Bevacizumab and ovarian cancer

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Abstract: Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor-A, and is indicated in the treatment of various tumors (colon, lung, renal, and glioblastoma). It has been recently approved for the treatment of ovarian cancer in various countries. This review summarizes the activity and toxicity of bevacizumab in the treatment of ovarian cancer, both as single-agent drug and in combination with cytotoxic chemotherapy. As a single-agent drug, it has shown response rates of 16–21% in the treatment of recurrent ovarian cancer. Two phase III randomized trials have been published evaluating the addition of bevacizumab to standard chemotherapy as front-line treatment of advanced ovarian cancer. In addition, trials evaluating the combination with chemotherapy in recurrent ovarian cancer (platinum-sensitive and platinum-resistant disease) have also been reported. All these trials showed a statistically significant improvement in progression-free survival although no improvement in overall survival has been reported. The main adverse event is hypertension. Other serious, but uncommon adverse events include gastrointestinal perforation as well as renal and central nervous system toxicity.

Keywords: bevacizumab, combination therapy, single-agent therapy, ovarian cancer, progression-free survival

Introduction

Ovarian cancer is the most lethal gynecologic cancer and fifth leading cause of cancer death in the United States. In the year 2012, there will be an estimated 22,280 new cases and 15,500 deaths in the US alone [Siegel *et al.* 2012]. Primary peritoneal cancer and fallopian tube cancer are managed similarly to epithelial ovarian cancer (EOC). EOC is highly curable when it is confined to the ovaries, with up to 90% expected 5-year survival. However, EOC is rarely diagnosed at an early stage because the disease causes few specific symptoms when it is localized to the ovary. More than 70% of women with EOC present with advanced stage III or IV disease, which is associated with high morbidity and mortality [Heintz *et al.* 2006].

Current management of advanced stage disease includes surgical tumor debulking, followed by adjuvant platinum- and taxane-based chemotherapy [McGuire *et al.* 1996; Piccart *et al.* 2000]. An approach to improve the outcome of treatment in

EOC has focused on modifying the dose, schedule, or route of administration of chemotherapy. The use of intraperitoneal chemotherapy has been reported to improve outcomes although with increase toxicity [Alberts *et al.* 1996; Armstrong *et al.* 2006; Markman *et al.* 2001]. For various reasons the use of intraperitoneal chemotherapy has not been uniformly adopted despite the positive results of these three randomized trials [Rowan, 2009]. More recently, it was reported that the administration of intravenous (IV) paclitaxel on a weekly schedule improved progression-free survival (PFS) and overall survival (OS) [Katsumata *et al.* 2009]. Another approach consisted of incorporating different cytotoxic agents in sequential doublet and triplet combinations (unfortunately, no combination demonstrated an improvement in OS) [Bookman, 2009]. Another recently described approach is the administration of chemotherapy in the neoadjuvant setting, before surgical resection in contrast to conventional postoperative chemotherapy [Vergote *et al.* 2010]. Although this approach is associated with

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a higher frequency of optimal cytoreduction and lower postoperative adverse events, it did not translate into improvements in OS. Nonetheless, this is now a valid approach that is being used more frequently. Therefore, despite more than 10 years of research the combination of carboplatin and paclitaxel remains the standard chemotherapy regimen in advanced ovarian cancer. However, OS for patients with advanced ovarian cancer is poor and the 5-year survival remains at only 27% [Siegel *et al.* 2012].

Despite the introduction of platinum and paclitaxel the majority of women with advanced stage recur within 5 years and drug resistance emerges [Heintz *et al.* 2006]. Recurrent ovarian cancer is classified as been platinum resistant, defined as relapsing within 6 months, or platinum sensitive, defined as relapsing more than 6 months after completing initial platinum-based chemotherapy [Markman *et al.* 1991]. Patients with platinum-resistant disease are typically treated with other agents, such as pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, weekly paclitaxel or participation in a clinical trial. However, the overall response rate with these alternate agents is only 10–25% with relatively short durations of response [Agarwal and Kaye, 2003]. Thus, exploration of alternative therapeutics has become an area of extensive and important research.

Based on increasing knowledge of key biologic pathways driving tumor progression, several targeted therapies have been recently investigated in recurrent ovarian cancer. Unfortunately, most of these therapies have shown limited activity [Bookman *et al.* 2003; Garcia *et al.* 2012; Gordon *et al.* 2005, 2006; Posadas *et al.* 2007; Schilder *et al.* 2005, 2008, 2009]. One of the targeted approaches most widely studied and most promising in the treatment of EOC is the inhibition of angiogenesis. Bevacizumab is the inhibitor of angiogenesis that has been most extensively studied in EOC. This review will focus on the potential role of bevacizumab in the management of ovarian cancer, including both upfront therapy and treatment of recurrent disease.

Tumor angiogenesis in epithelial ovarian cancer

Angiogenesis seems to play a major role in the natural history of ovarian cancer, promoting tumor growth and progression in the form of ascites formation and metastatic spread [Byrne

et al. 2003; Hollingsworth *et al.* 1995; Shen *et al.* 2000]. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor (VEGF)-A, and is indicated in the treatment of metastatic colorectal cancer, non-small cell lung cancer, renal cell carcinoma, and glioblastoma multiforme [Escudier *et al.* 2007; Friedman *et al.* 2009; Hurwitz *et al.* 2004; Sandler *et al.* 2006]. This antibody binds to and neutralizes all biologically active forms of VEGF-A, and then suppresses tumor growth and inhibits metastatic disease progression [Lin *et al.* 1999]. The utility of VEGF antibodies in the treatment of ovarian carcinoma was initially explored in animal models, where VEGF blockade was shown to inhibit ascites formation and slow tumor growth [Byrne *et al.* 2003]. In addition, VEGF-targeting agents are thought to enhance the effects of chemotherapy by normalization of primitive tumor vasculature, leading to decreased interstitial fluid pressure, increased tumor oxygenation, and enhanced delivery of cytotoxic drugs [Jain, 2005].

Single-agent bevacizumab in recurrent ovarian cancer

Two single-agent phase II trials have explored the utility of bevacizumab in the treatment of persistent or recurrent disease: The first and largest single-agent study was conducted by the Gynecologic Oncology Group (GOG) and termed GOG-0170D. In this trial 62 women with persistent or recurrent EOC or primary peritoneal cancer received bevacizumab monotherapy (15 mg/kg IV) repeated every three weeks. The study allowed up to two prior lines of chemotherapy and 58% of patients had platinum-resistant disease. Encouraging activity was reported as evidenced by an overall response rate of 21% and median PFS and OS of 4.7 and 17 months, respectively. In addition, 40% of patients remained progression-free at 6 months. Grade 3 or 4 adverse events thought to be related to bevacizumab included hypertension (9.7%, $n = 6$), thromboembolism (1.6%, $n = 2$, one pulmonary embolism, no arterial emboli), gastrointestinal (GI) events (6.4%, $n = 4$, no perforations or fistulas), proteinuria ($n = 1$), and hypersensitivity reactions (3.2%, $n = 2$) [Burger *et al.* 2007].

The second study (gENENTECH avf 2949g) evaluated the efficacy and safety of bevacizumab in 44 patients with platinum-resistant epithelial ovarian carcinoma or peritoneal serous carcinoma who

had experienced disease progression during or within 3 months of discontinuing topotecan or PLD. Almost 90% of patients had platinum-resistant disease. Results included an objective response rate of 15.9%, median PFS of 4.4 months [95% confidence interval (CI) 3.1–5.5 months], and median OS of 10.7 months. An estimated 28% of patients remained progression-free at 6 months. Bevacizumab-associated grade 3 to 4 events included hypertension (9.1%), proteinuria (15.9%), bleeding (2.3%), and wound healing complications (2.3%). Arterial thromboembolic events occurred in three patients (6.8%). Three deaths were related to bevacizumab treatment [Cannistra *et al.* 2007]. The incidence of GI perforation (GIP; 11.4%) was higher than reported in bevacizumab trials of other tumor types. GIP occurred in 23.8% of patients who had received three prior chemotherapy regimens, compared with 0% of patients receiving two prior chemotherapy regimens ($p < 0.01$). A trend toward higher risk of GIP was observed for patients with bowel wall thickening or bowel obstruction on CT scan [Cannistra *et al.* 2007].

Bevacizumab in combination with chemotherapy in platinum-resistant ovarian cancer

Several authors have evaluated the safety and activity of bevacizumab in combination with cytotoxic chemotherapy agents typically used in platinum-resistant ovarian cancer: topotecan, PLD, and weekly paclitaxel [Kudoh *et al.* 2011; McGonigle *et al.* 2011; O'Malley *et al.* 2011]. As summarized in Table 1, these studies show that the combination is safe and active and suggest bevacizumab may enhance the efficacy of the cytotoxic agent.

Recently, preliminary results of a phase III randomized trial evaluating the role of bevacizumab in platinum-resistant ovarian cancer were presented at the annual meeting of the American Society of Clinical Oncology [a randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC); AURELIA] [Pujade-Lauraine *et al.* 2012]. In this trial 361 patients were randomized to chemotherapy alone (PLD, weekly paclitaxel, or topotecan) or with bevacizumab. Patients with platinum-refractory EOC, history of bowel obstruction, or more than two prior anticancer regimens were ineligible. The primary endpoint of the study was PFS while secondary endpoints included objective response

rate, OS, and safety. The addition of bevacizumab significantly improved PFS (6.7 months *versus* 3.4 months for chemotherapy alone). Objective response rate increased from 12.6% with chemotherapy alone to 30.9% with chemotherapy and bevacizumab. GIPs, fistula, or abscesses occurred in four patients (2.2%) while thrombosis was reported in five (2.8%).

A somewhat different approach was to combine bevacizumab with low-dose metronomic oral cyclophosphamide. Metronomic chemotherapy (MC) was first shown to suppress tumor growth in experimental models, possibly by inhibiting angiogenesis through the release of thrombospondin [Hanahan *et al.* 2000]. This schedule of administration of chemotherapy is devoid of the typical toxicities associated with cytotoxic chemotherapy (alopecia, myelosuppression, nausea, vomiting, etc.). The combined use of MC of antiangiogenic therapies demonstrates marked inhibition of tumor growth in experimental models [Bello *et al.* 2001; Hashimoto *et al.* 2010; Klement *et al.* 2000; Merritt *et al.* 2010]. In this study (NCI-5789) 70 patients with recurrent ovarian cancer were treated with bevacizumab and oral cyclophosphamide administered at a dose of 50 mg/day [Garcia *et al.* 2008]. Up to three prior lines of therapy were allowed and 40% of patients had platinum-resistant disease. An overall response rate of 24% was reported with an additional 62% of patients achieving stable disease. At 6 months there was a PFS of 56% with a median time to progression of 7.2 months. This regimen was associated with a toxicity profile similar to that seen with single-agent bevacizumab in this patient population including two cases (3%) of grade 4 cerebral ischemia and four episodes (6%) of GIP or fistula. However, grade 3 or 4 cytotoxic chemotherapy-associated toxicities were not observed. Other authors have confirmed the activity and favorable toxicity profile of this regimen [Sanchez-Muñoz *et al.* 2010].

Bevacizumab plus chemotherapy as front-line treatment

The activity of single-agent bevacizumab and the ability to combine it with chemotherapy in recurrent ovarian cancer led to studies exploring its use as front-line therapy. Two single-arm phase II trials demonstrated the feasibility of combining carboplatin and paclitaxel with bevacizumab in this setting [Micha *et al.* 2007; Penson *et al.* 2010]. In the first study 20 patients were treated with six

Table 1. Phase II bevacizumab trials in recurrent ovarian and primary peritoneal cancer.

Trial	Setting	Platinum-resistant disease (%)	Treatment	RR (%)	Grade 3 to 4 AEs
GOG-0170D [Burger <i>et al.</i> 2007] <i>n</i> = 62	Recurrent EOC/ PPC; ≤2 prior regimens	42	Bevacizumab 15 mg/kg every 21 days	21	HTN <i>n</i> = 6 (10%)
Genentech AVF 2949g [Cannistra <i>et al.</i> 2007] <i>n</i> = 44	Recurrent EOC/ PPC; ≤3 prior regimens	84	Bevacizumab 15 mg/kg every 21 days	16	HTN <i>n</i> = 6 (14%) GIP <i>n</i> = 5
NCI-5789 [Garcia <i>et al.</i> 2008] <i>n</i> = 70	Recurrent EOC/ PPC; ≤3 prior regimens	40	Bevacizumab 10 mg/kg every 14 days + cyclophosphamide 50 mg daily	24	HTN <i>n</i> = 11 (16%) GIP <i>n</i> = 4 (6%) CI <i>n</i> = 2 (3%)
[McGonigle <i>et al.</i> 2011] <i>n</i> = 40	Platinum-resistant OC/ PPC/FTC; ≤2 prior regimens	70 (primary) 30 (secondary)	Bevacizumab 10 mg/kg every 14 days + topotecan 4 mg/m ² on days 1, 8, and 15	25	HTN (20%) Neutropenia (18%) GI toxicity (18%)
[Kudoh <i>et al.</i> 2011] <i>n</i> = 30	Recurrent OC; ≥1 prior regimen	97	Bevacizumab 2 mg/kg + PLD 10 mg/m ² weekly (3 weeks on, 1 week off)	33	Hand-foot syndrome (3%) GIP (3%)
[O'Malley <i>et al.</i> 2011] <i>n</i> = 41	Recurrent EOC; ≥1 prior regimen	29 (primary) 28 (secondary)	Bevacizumab 10–15 mg/kg every 14 days + paclitaxel 60–70 mg/m ² weekly	63	GIP (5%)
[Tillmanns <i>et al.</i> 2012] <i>n</i> = 48	Recurrent EOC/ PPC; ≥1 prior regimen	93%	Bevacizumab 10 mg/kg every 14 days + (nab)-paclitaxel 100 mg/m ² weekly	50	GI perforation (4%)

AE, adverse event; CI, cerebral ischemia; EOC, epithelial ovarian cancer; FTC, fallopian tube cancer; GI, gastrointestinal; GIP, gastrointestinal perforation; GOG, Gynecologic Oncology Group; HTN, hypertension; (nab)-, nanoparticle albumin-bound; OC, ovarian cancer; PLD, pegylated liposomal doxorubicin; PPC, primary peritoneal cancer; RR, response rate.

cycles of carboplatin, paclitaxel, and bevacizumab. This study reported a response rate of 80% and, more importantly, no evidence of bowel perforations or wound complications. The second study enrolled 62 patients who were treated with six to eight cycles of carboplatin, paclitaxel, and bevacizumab followed by maintenance bevacizumab for 1 year. Treatment was associated with two pulmonary embolisms and two GIPs, with no grade 4 toxicities seen during maintenance bevacizumab treatment [Penson *et al.* 2010]. These two studies showed that the addition of bevacizumab to front-line chemotherapy is feasible and well tolerated with encouraging activity and, along with the collective data previously discussed, supported exploring the use of bevacizumab in randomized trials in front-line therapy.

The first trial, GOG-0218, was a double-blinded, placebo-controlled phase III study enrolling 1873

women with previously untreated stage III or IV EOC. Patients were randomly assigned to one of three groups after maximal surgical cytoreduction: chemotherapy alone, chemotherapy plus concurrent bevacizumab, or chemotherapy plus concurrent bevacizumab followed by maintenance bevacizumab. All patients received six 21-day cycles of carboplatin and paclitaxel, plus a study treatment for cycles 2–22. Median PFS, which was the primary endpoint of the trial, was 10.3 months in the control group, 11.2 months in the bevacizumab-initiation group, and 14.1 months in the bevacizumab-throughout group. The hazard of progression or death was significantly lower in the bevacizumab-throughout group compared with the control group ($p < 0.001$).

Extended treatment with bevacizumab was relatively well tolerated. Compared with chemotherapy alone, the only significant difference was the rate of hypertension requiring medical therapy

Table 2. Front-line phase III trials of bevacizumab in patients with epithelial ovarian and primary peritoneal cancer.

Trial	Treatment arms	PFS (months)	OS (months)	GI events grade ≥ 2	HTN grade ≥ 2	CNS events grade ≥ 2
				No of patients (%)	No of patients (%)	No of patients (%)
GOG-0218 [Burger <i>et al.</i> 2011] $n = 1873$	CT	10.3	39.3	7 (1.2)	43 (7.2)	0
	CT+Bev	11.2	38.7	17 (2.8)	100 (16.5)	0
	CT+Bev $\rightarrow$ Bev	14.1	39.7	16 (2.6)	139 (22.9)	2 (0.3)
ICON7 [Perren <i>et al.</i> 2011] $n = 1528$	CT	22.4	28.8	3 (<1)	2 (<1)	0
	CT+Bev $\rightarrow$ Bev	24.1	36.6	10 (1)	46 (6)	2 (<1)

Bev, bevacizumab; CNS, central nervous system; CT, carboplatin and paclitaxel; GI, gastrointestinal; GOG, Gynecologic Oncology Group; HTN, hypertension; ICON7, International Collaborative Ovarian Neoplasm 7; OS, overall survival; PFS progression-free survival.

(23% *versus* 7%). Rates of GIP, fistula formation, necrosis, or leak $>$ grade 2 were twice as high with extended bevacizumab treatment (16 cases *versus* 7 cases; 2.6% *versus* 1.2%). There were no apparent differences in other adverse events including grade 4 neutropenia, febrile neutropenia, venous or arterial thrombosis, or clinically significant bleeding [Burger *et al.* 2011].

The Gynecologic Cancer Intergroup (GCIG) International Collaboration on Ovarian Neoplasms (ICON7) trial was an open-label phase III randomized trial. In this study 1528 women with high risk, early stage disease or advanced EOC were randomized to chemotherapy alone (carboplatin and paclitaxel) or chemotherapy with concurrent bevacizumab, followed by 12 cycles of maintenance bevacizumab or disease progression, whichever occurred earlier. The dose of bevacizumab was lower than in the GOG-0218 trial, with 7.5 mg/kg every 21 days. PFS at 36 months was 20.3 months for standard chemotherapy compared with 21.8 months for those who also received bevacizumab ($p = 0.04$). In updated analyses, PFS at 42 months was still higher with bevacizumab compared with standard chemotherapy (24.1 months *versus* 22.4 months; $p = 0.04$). This difference was greater in patients at a high risk of progression, defined as patients with stage IV disease or stage III disease and > 1.0 cm residual disease after debulking surgery (18.1 months *versus* 14.5 months; $p = 0.002$); this translated to an increased median OS (36.6 months *versus* 28.8 months; $p = 0.002$). Adverse events were reported as consistent with previous bevacizumab trials [Perren *et al.* 2011].

The results of these two studies (Table 2) led to the approval by the European Commission of

bevacizumab in combination with standard chemotherapy (carboplatin and paclitaxel) as a front-line treatment for women with advanced ovarian cancer. However, it is important to note that no improvement in OS has been reported in these two studies. In addition, two independent cost-effective analyses report that with no improvement in OS the use of bevacizumab as part of front-line therapy in ovarian cancer is not cost effective [Cohn *et al.* 2011; Lesnock *et al.* 2011].

Bevacizumab plus chemotherapy in recurrent platinum-sensitive ovarian cancer

In addition to GOG-0218 and ICON7 a third phase III randomized trial explored the use of bevacizumab in combination with platinum-based chemotherapy (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease; OCEANS) [Aghajanian *et al.* 2011]. This study evaluated 484 women with platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer, who were randomly assigned to six cycles of carboplatin plus gemcitabine, with or without bevacizumab. Preliminary results showed that PFS was significantly longer for women given bevacizumab [12.4 months compared with 8.4 months in the placebo-treated group, hazard ratio (HR) 0.484, 95% CI 0.388–0.605, $p < 0.0001$]. Objective response rate increased by 21.1% ($p < 0.0001$), from 57.4% in the placebo group to 78.5% in the bevacizumab-treated group; duration of response increased from a median duration of response of 7.4 months to 10.4 months, respectively [HR 0.534, 95% CI 0.408–0.698, $p < 0.0001$]. OS data are still premature, with median overall survival of 29.9 months in the placebo group and 35.5 months in the

treatment group. Discontinuation of treatment for adverse events was more common in the bevacizumab group (23% *versus* 5%). The bevacizumab arm had higher rates of hypertension grade 3 or higher (17% *versus* < 1%), proteinuria > grade 3 (9% *versus* 1%), and non central nervous system bleeding (6% *versus* 1%). There were no cases of GIP in either arm during therapy [Aghajanian *et al.* 2011]. The result of this study led to the approval by the European Commission of bevacizumab in combination with standard chemotherapy (gemcitabine and carboplatin) to treat women with first recurrence of platinum-sensitive ovarian cancer. The results of GOG-0213, an ongoing randomized trial comparing carboplatin and paclitaxel with or without bevacizumab in patients with platinum-sensitive disease, are eagerly expected [National Cancer Institute, 2012].

Conclusion

The VEGF-targeted recombinant humanized monoclonal antibody, bevacizumab, has demonstrated efficacy in advanced EOC. Amongst new biologic drugs, bevacizumab is the first agent to show clear therapeutic activity in recurrent disease and potential as part of first-line therapy along with an acceptable toxicity profile. However, it is unclear whether the improvement in PFS is clinically meaningful and will translate into better quality of life or prolonged survival. Questions also remain regarding the optimal dose and treatment duration. Three (GOG-0218, OCEANS, and AURELIA) of the phase III randomized trials evaluating the role of bevacizumab in ovarian cancer used a dose of 15 mg/kg every 3 weeks. ICON7 used a dose of 7.5 mg/kg. Together, these independent phase III trials show a benefit in the dose range of 7.5 mg/kg to 15 mg/kg. In the two upfront trials (GOG-018 and ICON7), bevacizumab was administered during a fixed period of time while in the two studies in the recurrent setting (OCEANS and AURELIA) it was administered until progression. The latter two studies showed a larger hazard ratio for PFS favoring the use of bevacizumab suggesting that administration until progression may represent the optimal schedule. The existing data suggest that at this time the main role of bevacizumab in the treatment of ovarian cancer may be in the setting of recurrent disease in combination with chemotherapy. However, efforts to identify biomarkers with potential prognostic and predictive value in EOC patients treated with bevacizumab are critical in

selecting patients for therapy and are the subject of ongoing research.

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Conflict of interest statement

Dr Garcia has participated in clinical trials evaluating bevacizumab in ovarian cancer. Dr Singh declares no conflicts of interest in preparing this article.

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