Targeted Therapies for Treatment of Recurrent Ovarian Cancer

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Abstract: Ovarian cancer remains the leading cause of death among women with gynecologic malignancies in the United States. Most women with epithelial ovarian cancer present with advanced disease. Despite good response rates to initial surgery and chemotherapy, the majority of patients experience relapse and ultimately die of their disease. A better understanding of the molecular differences underlying the histologic subtypes of epithelial ovarian cancer has led to recent advances in targeted therapeutic strategies. Here we review the most promising targeted therapeutics currently being used for the treatment of recurrent ovarian cancer.

Introduction

More than 225,000 new cases of ovarian cancer are diagnosed worldwide each year, with approximately 22,000 of these cases occurring in the United States. Ovarian cancer remains the leading cause of death amongst women with gynecologic malignancies in the United States.[1] The majority of women (>80%) present with advanced-stage disease. The current standard of care for the initial treatment of advanced ovarian cancer involves a combination of optimal cytoreductive surgery and platinum-based chemotherapy. Although 80% of patients respond to initial treatment, more than 70% ultimately experience disease recurrence. Virtually all patients with recurrent disease eventually develop platinum resistance, with expected response rates of only 10% to 25% to nonplatinum regimens.[2] It is necessary, therefore, to capitalize on alternative strategies in order to make further advances in the treatment of ovarian cancer. Multiple targeted therapies have displayed efficacy in patients with ovarian cancer, and represent a potential means to improve the outcomes in advanced disease. Additionally, by inhibiting signaling pathways that promote cancer cell growth and proliferation, these targeted therapies offer the possibility of greater selectivity and lower toxicity than conventional cytotoxic chemotherapy. Here we describe the most promising targeted therapeutics for patients with recurrent ovarian cancer.

Histologic Variations

Epithelial ovarian cancer is a heterogeneous disease with multiple histologic subtypes that display divergent molecular characteristics and response rates to chemotherapy. Out of these subtypes (high-grade serous, low-grade serous [LGS], clear cell, mucinous, and endometrioid), high-grade serous ovarian cancer is the most responsive to traditional cytotoxic chemotherapy. More than 95% of high-grade serous ovarian cancers display mutations in *TP53*; in addition, homologous recombination is defective in approximately half of these tumors, with a low prevalence of mutations in *NF1, BRCA1, BRCA2, RB1,* and *CDK12* also found.[3] In contrast to high-grade serous ovarian cancer, LGS tumors rarely harbor *TP53* mutations. Approximately one-third of LGS tumors contain *KRAS* or *NRAS* mutations. Some reports have also shown a high rate of *BRAF* mutations within this population, while others have reported that the incidence is much lower than previously reported.[4-11] Mucinous ovarian cancers display overexpression/amplification of *HER2* in 19% of tumors and *KRAS* mutations in 44% to 85% of tumors.[12-15] Both endometrioid and clear-cell ovarian cancers have been found to frequently harbor alterations in *ARID1A, PTEN, PIK3CA,* and/or *CTNNB1* (β-catenin).[16-22] Identifying the molecular drivers of these distinct histologic subtypes is essential to the informed use of targeted therapeutics in ovarian cancer.

Angiogenesis

Angiogenesis is a hallmark of neoplastic transformation and is critical for tumor growth and invasion. Antiangiogenic therapies have shown significant benefit in other cancer types and have been tested in advanced epithelial ovarian cancer as well. Tumor angiogenesis is regulated by a number of cytokines and growth factors, including fibroblast growth factors, platelet-derived growth factors (PDGFs), tumor necrosis factor-α, interleukins 6 and 8, and vascular endothelial growth factor (VEGF). Thus far, VEGF-A and its receptors are the best-characterized signaling pathways in developmental and tumor angiogenesis.[23]

Bevacizumab

Bevacizumab (Avastin, Genentech) is a humanized anti–VEGF-A monoclonal antibody that is approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer, nonsquamous non–small cell lung cancer, glioblastoma, and renal cell carcinoma.

Two phase 2 studies examining the use of single-agent bevacizumab in patients with recurrent ovarian cancer have been performed. A phase 2 trial of bevacizumab in patients who had been treated with 1 to 2 prior cytotoxic regimens reported a response rate of 21%, with 40.3% of patients progression-free for at least 6 months.[24] A second phase 2 study of bevacizumab was conducted in patients with platinum-resistant ovarian cancer who had received no more than 3 prior treatment regimens and had experienced progression of disease either during treatment or within 3 months of discontinuing topotecan or liposomal doxorubicin (Doxil, Janssen). The response rate in this trial was 15.9%, and 27.8% of patients were progression-free at 6 months.[25]

A third phase 2 clinical trial evaluated bevacizumab administered in conjunction with oral metronomic cyclophosphamide in patients with up to 3 prior lines of therapy. A response rate of 24% was reported, with 56% of patients progression-free at 6 months.[26]

The role of bevacizumab in combination with chemotherapy for recurrent ovarian cancer has been addressed in 2 phase 3 studies.[27,28] The OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease) study was a randomized, blinded, placebo-controlled phase 3 trial that compared treatment using bevacizumab, gemcitabine, and carboplatin with treatment using gemcitabine and carboplatin alone in patients with platinum-sensitive recurrent ovarian cancer. Patients who had platinum-sensitive recurrent ovarian cancer, defined as disease recurrence at least 6 months after completion of frontline platinum-based chemotherapy, and measurable disease were randomized to treatment with gemcitabine and carboplatin administered in combination with bevacizumab or placebo for 6 to 10 cycles. Bevacizumab or placebo was then continued until disease progression. The addition of bevacizumab led to a significant improvement in median progression-free survival (PFS; from 8.4 to 12.4 months [hazard ratio (HR), 0.484; *P*=.0001]). The objective response rate was also significantly improved with the addition of bevacizumab (78.5% vs 57.4%; *P*<.0001). Grade 3 or higher hypertension (17.4% vs 0.4%) and proteinuria (8.5% vs 0.9%) occurred more frequently in the bevacizumab-containing arm. Rates of neutropenia were similar in both arms. Two patients in the bevacizumab-containing arm experienced gastrointestinal perforation after study treatment discontinuation.[27]

More recently, AURELIA (A Study of Avastin [Bevacizumab] Added to Chemotherapy in Patients With Platinum-Resistant Ovarian Cancer), a randomized phase 3 trial, evaluated the administration of chemotherapy (liposomal doxorubicin, topotecan, or paclitaxel) with or without bevacizumab in patients with platinum-resistant recurrent ovarian cancer. The addition of bevacizumab to chemotherapy significantly improved PFS (median PFS, 6.7 vs 3.4 months) and overall response rate (30.9% vs 12.6%) when compared with chemotherapy alone.[28]

VEGF Receptor Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) targeting the VEGF receptor signaling axis are also actively being studied in recurrent ovarian cancer. Cediranib (AZD-2171) is a highly potent ATP-competitive inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, and c-Kit.[29] A phase 2 study of cediranib was conducted in patients with recurrent ovarian cancer who had received no more than 2 lines of chemotherapy for recurrent disease. Eight out of 47 patients displayed a partial response (PR), resulting in a 17.4% response rate. Twenty-three percent of patients were removed from the study owing to toxicities prior to completion of 2 cycles of treatment. Grade 3 toxicities occurred in more than 20% of patients and included hypertension (46%), fatigue (24%), and diarrhea (13%). Grade 4 toxicities included central nervous system hemorrhage (n=1), hypertriglyceridemia (n=1), and dehydration (n=1). No bowel perforations or fistulas were reported.[30] A randomized, placebo-controlled, 3-arm, phase 3 trial of chemotherapy alone (carboplatin and paclitaxel), chemotherapy in combination with cediranib, or chemotherapy plus cediranib followed by maintenance cediranib (ICON6) completed enrollment in 2011. A total of 456 eligible patients from 63 centers were enrolled. The restricted mean estimated an increased time to progression of 3.2 months, from 9.4 months with chemotherapy to 12.6 months for the cediranib/chemotherapy arm over a 2-year period. Also using the restricted mean, overall survival increased by 2.7 months, from 17.6 months in the reference arm to 20.3 months in the concurrent plus maintenance cediranib arm (HR, 0.70; log-rank test, P=.0419). The restricted mean for the reference arm vs the concurrent plus maintenance arm demonstrated an increase in PFS of 2 months, from 9.4 to 11.4 months, respectively (HR, 0.68; P=.0022).[31]

Pazopanib (Votrient, GlaxoSmithKline) is an oral angiogenesis inhibitor targeting the VEGF receptor, the PDGF receptor, and c-Kit.[32] A phase 2 study of single-agent pazopanib was conducted in patients with 2 or more prior lines of chemotherapy who had an elevated cancer antigen 125 (CA-125) level but low-volume disease. The primary endpoint of the study was biochemical response rate (defined as ≥50% decline in CA-125 from baseline). Eleven of 36 patients (31%) displayed a biochemical response to pazopanib. Forty-seven percent of patients had measurable disease at baseline, and no PRs or complete responses (CRs) were observed in patients with measurable disease based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) criteria. Pazopanib was well tolerated, with grade 3 elevation of alanine aminotransferase (8%) or aspartate aminotransferase (8%) being the most common causes for discontinuation of study drug. The only grade 4 toxicity reported was peripheral edema (n=1).[33]

Additional VEGF receptor TKIs, including sorafenib (Nexavar, Bayer/Onyx), vandetanib (Caprelsa, AstraZeneca), sunitinib (Sutent, Pfizer), and nintedanib (BIBF-1120), remain under investigation for treatment of recurrent ovarian cancer, either as monotherapy or in combination with chemotherapy.

DNA Repair Mechanisms

BRCA1 and BRCA2 are key components of homologous recombination-mediated repair of DNA double-stranded breaks. Twenty-two percent of high-grade serous ovarian cancers display either somatic or germline mutations in *BRCA1/2*, but additional alterations affecting homologous recombination, such as amplification or deletion of the gene for the EMSY protein, focal deletion or mutation of *PTEN*, or hypermethylation of *RAD51C*, are also commonly found in high-grade serous tumors.[3] In total, approximately 50% of high-grade serous ovarian cancers harbor defects in the homologous repair pathway, referred to as BRCAness.[3,34] The poly (adenosine diphosphate-ribose) polymerase (PARP) family of enzymes are pivotal in repairing single-strand breaks in DNA through the base excision repair pathway.[35] PARP inhibitors generate specific structural lesions within DNA that require functional *BRCA1/2* for repair. PARP inhibitors therefore induce cell cycle arrest and cell death in cancer cells lacking an intact *BRCA1/2*-dependent homologous recombination pathway through synthetic lethality.[36] BRCAness is felt to correlate both with response to platinum-based chemotherapy and treatment with PARP inhibition.[37]

In a phase 2 study of the oral PARP inhibitor olaparib, patients with recurrent ovarian cancer, a germline *BRCA1* or *BRCA2* mutation, and measurable disease displayed a 33% response rate with the 400-mg twice-daily dose.[38] A second phase 2 study of single-agent olaparib was conducted in patients with high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer. Objective responses were observed in 41% of patients with germline *BRCA1* or *BRCA2* mutations, and 24% of patients without *BRCA* mutations.[39]

A randomized, double-blind, placebo-controlled, phase 2 study of olaparib maintenance therapy was conducted in patients with platinum-sensitive ovarian cancer who displayed a PR or CR to their most recent line of chemotherapy. PFS was significantly longer with olaparib than with placebo (median, 8.4 months vs 4.8 months; HR for progression or death, 0.35; 95% CI, 0.25-0.49; P<.001), indicating that olaparib maintenance therapy may be an effective treatment strategy for this subgroup of patients.[40]

Multiple studies are ongoing with olaparib as well as other PARP inhibitors, including veliparib (ABT-888) and rucaparib (AG 014699, PF01367338), as single agents and in combination with chemotherapy.

Targeting the Ras/Raf/MEK/ERK Pathway

LGS ovarian cancer accounts for approximately 10% of cases of serous ovarian cancer. Patients with LGS ovarian cancer typically present at an earlier age (median age at diagnosis is 46 years) than those with high-grade serous ovarian cancer. In addition, LGS ovarian cancer tends to display an indolent clinical course, and has poor responses to both platinum- and non–platinum-based chemotherapies.[6,41-42] Mutations in *BRAF* and *KRAS*, components of the mitogen-activated protein kinase (MAPK) signaling cascade, are common in LGS ovarian cancer and its precursor lesion, serous borderline disease. In contrast, such alterations are present in less than 1% of high-grade serous ovarian tumors.[3,7-9,43] Two-thirds of patients with LGS ovarian cancer were reported to harbor *BRAF* or *KRAS* mutations, though more recent studies indicate that *BRAF* mutations are less frequently identified in LGS ovarian cancer than originally thought.[4,6,10,11,44]

A phase 2 trial with the MEK1/2 inhibitor selumetinib (AZD-6244) was conducted in patients with recurrent LGS ovarian cancer and reported a 15.4% response rate, with disease stabilization seen in an additional 65% of patients. Median PFS was 11 months. Three grade 4 toxicities were reported: cardiac (n=1), pain (n=1), and pulmonary (n=1). Forty-two percent of patients received dose reductions and 25% of patients were removed from the study owing to toxicity. Thirty-four out of 52 patients had sufficient tumor DNA available for mutation analysis. Of the 34 evaluable tumors, 6% harbored a *BRAF* mutation and 41% harbored a *KRAS* mutation. Response to treatment was not found to be associated with mutation status.[45]

The ongoing phase 3 MILO (MEK Inhibitor in Low-grade Serous Ovarian Cancer) study is randomizing patients with recurrent LGS ovarian cancer to either single-agent MEK inhibition with MEK162 or physician's choice of chemotherapy (liposomal doxorubicin, weekly paclitaxel, or topotecan). In addition, multiple ongoing phase 1 and 2 trials are examining the use of MEK inhibition, or MEK inhibition in combination with phosphoinositide 3-kinase inhibition, in patients with LGS ovarian cancer.

Forty-four percent to 85% of mucinous adenocarcinomas of the ovary also harbor *KRAS* mutations, indicating that targeting the MAPK pathway within this disease may be a viable option as well.[12-15,46]

Other Potential Targets

The folate receptor is overexpressed in nearly 90% of nonmucinous ovarian cancers. Farletuzumab (MORAb-003) is a humanized monoclonal antibody that targets folate receptor-α and has been shown in vitro to elicit antibody and complement-dependent cytotoxicity.[47] A phase 1 dose-escalation study of farletuzumab was conducted in heavily pretreated patients with platinum-resistant or platinum-refractory ovarian cancer. That study found the drug to be safe and well tolerated at doses of 12.5 to 400 mg/m². Although no responses were seen, stable disease was noted in 36% of patients.[48] Disappointingly, a phase 3 study of carboplatin and paclitaxel chemotherapy administered with or without farletuzumab (at 2 possible doses) did not meet its primary endpoint of PFS.

Wee-1 is a tyrosine kinase that is involved in G_2 checkpoint signaling. TP53 is a key regulator in the G_1 checkpoint, so TP53-deficient tumors rely exclusively on the G_2 checkpoint following DNA damage. MK-1775, a selective small-molecule inhibitor of Wee-1 kinase, resulted in apoptosis in TP53-deficient cells when given in combination with cytotoxic chemotherapy in vitro.[49] Mutations in *TP53* are found in greater than 95% of high-grade serous ovarian cancers and are therefore a promising target for Wee-1 inhibitors.[3] A phase 2 study of MK-1775 in combination with carboplatin for patients with *TP53*-mutated epithelial ovarian cancer and early relapse or progression during standard first-line treatment is currently ongoing.

The Aurora kinases are a family of proteins that regulate mitosis. Alterations in Aurora kinase signaling are associated with chromosomal instability and mitotic errors in cancer cells.[50] Amplification and/or overexpression of Aurora A kinase genes is associated with poorer survival in ovarian cancer.[51,52] A phase 2 study of the oral, small-molecule Aurora kinase inhibitor alisertib (MLN-8237) was conducted in patients with platinum-resistant or refractory ovarian cancer. Modest single-agent activity was seen, with 3 of 31 patients (10%) displaying objective response by either RECIST 1.1 criteria (n=2) or CA-125 level (n=1).[53] A study of weekly paclitaxel administered alone or in combination with alisertib in patients with recurrent ovarian cancer is accruing.

Conclusion

Improved understanding of the molecular drivers of epithelial ovarian cancer has led to an expanding repertoire of targeted therapeutics being tested in this disease. To date, bevacizumab and PARP inhibitors have shown the most promising results. The utility of histologic and/or genetic preselection of patients most likely to respond to targeted therapy is becoming increasingly evident. In the near future, early molecular profiling (at time of first recurrence) will help to better tailor treatment choices and lead to more personalized medical care for ovarian cancer patients.

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