

Irem Bilgetekin¹, Bulent Cetin², Ahmet Ozet¹

Antiangiogenic therapy in ovarian cancer – for whom and when?

Terapia antyangiogenna w raku jajnika – dla kogo i kiedy?

¹ Department of Internal Medicine, Division of Medical Oncology, Gazi University, Faculty of Medicine, Ankara, Turkey

² Department of Internal Medicine, Division of Medical Oncology, Recep Tayyip Erdogan University, Faculty of Medicine, Turkey

Correspondence: Bulent Cetin, MD, Division of Medical Oncology, Department of Internal Medicine, Recep Tayyip Erdogan University, Faculty of Medicine, Rize 53200, Turkey, tel.: +905058842694, fax: +904642170364, e-mail: caretta06@hotmail.com

Abstract

Tumor angiogenesis appears to be an important process in epithelial ovarian cancer development. Bevacizumab is a monoclonal antibody that can neutralize vascular endothelial growth factor, a promoter of the initiation phase of angiogenesis. First-line chemotherapy in combination with bevacizumab followed by maintenance bevacizumab demonstrated efficacy over chemotherapy alone in two phase III trials (Gynecologic Oncology Group, GOG 218 and ICON7); however, absolute progression-free survival benefit remains modest, with no demonstrated impact on overall survival. The addition of molecularly targeted agents to the treatment of women with recurrent and platinum-sensitive disease has been recently reported in the OCEANS study, which evaluated the benefit of adding bevacizumab to carboplatin and gemcitabine in women with platinum-sensitive recurrent disease. Bevacizumab-based therapy also extended progression-free survival from 8 to 12 months. However, overall survival was not different between the two arms. In the Gynecologic Oncology Group 213 (GOG 213) trial, women with platinum-sensitive recurrent epithelial ovarian cancer were randomly assigned to medical treatment (carboplatin plus paclitaxel with or without bevacizumab). A significant improvement in progression-free survival (14 versus 10 months, respectively) was observed. A trend towards a significant improvement in overall survival, which was not statistically significant, was reported. In November 14, 2014, based on AURELIA findings, the Food and Drug Administration approved bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, for the treatment of patients with platinum-resistant recurrent epithelial ovarian cancer. Ovarian cancer is a primary cancer against which these new agents are being tested. This review will describe the role of angiogenesis inhibitors in epithelial ovarian cancer.

Keywords: antiangiogenic agents, ovarian cancer, bevacizumab

Streszczenie

Angiogeneza nowotworowa wydaje się istotnym procesem w rozwoju raka jajnika. Bewacyzumab jest przeciwciałem monoklonalnym zdolnym do neutralizacji naczyniowo-śródbłonkowego czynnika wzrostu, promotora początkowej fazy angiogenezy. W dwóch badaniach klinicznych III fazy (Gynecologic Oncology Group – GOG 218 oraz ICON7) wykazano skuteczność chemioterapii pierwszego rzutu w skojarzeniu z bewacyzumabem i następowym leczeniem podtrzymującym bewacyzumabem w porównaniu z samą chemioterapią, jednak bezwzględne korzyści czasu wolnego bez progresji pozostają niewielkie, bez wpływu na przeżycie całkowite. W badaniu OCEANS oceniono korzyści wynikające z włączenia bewacyzumabu do terapii karboplatiną i gemcytabiną u kobiet z nawrotowym rakiem jajnika wrażliwym na platynę. Leczenie oparte na bewacyzumabie wydłużyło czas przeżycia bez progresji choroby z 8 do 12 miesięcy. Nie stwierdzono różnicy w odniesieniu do przeżycia całkowitego między dwiema grupami pacjentek. W badaniu klinicznym GOG 213 (Gynecologic Oncology Group 213) kobietom z nawrotowym rakiem jajnika wrażliwym na platynę losowo przypisywano rodzaj leczenia (karboplatinę plus paklitaksel z lub bez bewacyzumabu). Zaobserwowano istotną poprawę w zakresie przeżycia bez progresji choroby (odpowiednio 14 i 10 miesięcy). Odnotowano tendencję do poprawy w zakresie przeżycia ogólnego, jednak bez istotności statystycznej. W oparciu o wyniki badania AURELIA 14 listopada 2014 roku Agencja Żywności i Leków zatwierdziła bewacyzumab w skojarzeniu z paklitakselem, pegylowaną liposomalną doksorubicyną lub topotekaniem w leczeniu chorych z wrażliwym na platynę nawrotowym rakiem jajnika. Rak jajnika jest pierwszym nowotworem, wobec którego badane są te leki. W niniejszej pracy opisano rolę inhibitorów angiogenezy w nabłonkowym raku jajnika.

Słowa kluczowe: leki antyangiogenne, rak jajnika, bewacyzumab

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, with 238,700 new cases and 151,900 deaths in 2012⁽¹⁾. Despite optimal upfront surgery and the administration of front-line paclitaxel–carboplatin chemotherapy, ~70% of patients will relapse in the first 3 years⁽²⁾. Therefore, there is a strong need for effective first-line treatment that will increase response rates and progression-free survival (PFS). The primary goals of systemic treatment for advanced ovarian cancer include prolongation of survival, reduction of tumor burden, alleviation of symptoms associated with the disease, and minimization of toxicities associated with treatment⁽³⁾. Angiogenesis has an important role in normal ovarian physiology, pathogenesis of epithelial ovarian cancers, development of ascites and metastasis as well as plays an active part in the treatment of EOC via angiogenesis inhibitors (Fig. 1). Several therapeutic strategies to target angiogenesis in ovarian cancer are under investigation, including small molecular tyrosine kinase inhibitors of vascular endothelial growth factor receptor (VEGFR), vascular endothelial growth factor (VEGF) Trap (a soluble decoy VEGF receptor), trebananib (peptide-Fc fusion protein blocking angiopoietin 1/2-Tie2 receptor interaction), synthetic flavonoids impairing tumor vascularity and tubulin binders (Tab. 1). Bevacizumab is a human monoclonal antibody that binds to and neutralizes biological activities of VEGF isoforms. It inhibits the formation of new vessels and suppresses tumor growth and metastasis by leading to regression of tumor vascularity. It is the most successful antiangiogenic agent developed to date.

Drug	Main molecular targets
Bevacizumab	VEGF-A
VEGF Trap	VEGF-A (B, C, D, E)
Cediranib	VEGFR-1, VEGFR-2, VEGFR-3
Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α/β , c-kit
Trebananib	Angiopoietin 1 and 2
Nintedanib	VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR- α/β , FGFR-1, FGFR-2, FGFR-3, members of the v-src sarcoma viral oncogene homolog (Src) family, and Flt-3

VEGF – vascular endothelial growth factor; **VEGFR** – vascular endothelial growth factor receptor; **PDGFR** – platelet-derived endothelial cell growth factor receptor; **Flt-3** – fms-like tyrosine kinase 3.

Tab. 1. Targeted pathway angiogenesis for ovarian cancer

WHAT IS THE OPTIMAL SETTING FOR BEVACIZUMAB TREATMENT?

Questions regarding the optimal timing of bevacizumab in ovarian cancer continue to emerge. When should we start bevacizumab in ovarian cancer?

- A. First-line chemotherapy for advanced (stage III or IV) EOC.
- B. Platinum-resistant EOC.
- C. Platinum-sensitive EOC.

Addition of bevacizumab to standard chemotherapy in four randomized, double-blind, phase III trials have been performed both as front-line treatment (GOG 218⁽⁴⁾

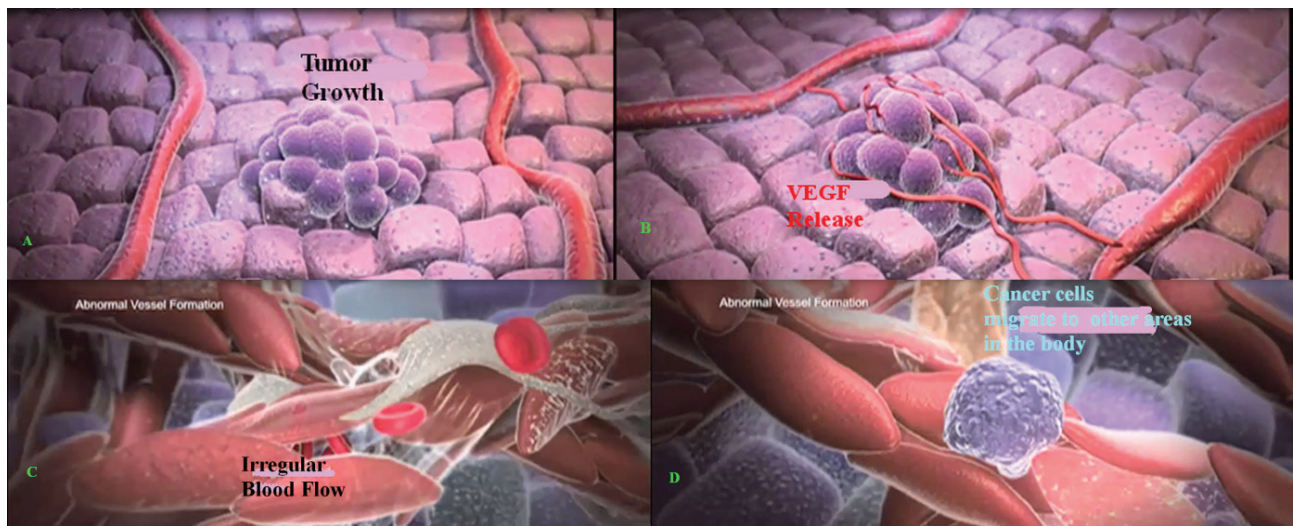


Fig. 1 **A.** The formation of tumor-associated vasculature, formed by the process of neoangiogenesis, is critical, rate-limiting determinant of the growth of all tumors larger in size than approximately 0.2 mm. **B–C.** Vascular endothelial growth factor (also known as VEGF-A) is one of the most potent angiogenic factors described and stimulates endothelial cells proliferation, survival, chemotaxis, and vessel permeability. **D.** Antiangiogenic therapy relies on stopping the formation of new capillary vessels around a tumor and breaking up the existing network of abnormal capillaries that feed the growing cancerous mass, thereby both starving it of nutrients and cutting off the pathway for primary metastasis through the endogenous circulatory system

and ICON7⁽⁵⁾) as well as in patients with recurrent disease (OCEANS⁽⁶⁾ and AURELIA⁽⁷⁾) (Tab. 2). In these four studies, the PFS was prolonged, while the overall survival (OS) improved in certain subgroups only in two studies. In ICON7 patients at high risk for progression (FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery), the benefit of adding bevacizumab was associated with improvement in OS⁽⁵⁾. In GOG 213, the OS was increased in women with platinum-sensitive recurrent ovarian cancer who were treated with chemotherapy plus bevacizumab⁽⁸⁾.

What explains the relatively short-lived responses observed in the clinical setting, given that bevacizumab clearly increases PFS in ovarian cancer? Compensatory signaling through alternative proangiogenic pathways (e.g. fibroblast growth factor, angiopoietin 1 – Ang1, delta-like ligand 4/Notch, and microRNAs) is likely to be a major factor in acquired resistance to bevacizumab⁽⁹⁾.

Tumors or ischemic tissues recruit proangiogenic endothelial cells and inflammatory cells independent of VEGF; the recruited cells may produce several proangiogenic molecules to rescue vascularization upon VEGF blockage⁽¹⁰⁾.

BEVACIZUMAB AS FIRST-LINE TREATMENT IN OVARIAN CANCER

GOG 218 was a randomized placebo-controlled study involving almost 1,900 women with stage III or IV EOC who had undergone surgical cytoreduction⁽⁴⁾. It was a three-arm trial designed to compare chemotherapy (carboplatin plus paclitaxel) alone (Arm 1) with chemotherapy plus bevacizumab (Arm 2) and with chemotherapy plus bevacizumab followed by maintenance

bevacizumab (Arm 3). The ICON7 trial randomly assigned 1,528 patients with high-risk early stage or advanced stage ovarian cancer to carboplatin AUC 5–6 and paclitaxel 175 mg/m² every 3 weeks with or without bevacizumab 7.5 mg/kg followed by bevacizumab maintenance treatment⁽⁵⁾.

In the GOG 218 study, PFS was significantly prolonged when bevacizumab was used concurrently and after chemotherapy compared to chemotherapy alone (median 14.1 vs. 10.3 months)⁽⁴⁾. There was no improvement in OS with bevacizumab in either arm receiving the drug. The addition of bevacizumab resulted in a significantly prolonged PFS in the ICON-7 study (19.8 vs. 17.4 months). In women at high risk of progression (stage III disease with >1.0 cm residual disease following surgery, inoperable patients with stage III and stage IV disease), bevacizumab was associated with improvement in OS (39.3 vs. 34.5 months)⁽⁵⁾. While the GOG 218 study is a placebo controlled study with three study arms, ICON7 is a trial with two arms without placebo including stage I/II patients. It remains a major question as to why such significant gains in PFS seen in the completed phase III trials with bevacizumab and chemotherapy frequently did not correspond to significant gains in OS.

GOG 218 showed that there was no benefit of the combination of bevacizumab with chemotherapy without subsequent bevacizumab maintenance (11 vs. 10 months), but median PFS advantage of bevacizumab added to chemotherapy followed by maintenance treatment compared with chemotherapy alone (plus placebo in GOG 218) in first-line was 3.8 months (GOG 218, from 10.3 to 14.1 months with and without bevacizumab), and 2 months (ICON7, from 22 to 24 months). The lower increase in PFS achieved in ICON7 compared to GOG 218 may be secondary to the

Trial	Arms	Number of patients	Median PFS (months)	Hazard ratio	p value	Survival advantage
GOG 218 ⁽⁴⁾	Arm 1: carboplatin + paclitaxel + placebo Arm 2: carboplatin + paclitaxel + bevacizumab + placebo Arm 3: carboplatin + paclitaxel + bevacizumab maintenance (15 months)	625 623 625	10.3 11.2 14.1	0.91 0.72	0.16 <0.0001	No Patients with ascites
ICON7 ⁽⁵⁾	Arm 1: carboplatin + paclitaxel Arm 2: carboplatin + paclitaxel + bevacizumab maintenance (15 months)	764 764	22 24	0.81	0.004	Patients with a high risk of relapse
AURELIA ⁽⁷⁾	Arm 1: chemotherapy Arm 2: chemotherapy + bevacizumab	182 179	3.8 6.7	0.48	0.001	No
OCEANS ⁽⁶⁾	Arm 1: carboplatin + gemcitabine + placebo Arm 2: carboplatin + gemcitabine + bevacizumab to progression	242 242	8.4 12.4	0.48	<0.0001	No
GOG 213 ⁽⁸⁾	Arm 1: paclitaxel + carboplatin Arm 2: paclitaxel + carboplatin + bevacizumab; bevacizumab maintenance	374 374	10.4 13.8	0.61	0.056	Yes

80 Tab. 2. Summary of the four positive phase III trials adding bevacizumab to chemotherapy in epithelial ovarian carcinoma

lower doses of bevacizumab used and the more favorable prognosis groups of patients. Angiogenesis inhibitors as initial therapy for advanced EOC are not recommended because only modest benefits have been demonstrated in randomized first-line trials^(4,5,11,12) (Fig. 2).

BEVACIZUMAB AS SECOND-LINE TREATMENT FOR OVARIAN CANCER

Recurrent disease is typically not curable; therefore symptom palliation and prevention of complications, such as bowel obstruction, remain the goals of management. However, for women who achieve a response or remission after platinum-based retreatment, the durability of the second remission is an important issue.

OCEANS is a randomized trial of bevacizumab in 484 women with platinum-sensitive recurrent ovarian cancer. Patients were randomized to receive carboplatin AUC (area under the curve) 4 on day 1 in combination with gemcitabine 1,000 mg/m² on day 1 and 8 plus bevacizumab 15 mg/kg or placebo on day 1, every 21 days. Bevacizumab or placebo was then continued until disease progression. An improvement in PFS (12 vs. 8 months, hazard ratio – HR 0.48, 95% CI 0.39–0.61) was observed. However, OS was not different between the two arms (34 vs. 33 months). The data consistently demonstrate that incorporating bevacizumab can improve PFS in women with platinum-sensitive recurrent EOC. However, there has been no demonstrable improvement in OS in this setting.

GOG 213 is a randomized open label phase III trial assessing carboplatin and paclitaxel with or without 15 mg/kg of bevacizumab every 3 weeks followed by maintenance therapy⁽⁸⁾. Chemotherapy alone, compared with chemotherapy plus bevacizumab, improved the stratified estimated treatment HR of death by 18.6% (HR: 0.827, 95% CI: 0.683–1.005, *p* = 0.056) with median OS of 42.2 vs. 37.3 months, respectively. PFS was similarly improved by adding bevacizumab to chemotherapy (median PFS 13.8 vs. 10.4 months) (HR: 0.614, 95% CI: 0.522–0.722, *p* < 0.0001).

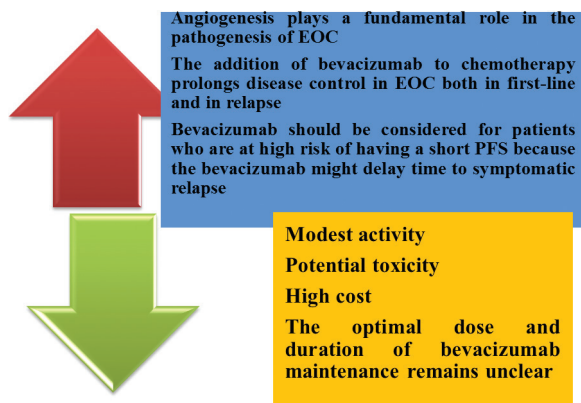


Fig. 2. Incorporating bevacizumab into ovarian cancer treatment

There are many important treatment-related issues to consider in patients diagnosed with recurrent platinum-sensitive cancer: what medications should be used and in what order? Could this simply be related to the chemotherapy backbone suggesting that carboplatin plus paclitaxel is better than carboplatin plus gemcitabine as a companion for bevacizumab?

There are many treatments available for recurrent ovarian cancer. Combination of chemotherapy plus bevacizumab is a level 2B recommendation according to the National Comprehensive Cancer Network (NCCN) for patients with recurrent platinum-sensitive EOC (as per OCEANS)⁽¹²⁾. Patients with platinum-resistant EOC are not curable. Hence, treatments should aim to maximize the quality of life while attempting to control the disease.

The AURELIA trial evaluated the impact of adding bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) to either dose-dense paclitaxel 80 mg/m² weekly or topotecan 4 mg/m² on days 1, 8, and 15 of each 4-week cycle (or 1.25 mg/m² on day 1 through 5 of each 3-week cycle) or liposomal doxorubicin 40 mg/m² every 4 weeks. Only patients with platinum-resistant ovarian cancer were eligible. Women at high risk for gastrointestinal (GI) perforations and patients who had more than 3 lines of prior chemotherapy were excluded. A reduction in the risk of disease progression (HR 0.48, 95% CI 0.38–0.60; median duration 6.7 vs. 3.4 months), with no statistically significant improvement in OS (HR 0.85, 95% CI 0.66–1.08; median 16.6 vs. 13.3 months) was observed (Fig. 3).

ADVERSE EFFECTS AND TOXICITY PROFILE OF BEVACIZUMAB IN OVARIAN CANCER

Will antiangiogenic drugs that have lethal effects on malignant growths while having minimal adverse effects on normal tissues ever be developed? Bowel perforation

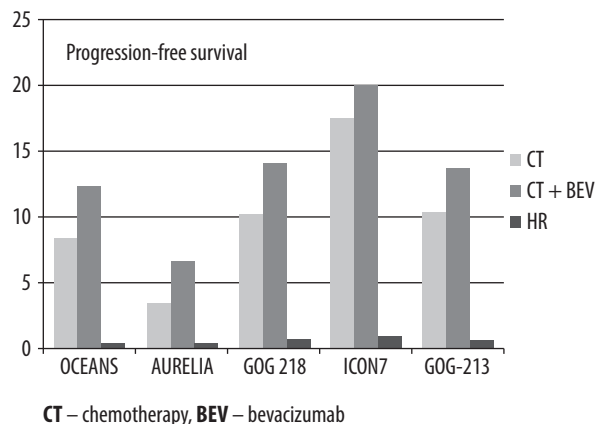


Fig. 3. The HRs were 0.72 and 0.93 for GOG 218 and ICON7, respectively, in first-line and 0.48 for both the OCEANS and AURELIA trials in relapse. The HRs was 0.61 for GOG 213

or fistula formation may be more common in patients who are heavily pretreated or who have diffuse peritoneal disease or substantial pelvic disease with previous bowel surgery or bowel obstruction⁽¹³⁾. Thus, bevacizumab is avoided in this population, especially because bowel perforation in such patients can be fatal. In GOG 218 trial, the risk of gastrointestinal perforation/fistula formation with and without bevacizumab was 3% vs. 1%⁽⁴⁾. Similarly, low rates of gastrointestinal perforation were reported in the ICON7 trial of first line carboplatin plus paclitaxel with or without bevacizumab (1.7% vs. 1.3%)⁽⁵⁾. In the OCEANS trial, there were no reported cases of gastrointestinal perforation, and the rates of fistula/abscess formation were also low in the bevacizumab group (4% vs. 1% in the control group, 1.6% vs. 0.4%)⁽⁶⁾. In GOG 213 trial, the risk of gastrointestinal perforation/necrosis/fistula with and without bevacizumab was 1% vs. 1.8%, respectively⁽⁸⁾. Bevacizumab has 3 black box warnings: gastrointestinal perforation, surgery and wound healing complications as well as severe or fatal hemorrhage including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, and vaginal bleeding. Hypertension is common (20%), but arterial thromboembolic risk is estimated at 3.8% compared with 1.7% for chemotherapy alone⁽¹⁴⁾. Other toxicities include small (<1%) but potentially severe risk of grade 3 to 4 heart failure and reversible posterior leukoencephalopathy, both of which justify permanent bevacizumab discontinuation⁽¹⁴⁾. Given that women with EOC often present or recur with peritoneal involvement, the risk of gastrointestinal perforation is of significant concern.

UNRESOLVED ISSUES IN THE USE OF BEVACIZUMAB IN OVARIAN CANCER

There are several unanswered questions regarding the use of bevacizumab in EOC. In view of the increasing use of bevacizumab in first-line regimens, an important clinical issue is whether it should be continued in patients who switch to an alternative regimen after failing first-line bevacizumab-containing therapy. There is evidence that bevacizumab can be used at all treatment stages. Bevacizumab as first line treatment does not preclude its use in recurrent disease⁽¹⁵⁾. Re-treatment with bevacizumab was not associated with a negative rebound effect in GOG 213. Re-introduction of bevacizumab was associated with a higher objective response rate and had no significant impact on toxicity⁽¹⁶⁾.

Should bevacizumab be used on its own or in combination? It is plausible that the synergistic effects of bevacizumab with conventional chemotherapeutic drugs derive directly from the ability of this VEGF-A inhibitor to normalize tumor-associated vasculature, thereby greatly facilitating the delivery of drugs to the tumor parenchyma⁽¹⁷⁾.

This agent is frequently administered in the context of chemotherapy; however, several phase II trials evaluating

its activity as a single agent have included patients with platinum-sensitive disease. In the GOG 170-D trial, 11 responses (44%) were seen among 25 patients (41% of the total population) with potentially platinum-sensitive recurrent disease, including two complete responses⁽¹⁸⁾. Future clinical developments of bevacizumab in ovarian cancer treatment will include the combination of this agent with other targeted therapies in advanced disease and the integration of this agent into combined modalities approaches for the treatment involving intraperitoneal chemotherapy and dose-dense chemotherapy.

NOVEL AGENTS: PAZOPANIB, NINTEDANIB AND TREBANANIB IN OVARIAN CANCER

Pazopanib is an oral tyrosine kinase inhibitor developed against VEGF, platelet-derived growth factor (PDGF) and c-kit receptor. The role of pazopanib in maintenance treatment was evaluated in AGO-OVAR study including 900 EOC patients⁽¹⁹⁾. The aim of this study was to determine whether therapy with pazopanib was effective and safe in women with epithelial ovarian, fallopian tube, or primary peritoneal cancer whose cancer did not progress on first line chemotherapy. Patients were randomized into pazopanib 800 mg daily and placebo arms for 24 months. Median PFS was significantly longer for pazopanib group (18 vs. 12 months, HR 0.766, 95% CI 0.64–0.91), but interim analysis showed no OS difference between the two arms. Pazopanib treatment was found to be associated with grade ≥ 2 hypertension (52% vs. 17%) grade 3 or 4 diarrhea (8% vs. 1%) and grade 3 or 4 hepatotoxicity (9% vs. <1%). In conclusion, this study did not lead to any change in daily clinical practice.

Nintedanib is an oral tyrosine kinase inhibitor used against VEGF, fibroblast growth factor (FGF) and PDGF receptor. A phase III trial is investigating the combination of nintedanib with carboplatin and paclitaxel in the first-line setting followed by nintedanib alone as maintenance therapy⁽²⁰⁾. Compared to placebo, nintedanib led to moderate improvement in PFS (median 17.3 vs. 16.6 months, HR 0.84, 95% CI 0.72–0.98) and survival analysis is ongoing. Severe grade 3 to 5 toxicity including thrombocytopenia, anemia, neutropenia, diarrhea, fatigue, hypertension and hepatotoxicity was observed more frequently in nintedanib arm.

Trebananib (AMG386) is an angiopoietin antagonist peptide-Fc fusion protein (also known as a peptibody) that inhibits Ang1 and Ang2 from binding to their tyrosine kinase receptors, leading to inhibition of angiogenesis⁽²¹⁾. Ang1 stabilizes endothelial junction and Ang2 leads to vessel sprouting in endothelium. They all increase vessel density⁽²²⁾. In phase III (TRINOVA-1) study including 919 women, patients were randomized into paclitaxel and trebananib or placebo arms⁽²³⁾. The eligibility was limited to women with a platinum-free interval (PFI)

of less than 12 months and allowed up to three prior anticancer therapies (22% of patients). The primary end point was PFS and the authors have recently reported that there was a significant improvement in PFS compared with weekly paclitaxel plus placebo (median 7.2 vs. 5.4 months, respectively, HR 0.66, 95% CI 0.57–0.77). When in November 2014, survival outcome of trebananib was compared with placebo, no significant difference was found (median 18 vs. 19 months)⁽²⁴⁾. When paclitaxel plus placebo was compared with paclitaxel plus trebananib, toxicity was shown to occur at higher rates: localized edema (57% vs. 26%), pleural effusion (13% vs. 4%), generalized edema (11% vs. 3%), ascites (20% vs. 12%), peripheral neuropathy (21% vs. 16%).

Cediranib is an oral antiangiogenic VEGF receptor 1–3 inhibitor. A phase III trial of platinum-based chemotherapy (carboplatin plus paclitaxel) alone versus chemotherapy with cediranib (as concurrent and/or maintenance therapy) in women with platinum-sensitive recurrent ovarian cancer was performed⁽²⁵⁾. The patients enrolled in cediranib-maintenance arm experienced longer PFS (HR 0.57, 95% CI 0.45–0.74, $p = 0.0024$) and a 2.7-month improvement in OS (HR 0.70, 95% CI 0.51–0.99, $p = 0.042$) when compared with those treated with chemotherapy alone. The most common cediranib-related adverse events included diarrhea, nausea, and fatigue. We await final reporting of OS data from this study before altering our approach.

Aflibercept is a fusion molecule containing the binding domains of VEGF receptors 1 and 2 bound to the human immunoglobulin IgG Fc fragment, forming a VEGF Trap molecule. It acts as a soluble “decoy” receptor that binds to human VEGF-A, VEGF-B, and placental growth factor (PlGF), thereby inhibiting the binding of these ligands and activation of their respective receptors. A randomized phase 2 study assessed the efficacy and safety of intravenous aflibercept at 2 different doses (2 mg/kg or 4 mg/kg) in patients with recurrent, platinum-resistant ovarian, peritoneal, or fallopian tube cancer who developed disease progression after receiving topotecan and/or pegylated liposomal doxorubicin. The results were disappointing. Two-hundred and fifteen evaluable patients were analyzed, including 1 responder among 106 patients (0.9%) in the 2 mg/kg cohort, and 5 responders among 109 patients (4.6%) in the 4 mg/kg cohort⁽²⁶⁾. In a double-blind, placebo-controlled, parallel-group, phase 2 study, patients with advanced chemoresistant ovarian cancer and recurrent symptomatic malignant ascites were randomly assigned to intravenous aflibercept (4 mg/kg every 2 weeks) or placebo arm. Mean time to repeated paracentesis was significantly longer with aflibercept (55.1 vs. 23.3 days; $p = 0.0019$)⁽²⁷⁾. Combination of this drug (6 mg/kg) and docetaxel (75 mg/m²) had significant activity (54% response rate) in a phase I–II trial that included patients with platinum-sensitive as well as recurrent disease⁽²⁸⁾. None of these agents is currently approved

by the US Food and Drug Administration for treating patients with relapsed ovarian cancer, and their ultimate value needs to be better defined.

RESISTANCE TO ANTIANGIOGENIC THERAPY

Resistance to VEGF inhibitors may be observed in late-stage tumors when tumors regrow during treatment after the initial period of growth suppression from these antiangiogenic agents. This resistance involves the reactivation of tumor angiogenesis and increased expression of other proangiogenic factors. A fraction of tumor vessels are lined by malignant cells and are thus unresponsive to antiangiogenic agents (vascular mimicry). The outgrowth of tumor cell clones expressing elevated levels of certain angiogenic factors may be naturally favored at advanced stages of tumor progression (angiogenic switch). For example, inhibition of the VEGF pathway leads to resumption of tumor angiogenesis through upregulation of fibroblast growth factor-2 (FGF2)⁽²⁹⁾, interleukin-8⁽³⁰⁾, and Ang2⁽³¹⁾. Mutant tumor cell clones (e.g. those lacking p53) are able to survive in hypoxic tumors (vascular independence). Preexisting vessels are covered by a full complement of supporting pericytes and are unable to maintain vascular regression induced by antiangiogenic treatments. Tumors or ischemic tissues recruit proangiogenic endothelial cells and inflammatory cells independent of VEGF; the recruited cells may produce several proangiogenic molecules to rescue vascularization upon VEGF blockage.

CONCLUSION

EOC remains an important problem worldwide. The majority of patients with ovarian cancer will require palliative treatment at some point in the course of their disease. Tumor angiogenesis remains a critical target for the treatment of patients with ovarian cancer. There was no consensus regarding the incorporation of bevacizumab in first line therapy trials. The NCCN Panel recommends (category 2B) bevacizumab in upfront chemotherapy followed by maintenance therapy⁽¹²⁾.

On the other hand, the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommends (category IB) bevacizumab in patients with advanced ovarian cancer with poor prognostic factors such as stage IV or suboptimal debulking as defined in the ICON7 trial⁽²⁾. In recent years, a better understanding of the biological properties of tumors and the development and application of molecular targeted drugs have created hope for the individualized treatment of advanced ovarian cancer.

Future perspective

We still do not understand how cancer cells create metastases that are responsible for 90% of cancer-associated

mortality. With enhanced understanding of vascular biology and advances in targeted therapy design, medical oncology practice will see an expanding role of tumor endothelial directed therapies. And while we know much about the individual signaling molecules operating inside individual human cells, we lack a clear understanding of how the complex signaling circuitry formed by these molecules makes the life and death decisions that determine the fate of individual cells within our body. Although antiangiogenic drugs improved PFS and, in some cases, OS, phase 3 trials showed that the benefits were clinically modest. More importantly, these studies would represent a major step forward in the field of targeted antiangiogenesis therapies which is tremendously important for oncology and encourage further molecular and clinical studies to identify reliable biomarkers suitable for use in the clinical setting and to provide increased benefits from therapies targeting angiogenesis with selection of appropriate patients. A first prospective biomarker study (MERiDiAN) in metastatic breast cancer is currently underway to evaluate the impact of bevacizumab in patients stratified for plasma short VEGF-A isoforms. If validated, these findings could help identify which subgroup of patients should receive antiangiogenic therapy and could lead the way to possible future tailoring of individualized antiangiogenic therapy. It is likely that our current understanding of tumor angiogenesis and our ability to manipulate it clinically will have once again been greatly altered by the next edition of this review.

Conflict of interest

There are no conflicts of interest to report, and no disclaimers.

References

- International Agency for Research on Cancer: GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available from: http://globocan.iarc.fr/Pages/bar_sex_pop_sel.aspx [cited 8 August 2014].
- Ledermann JA, Raja FA, Fotopoulou C *et al.*; ESMO Guidelines Working Group: Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 24 Suppl 6: vi24–vi32.
- Pujade-Lauraine E: How to approach patients in relapse. *Ann Oncol* 2012; 23 Suppl 10: x128–x131.
- Burger RA, Brady MF, Bookman MA *et al.*; Gynecologic Oncology Group: Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; 365: 2473–2483.
- Perren TJ, Swart AM, Pfisterer J *et al.*; ICON7 Investigators: A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; 365: 2484–2496.
- Aghajanian C, Blank SV, Goff BA *et al.*: OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; 30: 2039–2045.
- Pujade-Lauraine E, Hilpert F, Weber B *et al.*: Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol* 2014; 32: 1302–1308.
- Coleman RL, Brady MF, Herzog TJ *et al.*: A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 213). Presented at the 46th Annual Meeting on Women's Cancer of the Society of Gynecologic Oncology, Chicago, 2015.
- Graybill W, Sood AK, Monk BJ *et al.*: State of the science: Emerging therapeutic strategies for targeting angiogenesis in ovarian cancer. *Gynecol Oncol* 2015; 138: 223–226.
- Nagy JA, Dvorak HF: Heterogeneity of the tumor vasculature: the need for new tumor blood vessel type-specific targets. *Clin Exp Metastasis* 2012; 29: 657–662.
- Oza AM, Cook AD, Pfisterer J *et al.*: ICON7 trial investigators: Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015; 16: 928–936.
- National Comprehensive Cancer Network. Available from: <http://www.nccn.org> [cited: 21 November 2015].
- Simpkins F, Belinson JL, Rose PG: Avoiding bevacizumab related gastrointestinal toxicity for recurrent ovarian cancer by careful patient screening. *Gynecol Oncol* 2007; 107: 118–123.
- Randall LM, Monk BJ: Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol* 2010; 117: 497–504.
- McCann GA, Smith B, Backes FJ *et al.*: Recurrent ovarian cancer: is there a role for re-treatment with bevacizumab after an initial complete response to a bevacizumab-containing regimen? *Gynecol Oncol* 2012; 127: 362–366.
- Coleman RL, Brady MF, Herzog TJ *et al.*: Bevacizumab after bevacizumab in platinum-sensitive recurrent ovarian cancer: a subgroup analysis of GOG0213. *J Clin Oncol* 2016; 34 (Suppl; abstr 5523).
- Zhou Q, Guo P, Gallo JM: Impact of angiogenesis inhibition by sunitinib on tumor distribution of temozolomide. *Clin Cancer Res* 2008; 14: 1540–1549.
- Burger RA, Sill MW, Monk BJ *et al.*: Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007; 25: 5165–5171.
- du Bois A, Floquet A, Kim JW *et al.*: Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol* 2014; 32: 3374–3382.
- du Bois A, Kristensen G, Ray-Coquard I *et al.*; AGO Study Group led Gynecologic Cancer Intergroup/European Network of Gynaecologic Oncology Trials Groups Intergroup Consortium: Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol* 2016; 17: 78–89.
- Robson EJ, Ghatage P: AMG 386: profile of a novel angiopoietin antagonist in patients with ovarian cancer. *Expert Opin Investig Drugs* 2011; 20: 297–304.
- Eskander RN, Tewari KS: Incorporation of anti-angiogenesis therapy in the management of advanced ovarian carcinoma – mechanistics, review of phase III randomized clinical trials, and regulatory implications. *Gynecol Oncol* 2014; 132: 496–505.
- Monk BJ, Poveda A, Vergote I *et al.*: Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol* 2014; 15: 799–808.
- Amgen announces top-line secondary endpoint results of phase 3 trebananib TRINOVA-1 trial in patients with recurrent ovarian cancer. Available from: <http://www.prnewswire.com/news-releases/amgen-announces-top-line-secondary-endpoint-results-of-phase-3-trebananib-trinova-1-trial-in-patients-with-recurrent-ovarian-cancer-281442761.html> [cited 5 November 2014].
- Ledermann JA, Embleton AC, Raja F *et al.*; ICON6 collaborators: Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 387: 1066–1074.

26. Tew WP, Colombo N, Ray-Coquard I *et al.*: Intravenous aflibercept in patients with platinum-resistant, advanced ovarian cancer: results of a randomized, double-blind, phase 2, parallel-arm study. *Cancer* 2014; 120: 335–343.
27. Gotlieb WH, Amant F, Advani S *et al.*: Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Oncol* 2012; 13: 154–162.
28. Coleman RL, Duska LR, Ramirez PT *et al.*: Phase 1–2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. *Lancet Oncol* 2011; 12: 1109–1117.
29. Casanovas O, Hicklin DJ, Bergers G *et al.*: Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005; 8: 299–309.
30. Huang D, Ding Y, Zhou M *et al.*: Interleukin-8 mediates resistance to antiangiogenic agent sunitinib in renal cell carcinoma. *Cancer Res* 2010; 70: 1063–1071.
31. Rigamonti N, Kadioglu E, Keklikoglou I *et al.*: Role of angiopoietin-2 in adaptive tumor resistance to VEGF signaling blockade. *Cell Rep* 2014; 8: 696–706.

Zasady prenumeraty kwartalnika „Current Gynecologic Oncology”

1. Prenumeratę można rozpocząć od dowolnego numeru pisma. Prenumerujący otrzyma zamówione numery kwartalnika pocztą na podany adres.
2. Pojedynczy egzemplarz kwartalnika kosztuje 40 zł. Przy zamówieniu rocznej prenumeraty (4 kolejne numery) koszt całorocznej prenumeraty wynosi 120 zł. Koszt całorocznej prenumeraty zagranicznej wynosi 40 euro.
3. Istnieje możliwość zamówienia numerów archiwalnych (do wyczerpania nakładu). Cena numeru archiwalnego – 40 zł.
4. Zamówienie można złożyć:
 - Dokonując przelewu z własnego konta bankowego (ROR) – wpłaty należy kierować na konto: Medical Communications Sp. z o.o., ul. Powsińska 34, 02-903 Warszawa Deutsche Bank PBC SA 42 1910 1048 2215 9954 5473 0001 Prosimy o podanie dokładnych danych imiennych i adresowych.
 - Drogą mailową: redakcja@ginekologia.com.pl.
 - Telefonicznie: 22 651 97 83.
 - Wypełniając formularz prenumeraty zamieszczony na stronie www.ginekologia.com.pl.
5. Zamawiający, którzy chcą otrzymać fakturę VAT, proszeni są o kontakt z redakcją.

Rules of subscription to the quarterly “Current Gynecologic Oncology”

1. Subscription may begin at any time. Subscribers will receive ordered volumes of the journal to the address provided.
2. A single volume of the quarterly costs 40 PLN (10 EUR). The cost of annual subscription (4 consecutive volumes) is 120 PLN. The cost of annual subscription for foreign subscribers is 40 EUR.
3. Archival volumes may be ordered at a price of 40 PLN per volume until the stock lasts.
4. Orders may be placed:
 - By making a money transfer from own bank account – payments should be made payable to: Medical Communications Sp. z o.o., ul. Powsińska 34, 02-903 Warszawa Deutsche Bank PBC SA 42 1910 1048 2215 9954 5473 0001 For foreign subscribers: Account Name: Medical Communications Sp. z o.o. Bank Name: Deutsche Bank PBC S.A. Bank Address: 02-903 Warszawa, ul. Powsińska 42/44 Account number: 15 1910 1048 2215 9954 5473 0002 SWIFT Code/IBAN: DEUTPLPK Please provide a precise address and nominative data.
 - By e-mail: redakcja@ginekologia.com.pl.
 - Filling-in a subscription form, which may be found on the page www.ginekologia.com.pl.
5. Customers wishing a VAT invoice, are requested to contact directly the Editor.