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Antiangiogenic agents as a maintenance strategy for advanced epithelial ovarian cancer

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Contents

Abstract

Bevacizumab is the first antiangiogenic agent to have demonstrated benefit as first-line and maintenance therapy in epithelial ovarian cancer (EOC), with the Gynecologic Oncology Group 218 and ICON 7 phase III trials revealing significantly prolonged progression-free survival (PFS) for carboplatin/paclitaxel plus bevacizumab followed by bevacizumab maintenance versus carboplatin/paclitaxel alone. Results are forthcoming from several phase III maintenance trials of investigational antiangiogenic agents, each evaluating PFS as the primary endpoint: AGO-OVAR12/LUME-Ovar1 (nintedanib [BIBF 1120]), AGO-OVAR16 (pazopanib), and TRINOVA-1, -2, and -3 (AMG 386). Here we review available data and ongoing clinical trials of investigational antiangiogenic agents as maintenance therapy for EOC. Current controversies, including uncertainties regarding the (1) most appropriate clinical trial endpoints, (2) optimal dosing, duration, and timing

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of therapy (e.g., with first-line chemotherapy and/or as maintenance monotherapy), and (3) feasibility, tolerability, and cost of adding these agents to platinum/taxane regimens are also highlighted.

Keywords: Angiogenesis inhibitors; Epithelial ovarian cancer; Vascular endothelial growth factor; Molecular targeted therapy; Bevacizumab

1. Introduction

Since supplanting cisplatin/cyclophosphamide during the 1990s, platinum/taxane chemotherapy remains the international standard of care for the first-line treatment of advanced epithelial ovarian cancer (EOC). Despite initial chemosensitivity to platinum/taxane combinations, most patients with advanced EOC relapse after first-line therapy [1]. Thus, effective maintenance therapies are needed to extend these responses to delay or prevent recurrence. Currently, there is no established role for maintenance chemotherapy for EOC, as studies have been primarily negative due to uncertain clinical benefit and increased risk of cumulative toxicity [2–8]. The National Comprehensive Cancer Network guidelines list a 12-month course of single-agent paclitaxel 135 mg/m^2 to 175 mg/m^2 every 4 weeks for 12 cycles as a category 2B option (e.g., based on lower-level evidence and non-uniform consensus, but no major disagreement) for maintenance therapy for advanced EOC [9], stemming from results of Gynecologic Oncology Group (GOG) 178. This trial demonstrated prolonged progression-free survival (PFS) with maintenance paclitaxel 175 mg/m^2 every 4 weeks for 12 months versus 3 months (28 vs 21 months; adjusted $P = 0.0023$) but with high toxicity and no overall survival (OS) benefit [3]. More recent results of After-6 Protocol 1, an Italian phase III trial of paclitaxel 175 mg/m^2 every 3 weeks as 6-cycle maintenance therapy in patients achieving complete response (CR) from 6 cycles of platinum/paclitaxel, demonstrated no significant benefits for paclitaxel versus observation with respect to 2-year PFS (59% vs 54%) or 2-year OS (87% vs 90%) [8]. The lack of clear benefit observed to date for cytotoxic chemotherapeutic agents makes the suggestion of consolidative therapy using molecular agents more appealing.

Several ongoing clinical trials are evaluating molecularly targeted agents, including antiangiogenic agents, as maintenance therapy in EOC, with the hope that these agents will provide an optimized treatment strategy for these patients. Angiogenesis plays a fundamental role in normal ovarian physiology as well as in the pathogenesis of ovarian cancer, promoting tumor growth and progression through ascites formation and metastatic spread [10–12]. Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are expressed in ovarian cancer [11,13,14], and increased VEGF expression has been associated with the development of malignant ascites [11]. Other angiogenesis pathways involved in ovarian cancer pathogenesis include platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). Higher PDGF levels have been observed in ovarian carcinomas than in benign tissue and in malignant ascites, and have been linked to poor survival [15–21]. Additional evidence supports the involvement of the FGF pathway in angiogenesis, ovarian physiology [22–27], and ascites [25]. Moreover, both PDGF [18,28,29] and FGF signaling pathways [30–32] appear to be involved in VEGF resistance described across various solid tumors, suggesting that combined inhibition of VEGF and PDGF and/or FGF may more completely block angiogenesis than VEGF inhibition alone [29,33–35].

Herein, the current evidence (based on publications indexed on the U.S. National Library of Medicine *PubMed.gov* and abstracts/presentations at key oncology congresses) and ongoing clinical trials (indexed on the U.S. National Institutes of Health *ClinicalTrials.gov*) for the use of investigational antiangiogenic agents as maintenance therapy for EOC are reviewed, including a discussion of current controversies surrounding use of these agents in this treatment setting.

1.1. Bevacizumab in ovarian cancer

Of the antiangiogenic agents currently being evaluated as maintenance therapy for EOC (Table 1), bevacizumab (Avastin®, Genentech; South San Francisco, CA, USA), an anti-VEGF monoclonal antibody, is the most widely studied both across tumor types and specifically in EOC. Preclinical data suggest benefit with bevacizumab as maintenance therapy after cisplatin-based chemotherapy. Single-agent bevacizumab inhibited or delayed disease recurrence and prolonged survival in a murine ovarian cancer model [45]. Clinical study results in gynecologic malignancies collectively support the rationale for studying bevacizumab in EOC [46–53], including as maintenance therapy. In a phase II study ($N = 62$) of carboplatin/paclitaxel plus bevacizumab 15 mg/kg (followed by bevacizumab maintenance therapy for 1 year), which enrolled patients with previously untreated stage ≥IC EOC, primary peritoneal cancer (PPC), fallopian tube cancer (FTC), or uterine papillary serous carcinoma, the overall response rate (RR) based on Response Evaluation Criteria in Solid Tumors (RECIST) was 75% (45/60 [95% confidence interval (CI), 62–85%]) with a median PFS of 29.8 months. Median OS had not yet been reached at the time of publication [54]. Two cases of gastrointestinal perforation (GIP) were reported, both during the chemotherapy phase, but no grade 4 toxicities were associated with bevacizumab during the maintenance phase. These results support the treatment strategy being evaluated in GOG 218.