitoneal carboplatin and cisplatin along with the addition of bevacizumab. In the first phase of the study, patients are randomized into three treatment arms: weekly intravenous paclitaxel + intravenous carboplatin every 3 weeks + intravenous bevacizumab starting cycle 2; weekly intravenous paclitaxel + intraperitoneal carboplatin + intravenous bevacizumab starting cycle 2; or intravenous paclitaxel cycle 1 + intraperitoneal cisplatin + intraperitoneal paclitaxel cycle 2 + intravenous bevacizumab starting cycle 2. The second phase of the trial will maintain all three groups on intravenous bevacizumab starting on cycle 7.[74] Other studies involving bevacizumab as well as

other antiangiogenesis agents in first-line therapy for EOC are noted in Table 3.

Few other targeted agents have been designed as initial therapy for advanced EOC, primary peritoneal cancer, and fallopian tube cancer. In a Phase II trial by Konner et al, cetuximab, a monoclonal antibody synthetically designed to block tyrosine kinase inhibitors, was added to paclitaxel and carboplatin, and patients were then continued on weekly cetuximab for 6 months.[75] However, while treatment was generally well tolerated, cetuximab had only limited efficacy compared with conventional chemotherapy.[75] Another Phase II trial led by Vasey et al added erlotinib, a tyrosine kinase inhibitor, to docetaxel and carboplatin.[76] The overall response rate was 52%, with five of 24 patients having a complete response for at least 6 months. The results are encouraging and future studies are necessary. Current first-line therapy with PARP inhibitors and PI3K/mTOR inhibitors are ongoing (Table 3).

Maintenance therapy for primary ovarian caner

Once a complete response to treatment with cytoreductive surgery and chemotherapy has been established, a variety of maintenance therapies are used to prevent relapse or recurrence. A multicenter Phase III trial by the Southwest Oncology Group randomized patients to receive three cycles or 12 cycles of maintenance intravenous paclitaxel after a complete response to conventional platinum-based and paclitaxel-based treatment.[77] A follow-up to their initial results shows a median progression-free survival of 22 months for 12 cycles of paclitaxel and 14 months for those who received only three cycles. The overall survival rate was better by 5 months (53 versus 48 months) in the 12-cycle group, but the results were not statistically significant.[78]

In contrast, another study by the Italian Gynecologic Oncology Group, looked at consolidation treatment with intravenous paclitaxel for six cycles versus observation in patients who had a complete response to first-line standard chemotherapy for advanced ovarian cancer. Two hundred patients were enrolled, and a median follow-up duration of 43 months showed no significant improvement in progression-free survival or overall survival between the two arms.[79] Similar negative findings were also noted in EOC patients with stage IA/B (grade 3 or clear cell), IC, or II disease.[80] In this study, patients were randomized to observation or to maintenance paclitaxel 40 mg/m^2/week × 24 weeks, and patients in the maintenance arm had a higher incidence of peripheral neuropathy, infection/fever, and dermatologic events.[80] In a study by Berek et al, patients were randomized to receive either oregovomab, a monoclonal antibody to CA125, or placebo after front-line carboplatin and paclitaxel treatment for advanced EOC.[81] This Phase III study unfortunately did not show any advantage of oregovomab over placebo.[81]

An ongoing protocol by the Gynecologic Oncology Group (GOG 212) is studying the novel compound, CT-2103 (Xyotax™), a synthetic taxane derived from conjugation of paclitaxel with a polyglutamate polymer. Preliminary data show reduced toxicity with this novel compound compared with paclitaxel. Like paclitaxel, CT-2103 does not demonstrate

Table 3 Summary of current clinical trials of first-line targeted therapies for ovarian cancer*

Class	Drug	Intervention	Phase	Protocol ID
Angiogenesis inhibitors	Bevacizumab	Carboplatin, bevacizumab, paclitaxel in dose escalation	I	2010C0049, OSU 09149, NCT01219777
	Bevacizumab	IP carboplatin, IV paclitaxel, IV bevacizumab in dose escalation	I	2010CO062, OSU09115, NCT 01220154
	Bevacizumab	Standard chemotherapy plus bevacizumab for 30 months Standard chemotherapy plus bevacizumab for 15 months	III	AGO-OVAR 17, NCT01462890
	Bevacizumab	Carboplatin, paclitaxel, bevacizumab	II	2009-0186, NCT01097746
	AMG 386	Carboplatin, paclitaxel, AMG 386 Carboplatin, paclitaxel, placebo	III	TRINOVA3: 20101129/ ENGOT-ov2, NCT01493505
PARP inhibitors	Veliparib	IV carboplatin, paclitaxel, bevacizumab, veliparib IP cisplatin IV/IP paclitaxel, bevacizumab, veliparib	I	GOG-9923, NCT00989651
	ABT-767	ABT-767 dose escalation study	I	M10-976, 2010-020795-37, NCT01339650
PI3K/mTOR inhibitor	BKM120	BKM120 once daily	II	11-211, NCT01501604
	Temsirolimus	Carboplatin, paclitaxel, temsirolimus ≥ temsirolimus consolidation	II	GOG-0268, NCT01196429

Note: *Data for table obtained from http://www.cancer.gov/clinicaltrials and was accessed February 9, 2012.
Abbreviations: IV, intravenous; IP, intraperitoneal; PARP, polyadenosine ribose pathway; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin.

an increase in response rate with an increase in dosage. A 135 mg/m^2 dose of CT-2103 appears to be as safe and as efficacious as unconjugated paclitaxel at 135 mg/m^2.[82] Another ongoing multicenter, international Phase III study involves the use of pazopanib, a VEGF receptor and PDGF receptor inhibitor, as monotherapy for consolidation treatment following complete response to first-line chemotherapy.[83] This study has finished data accrual and is set for primary data results by 2012.

Conclusion

Advances in therapies are changing the way we manage patients with EOC. Through the testing of novel agents in patients with recurrent disease, changes to first-line therapy are occurring. The addition of bevacizumab to a platinum/taxane-based regimen may become the new standard if the mature overall survival data support continued benefit in patients. However, the debate over utilizing intravenous versus intraperitoneal chemotherapy is not resolved. It is assumed that use of bevacizumab in either treatment setting will be beneficial, but there are no specific clinical trials addressing the use of novel therapeutic agents in patients undergoing intraperitoneal chemotherapy.

The use of targeted agents in patients with recurrent disease is constantly evolving. Because many of these new drugs seem to show fewer side effects compared with cytotoxic chemotherapy, it will be interesting to see how these new therapies will be incorporated into the management of patients with EOC. Should we be utilizing targeted agents much sooner in the patient's therapy? Should we always combine the targeted agents with cytotoxic therapies? Certainly clinical trials will be important to help address these issues. However, improved biomarkers are desperately needed to determine the efficacy and response of targeted agents and to aid in determining whether the targeted agent requires further clinical evaluation or should be abandoned. Cost issues and access to these new agents will also need to be addressed as new targeted agents come onto the market.

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