Use of Targeted Therapeutics in Epithelial Ovarian Cancer: A Review of Current Literature and Future Directions

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ABSTRACT

Purpose: Epithelial ovarian cancer (EOC) is the leading cause of gynecologic cancer death in the United States. Most patients will ultimately fail platinum-based chemotherapy and have the disease recur. Interest is increasing in the use of targeted therapies in the treatment of EOC. This review focuses on the current use of targeted therapeutics in EOC as well as future directions.

Methods: A literature search of Medline and PubMed was conducted (January 2000–October 2017) to identify recent reports of targeted drugs in EOC.

Findings: A wide range of targeted therapeutics is currently being used as both monotherapy and in combination in the treatment of EOC. Clinically, the most commonly used classes of drugs currently are antiangiogenics and poly (ADP-ribose) polymerase inhibitors. However, a number of drugs in varying stages in development target a wide range of biochemical pathways. Activity and response rates of these drugs vary greatly. Questions continue about combination drug therapy and appropriate patient selection.

Implications: The use of targeted therapeutics in the treatment of EOC, both as monotherapy and in combination, will continue to expand as more mechanisms of tumorigenesis are identified. Multiple clinical trials of a wide range of targeted therapeutics are currently ongoing. Evidence-based selection of drug targets and appropriate patient populations will allow strategic application of targeted therapeutics. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: antiangiogenics, chemotherapy, epithelial ovarian cancer, PARP inhibitors, targeted therapeutics.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic cancer in the United States.[1] It is estimated that 22,440 new cases of EOC will be diagnosed in 2017 with an estimated 14,080 EOC deaths.[2] The 5-year survival rate for EOC is only 46% because >60% of patients are diagnosed with advanced disease. Patients with advanced stage EOC are typically managed with cytoreductive surgery and perioperative platinum-based chemotherapy, either in the adjuvant setting or with neoadjuvant chemotherapy and interval debulking surgery.[3–5] Although primary advanced stage EOC is initially sensitive to this treatment paradigm, >75% will eventually recur.[6] Patients with recurrent disease are treated with additional lines of chemotherapy that may increase survival but is ultimately not curative.

Given the high relapse rate and poor prognosis of advanced stage EOC, interest is increasing in the development of new approaches to treat recurrent EOC. Increased understanding of the biology of EOC has led to the development of a number of targeted molecular and biologic therapies, including antiangiogenic agents, poly (ADP-ribose) polymerase (PARP) inhibitors, signaling pathway inhibitors, and immunotherapies.[7] The purpose of this review is to discuss the current use of targeted therapeutics in the treatment of EOC, discuss future directions, and reflect on unanswered questions.

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METHODS

A literature search of Medline and PubMed was conducted (January 2000–October 2017) and included systematic reviews, randomized control trials, observation studies, and case series. Search terms included ovarian cancer, targeted therapeutics, phosphatidylinositol 3-kinase (PI3K)/AKT inhibitors, mammalian target of rapamycin (mTOR) pathway inhibition, mitogen-activated protein kinase (MAPK) pathway inhibition, and the names of generic drugs used in Phase I to III trials in EOC such as bevacizumab, aflibercept, olaparib, niraparib, rucaprib, temsirolimus, trastuzumab, and pertuzumab.

MONOTHERAPY

Antiangiogenics

Angiogenesis is the process by which tumors develop their own endogenous vasculature and is required for tumors to grow beyond 1 to 2 mm in diameter.[8] Vascular endothelial growth factor (VEGF) and various circulating proinflammatory cytokines are a major driver of this angiogenesis and exert their effects by initiating signaling cascades through intracellular tyrosine kinases.[9] Several studies have found that high circulating serum levels of VEGF in patients with EOC are correlated with a higher risk of recurrence and death.[10] Similarly, levels of interleukin (IL)-6, IL-8 and tumor necrosis factor α have correlated with shortened progression-free survival (PFS).[11–13] Several antiangiogenic agents have been developed to interrupt angiogenesis signaling pathways, including agents that inhibit the actions of extracellular growth factors to inhibitors of intracellular kinases.[9]

Bevacizumab is a humanized monoclonal antibody against VEGF and was the first clinically available, targeted antiangiogenic agent in the United States. Monotherapy with bevacizumab for the treatment of EOC has been studied in several Phase II trials. A Phase II, single-arm trial with bevacizumab was conducted by the Gynecologic Oncology Group (GOG) and included 62 patients with recurrent, platinum-resistant EOC.[14] An overall response rate (ORR) of 21.1% (90% CI, 10.3%–27.7%) was achieved with a median response duration of 10 months. In a second study of patients with recurrent EOC and progression on topotecan or liposomal doxorubicin, an ORR of 15.9% was found with a median PFS of 4.7 months and a median overall survival (OS) of 10.7 months.[15]

Although bevacizumab is currently the only approved antiangiogenic agent for the treatment of EOC, other antiangiogenic agents are being evaluated in clinical trials of patients with EOC. Aflibercept is a protein that contains VEGF-binding domains from both the VEGF receptor (VEGF)-1 and -2 fused to the Fc portion of human immunoglobulin G1.[7] It currently has Food and Drug Administration (FDA) approval for the treatment of patients with metastatic colorectal cancer in combination with folinic acid, fluorouracil, and irinotecan chemotherapy.[16] In a recent Phase II trial, the ORR was 0.9% and 4.6% for patients receiving a 2-mg/kg dose and 4-mg/kg dose, respectively, suggesting that this drug as a single agent does not have significant activity in EOC.[17] Pazopanib, an oral receptor tyrosine kinase inhibitor with activity against VEGFR1/2/3, platelet-derived growth factor receptor (PDGFR), and c-Kit, had modest activity with a 31% RR, measured by cancer antigen 125 levels, in patients with recurrent EOC.[18] Cediranib, an oral pan-VEGFR tyrosine kinase inhibitor, was found to have efficacy in patients with recurrent EOC with a clinical benefit rate (complete response + partial response + stable disease) of 30%.[19] Nintedanib, an oral triple angiokinase inhibitor of VEGFR, PDGFR, and fibroblast growth factor receptor, has been examined in patients with recurrent ovarian cancer. In both the maintenance setting and in combination with cytotoxic chemotherapies, only minimal, albeit significant, improvements in PFS were observed with associated significant gastrointestinal (GI) toxicity increases.[20,21] Sunitinib, vandetanib, and sorafenib are multiple target tyrosine kinase inhibitors with anti-VEGFR activity that have been evaluated in EOC with poor clinical activity as single agents.[20,22–25]

The most commonly encountered adverse events (AEs) with antiangiogenic agents include increased rates of hypertension, bleeding, thromboembolic events, delayed wound healing, proteinuria, and GI events, including obstruction and perforation.[9,17,26] Aflibercept is also associated with headache, dysphonia, fatigue, and skin rash. As expected, oral antiangiogenic kinase inhibitors share similar toxicity profiles with the other antiangiogenic agents; however, they also cause significantly increased fatigue and diarrhea compared with bevacizumab.[19] Of note,