Antiangiogenic therapies in ovarian cancer

Standard palliative options in the context of platinum-resistant metastatic disease, such as ovarian cancer, include a variety of single-agent chemotherapy drugs all of which afford objective response rates of approximately 10–20% and median overall survival of only approximately 4–8 months. More recently, molecular-targeted approaches have been explored in this disease, with bevacizumab being the most extensively studied and promising candidate. Bevacizumab and other VEGF-targeted agents have demonstrated activity in ovarian cancer, both as a single agent and in combination. Toxicities observed with this class of agent have included hypertension, proteinuria, thromboembolic events, impaired wound healing, neurologic complications and gastrointestinal perforation. However, overall this class of drugs is well tolerated and represents a novel therapeutic choice for clinicians.

KEYWORDS: bevacizumab ■ ovarian cancer ■ targeted agents ■ VEGF

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Ovarian cancer is the fifth leading cause of cancer deaths among women and the leading cause of death from cancer of the gynecologic organs [1]. Often termed 'the silent killer', it usually produces no symptoms until it is in an advanced stage [2]. Few women have ovarian cancer detected early and almost 75% of women diagnosed with ovarian cancer present at an advanced stage. Although the 5-year survival rate is approximately 95% when ovarian cancer is detected in its earliest stages, three-quarters of cases are diagnosed at an advanced stage where 5-year survival is 15–20% at best.

Ovarian cancer is sensitive to initial therapy with responses being seen in 70–80% of women with combination chemotherapy. However, this is commonly followed by incurable recurrence within 18–24 months [3]. Platinum-resistant ovarian cancer is a highly treatment-resistant and ultimately fatal phenotype. Standard palliative options in this context include a variety of single-agent chemotherapy drugs, all of which afford objective response rates of approximately 10–20% and median overall survival rates of approximately 4–8 months [4,5]. More recently, molecularly targeted approaches have been explored in this disease, with bevacizumab being the most extensively studied and promising candidate. This article will examine some of the recent antiangiogenic agents used in ovarian cancer, with a particular focus on bevacizumab.

Targeting VEGF in ovarian cancer

There is a strong rationale for using antiangiogenic drugs in ovarian cancer (Figure 1). Angiogenesis is the process of new blood vessel formation and is crucial for the growth of tumors in order to diffuse nutrients and oxygen from nearby capillaries. In the late 1980s and early 1990s, Folkman demonstrated an angiogenic 'switch' that sometimes occurs in tumorgenesis that results in an upregulation of proangiogenic factors such as VEGF and FGF-2 and their receptors [6]. As the tumor increases in size it becomes more hypoxic as it outgrows the blood supply. In turn, this lack of oxygen leads to the upregulation of several angiogenic signals. The intratumoral vasculature tends to be abnormal both in structure and in function; there is poor blood flow with abnormal, tortuous, leaky and dilated blood vessels. Endothelial cells in this setting are more dependent on VEGF for survival then elsewhere in the body [7]. It has also been hypothesized that using a VEGF inhibitor can improve this vasculature within the tumor, resulting in an improved delivery of oxygen and chemotherapy to the tumor [8].

Many preclinical trials have also demonstrated a role for angiogenesis in ovarian cancer. Shen *et al.* noted a worsening prognosis with increasing VEGF levels in patients with advanced ovarian cancers and this had also been observed in patients with earlier-stage disease [9,10]. VEGF expression was very highly correlated with disease stage, histologic grade and patient outcome. It was also noted that survival was significantly worse in patients with high VEGF levels compared with negative/low VEGF levels. In a multivariate model, VEGF expression, along with disease stage, was

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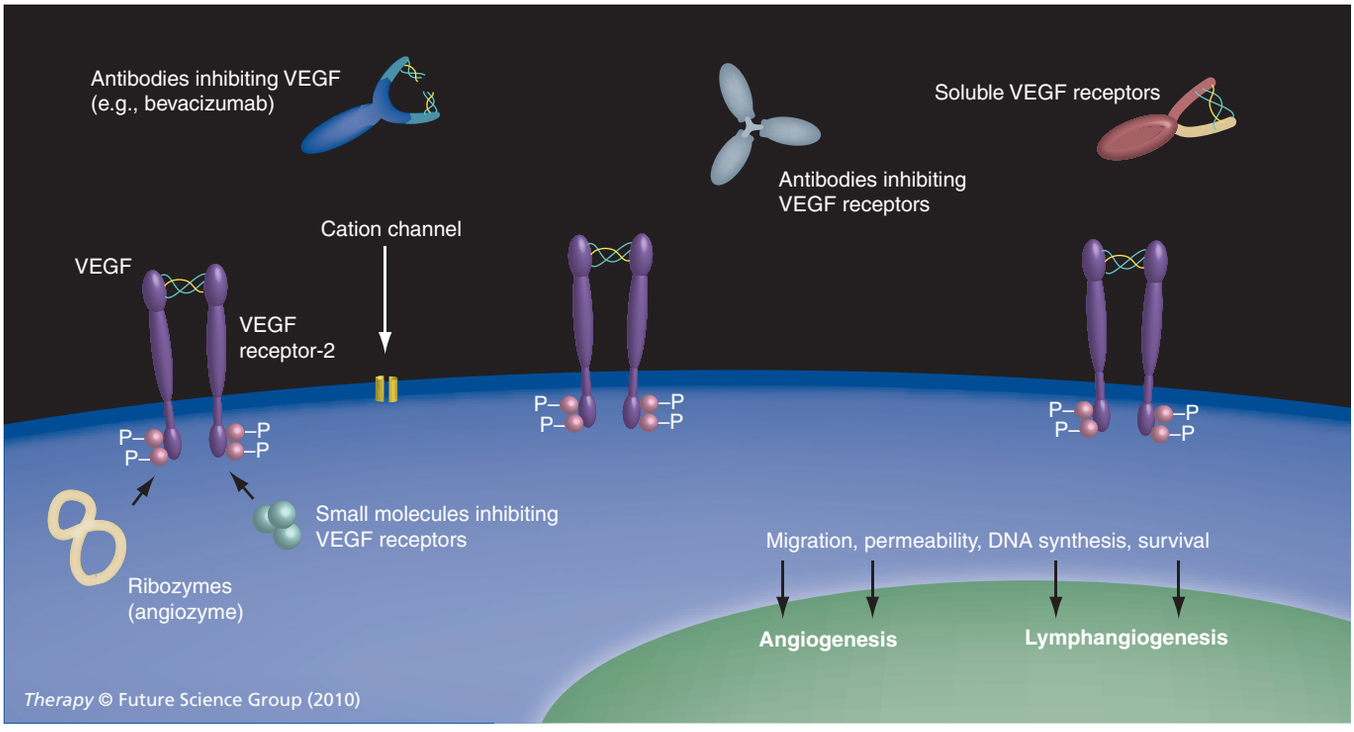

Figure 1. Agents targeting the VEGF pathway.

a significant independent predictor of survival. Some studies have also suggested a link between angiogenesis by greater microvessel density count and poorer overall prognosis, although this remains controversial [11]. It has also been recently understood that VEGF receptors can be expressed and functional on the cancer cells themselves, suggesting that anti-VEGF treatments may also have more direct antitumor effects [12].

Characterization of these angiogenesis pathways has improved in the past 20 years, but it has only been more recently that we have been able to effectively target them with any observed clinical benefit. Agents under investigation, which act by targeting angiogenesis, include monoclonal antibodies to the VEGF ligand, small TKIs that seek out the VEGF receptor (VEGFR) and soluble decoy VEGFRs, among others. The most characterized of all of these to date is bevacizumab, a recombinant humanized monoclonal antibody to the VEGF ligand.

Bevacizumab in ovarian cancer

Bevacizumab is a humanized antibody that binds to all isoforms of VEGF-A, but does not bind to other VEGFR family members. It is derived from murine monoclonal antibody VEGF 4.6.1, with approximately 93% human and 7% murine sequences. The estimated half-life of bevacizumab is approximately 20 days with a range from 11 to 50 days. It has been demonstrated to have a very high ability to neutralize VEGF, with a dissociation constant of 1.1 nmol/l. The mechanism by which bevacizumab is able to inhibit angiogenesis is not completely understood. However, it is clear that by blocking the binding of VEGF-A to the VEGFR-2 there will be a decrease in the activation of downstream events, such as endothelial cell migration, proliferation and survival.

Bevacizumab was the first antiangiogenic agent to be licensed in the treatment of cancer and has made an improvement in overall survival, when given in combination with cytotoxic agents, in a broad range of epithelial malignancies [13–15]. It has already been approved for use in the treatment of colorectal cancer and non-small-cell lung cancer. In 2005, Monk *et al.* reported the first case of a patient with ovarian cancer treated with bevacizumab [16]. Although response rates to single-agent bevacizumab in other tumor types have been quite disappointing, it has shown single-agent activity at a dose of 15 mg/kg every 3 weeks in two Phase II trials in patients with recurrent ovarian cancer [17,18]. Despite the fact that most of the patients had platinum-resistant disease, response rates of 16 and 21% were recorded with median progression-free survival of 4.4 and 4.7 months, respectively. These results are similar to results seen with standard single-agent cytotoxic regimens.

More recently, several Phase II studies have also demonstrated activity with bevacizumab in recurrent ovarian cancer. Gynecologic Oncology Group (GOG)-170-D [19] was a Phase II study of bevacizumab in recurrent or persistent, ovarian or primary peritoneal cancer at a dose of 15 mg/kg delivered every 3 weeks. The study population was not very heavily pretreated with two or fewer previous cytotoxic regimens. A 17.7% response rate was observed with 38.7% of patients without progression of their disease at 6 months. Another avenue that has been explored with this agent is the addition of metronomic chemotherapy. The hypothesis is that low-dose continuous chemotherapy may be more effective at preventing the regrowth of blood vessels when patients are on an antiangiogenic, then higher doses of chemotherapy with a break given in between doses. In a Phase II clinical trial of bevacizumab at 10 mg/kg given every 2 weeks and metronomic oral cyclophosphamide at 50 mg daily, in 70 patients with platinum-resistant/partially platinum-sensitive ovarian cancer, the median time to progression was 7.2 months and median survival time was 16.9 months [20].

After these results with single-agent bevacizumab, studies began with combination regimens, including one or more cytotoxic agents (Table 1). One of these studies combined bevacizumab with the current standard first-line chemotherapy of carboplatin and paclitaxel [21] in the first-line treatment of ovarian cancer. It demonstrated this combination to be safe and tolerable and this regimen is currently being compared against chemotherapy alone in two large randomized Phase III trials (International Collaborative Oncology Neoplasm [ICON]7 and GOG-218). These two prospective studies have been designed in a complementary manner. ICON7 is a two-armed trial comparing carboplatin and paclitaxel, for a total of six cycles, against carboplatin and paclitaxel and bevacizumab for six cycles followed by 12 cycles of maintenance bevacizumab. The bevacizumab is being administered at a dose of 7.5 mg/kg, every 3 weeks [101]. GOG-218 is a three-arm, placebo-controlled trial where all patients receive carboplatin and paclitaxel for six cycles. In the first experimental arm, patients also receive concurrent and maintenance bevacizumab at a dose of 15 mg/kg, administered every 3 weeks for up to 16 doses, whereas the second experimental arm receives only concurrent bevacizumab followed by placebo maintenance. Initial results from GOG-218 have very recently been released and demonstrate an improved progression-free survival on the maintenance arm of the study [102].

Another area being investigated with this class of drugs is the possibility of maintenance therapy in ovarian cancer. The rationale being that this agent, which is considered a biologic, is thought to cause tumor dormancy with protracted exposure. Furthermore, it is becoming more acceptable to treat patients continuously until progression. A recent Phase II study of carboplatin, paclitaxel and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors was performed by Penson *et al.* [22]. They treated patients in the first-line setting after surgery with intravenous carboplatin (area under the curve of 5), paclitaxel (175 mg/m^2 intravenously) and bevacizumab (15 mg/kg intravenously) for between six and eight cycles on day 1 every 21 days. Bevacizumab was then continued as a single-agent maintenance regimen for 1 year. The results revealed radiographic responses in 21 out of 28 (75%) women with measurable disease, with cancer antigen 125 responses in 76% of patients. The

Table 1. Bevacizumab in combination studies.

Study (year)	Prior lines of treatment	Participants (n)	Response rate (%)	Ref.
Garcia *et al.* (2008)	1–3	70	24	[39]
Wright *et al.* (2006)	2–15	23	35	[40]
Chura *et al.* (2007)	5–15	15	43	[41]
Nimeri *et al.* (2008)	1–3	13	15	[42]
Simpkins *et al.* (2007)	2–12	25	28	[43]
McGonigle *et al.* (2008)	0–2	18	22	[44]
Azad *et al.* (2008)	NR	13	46	[45]
Micha *et al.* (2007)	First-line treatment	20	80	[46]
Campos/Penson *et al.* (2008)	First-line treatment	58	75	[47]

NR: Not reported.

progression-free survival rate at 36 months was 58%, suggesting that this type of maintenance therapy merits further investigation.

Many of the questions that still remain regarding the effectiveness of bevacizumab in this population, how to choose the patients most suited for this type of drug and how to control any side effects will hopefully be better understood after the complete results of the ongoing trials become known.

Other VEGF inhibitors in ovarian cancer

There are multiple agents targeting different areas in the angiogenesis signaling pathway that are in different stages of development (TABLE 2). Some responses have been observed with the small molecule TKIs that target VEGFR. Many have been investigated in the Phase II setting in patients with relapsed ovarian cancer with promising response rates. One area that investigators have been extensively working on is the small-molecule TKIs that target the VEGFR. AZD2171 (cediranib) is a novel oral TKI of VEGFR-2 and -1, and c-kit. The initial study involving this compound was quite promising. Patients with recurrent ovarian cancer were treated with single-agent AZD2171 and five patients had confirmed partial responses with an overall response rate of 18.5%. There were also three patients with prolonged stable disease lasting 30 weeks, more than 27 weeks and 24 weeks each [23]. The most commonly observed side effects have included mainly fatigue and hypertension. Another study conducted by Hirte *et al.* that examined AZD2171 in both platinum-sensitive and platinum-resistant ovarian cancer patients reported response rates of 40.5 and 29%, respectively [24]. ICON6 is a study currently underway examining platinum-sensitive relapsed ovarian cancer. It is a three-arm, randomized trial. Cediranib is administered concurrently with chemotherapy in both experimental arms, but is continued in a maintenance phase of up to 18 months duration in one of these.

Pazopanib is a TKI of VEGFR-1, -2 and -3, PDGF receptor (PDGFR)-α and -β, and c-Kit. Pazoanib has been studied in women with advanced epithelial ovarian cancer [25]. A total of 36 patients were enrolled onto the study and the median progression-free survival was 84 days. The overall response rate was 18% in subjects with measurable disease at baseline and was 21% in subjects without measurable disease at baseline.

Sunitinib is an inhibitor of VEGFR-1, -2 and -3, and PDGFRs. Sunitinib was investigated in patients with ovarian cancer by Biagi *et al.* [26]. It was administered at 50 mg every day on a 4-weeks-on, 2-weeks-off schedule. Interestingly, this study reported the development of pleural effusions during the 2-week rest period. Of the 17 patients that were studied, 12% had a partial response and 59% had disease stabilization. There is also an ongoing Phase II study of sunitinib, at a dose of 37.5 mg per day, in resistant ovarian cancer patients by the Harvard Cancer Center Gynecological Group.

Aflibercept, or VEGF-Trap, which is a soluble decoy receptor, is composed of a fusion protein comprising the VEGF-binding domains of both VEGFR-1 and -2 linked to the human antibody IgG1. It binds VEGF-A and is then able to neutralize all VEGF-A isoforms as well as PGF. Aflibercept has been studied, at two different dose levels, in a population of patients with relapsed platinum-resistant ovarian cancer. This randomized Phase II study demonstrated five partial responses in 45 patients (11%) with acceptable toxicities [27].

Table 2. Phase II studies of single-agent VEGF inhibitors being used in ovarian cancer.

Drug	Study (year)	Prior lines of treatment	Participants (n)	Response rate† (%)	Ref.
Bevacizumab	Burger *et al.* (2005)	1–2	62	21	[48]
Bevacizumab	Cannistra *et al.* (2006)	2–3	44	15.9	[49]
Bevacizumab	Monk *et al.* (2006)	2–10	32	16	[50]
Pazopanib	Friedlander *et al.* (2007)	1	17	47	[51]
Cediranib	Hirte *et al.* (2008)	1	60	41	[52]
Sunitinib	Biagi *et al.* (2008)	1–2	17	12	[53]
Cediranib	Matulonis *et al.* (2008)	1–2	29	18.5	[54]
Sorafenib	Matei *et al.* (2008)	1–2	59	3	[55]

†*Response rate = complete response + partial response.*

When aflibercept was administered to patients with advanced ovarian cancer and symptomatic ascites, eight out of ten patients evaluated achieved a repeat paracentesis response, defined as a minimum of doubling of time to the first paracentesis compared with baseline average. The drug was well tolerated with adverse events that included bowel obstruction, nausea, vomiting, anorexia, edema and one case of bowel perforation [28].

The idea of targeting more than one area in the VEGF signaling pathway has also been explored based on the thought that blocking more than one different point in the angiogenesis pathway may result in better efficacy. Azad *et al.* recently performed a study combining sorafenib and bevacizumab [29]. Six out of 13 ovarian cancer patients enrolled in the study obtained durable partial disease responses, ranging between 4 and 22 months. However, the toxicity appears higher than that with single-agent anti-VEGF therapy. A total of 79% of patients developed grade 1 or 2 hand–foot syndrome and two-thirds of the patients developed hypertension [29]. Enteral fistulae were also observed in two of the 13 ovarian cancer patients studied.

Toxicities with VEGF inhibitors

Biologic therapeutic agents, although often well tolerated, have been associated with rare but serious toxicities. The most commonly associated toxicities with inhibitors of VEGF are hypertension (requiring medical management in approximately 10% of patients), proteinuria, hemorrhage, arterial and venous thromboembolic events, impaired wound healing, neurologic complications and gastrointestinal perforation. Although the pathophysiology of these adverse events is not completely understood, recent data have started to unravel the underlying mechanism that might account for these rare, albeit significant, consequences. It has been demonstrated in animals that within a few days of starting treatment with VEGF inhibitors a rapid regression of capillaries occurs in several different tissues, such as pancreatic islets, thyroid, adrenal cortex, choroid plexus and small intestinal villi [30]. There is also a loss of fenestration of renal glomerular capillaries, which may be the cause of hypertension and proteinuria in patients on these medications [31]. It has also been noted that VEGF can promote endothelial nitric oxide production. By inhibiting VEGF, this stimulus is turned off, which in turn may lead to vasoconstriction and hypertension [32]. Other rare but serious adverse events associated with this class of drugs include reversible posterior leukoencephalopathy syndrome and tracheoesophageal fistulae as well as clinical hypothyroidism, which may be the result of inhibition of iodine uptake in the thyroid [33].

An important and potentially serious adverse event with bevacizumab treatment is bowel perforation. It came to light when it was observed at a higher frequency in colorectal cancer patients receiving concurrent chemotherapy (1.5% of cases compared with 0% of patients receiving chemotherapy alone) [34]. This study included 402 patients with colorectal cancer, of whom a total of six developed bowel perforation. Of these, five patients recovered and three were able to resume treatment but one patient died as a direct result of the perforation. The authors identified a few risk factors that may have contributed to the risk of bowel perforation, including colon surgery within 2 months, a history of peptic ulcer disease and a partial or complete response to therapy.

Ovarian cancer patients most likely have a higher risk of adverse events, such as bowel perforation, with VEGF inhibitors, by the innate pathophysiology of their disease. They often develop problems with bowel motility and subacute bowel obstructions that put them at risk. Another hypothesis that has been postulated is that a bevacizumab response in ovarian cancer involving the bowel wall itself may lead to a weakened bowel wall, putting the patient at risk of perforation. Bevacizumab may also inhibit healing of the bowel wall. A study performed in 2007 in patients with heavily pretreated ovarian cancer was stopped early owing to a perforation rate of 11.4% (five of 44 patients) [35]. There was a trend towards higher perforation rates in patients with documented bowel wall involvement or previous bowel obstruction. It was also noted that the perforations occurred in patients who were very heavily pretreated, having received three or more chemotherapy regimens. An Investigational New Drug Action letter was released shortly after that by the National Cancer Institute alerting investigators to the risk of gastrointestinal perforations [103]. Two other studies of bevacizumab in ovarian cancer have also found the development of bowel perforations and enteral fistulae [36,37]. Hopefully, the results from the two Phase III ovarian trials using bevacizumab, GOG-218 and ICON7, may help to clarify risk factors for these adverse events.

A case series performed by Bagdwell *et al.* examined the overall incidence of bevacizumab-associated gastrointestinal perforation in patients of different tumor types [38]. They found an overall incidence of 1.7%, but the incidence varied among malignancies, with pancreatic, ovarian and gastroesophageal carcinoma associated with the highest percentage of bowel perforations. This is in agreement with the literature describing bowel perforation numbers in these individual tumor sites. The presenting signs and symptoms of the patients with bowel perforation were fairly typical of patients with abdominal inflammation. A leukocytosis was frequently observed; however, few patients displayed tachycardia, hypotension or sepsis, which may be the result of heightened awareness of possible side effects and the prompt recognition of complications in these high-risk patients. Three patients in the case study were actually completely asymptomatic. The median time to perforation after the initiation of bevacizumab treatment was 71 days. The overall management varied distinctly between all of the patients, which emphasizes the difficulty of decision making in the setting of advanced cancer. However, the success of the conservative approach to treatment was demonstrated by the fact that four of the patients in this study cohort, who were treated conservatively, were discharged to a hospice with resolution of their acute symptoms. While these patients ultimately died of progressive disease, they were spared the morbidity and potential mortality of a surgical procedure.

Conclusion

Ovarian cancer is the second most common gynecologic malignancy and, unfortunately, it typically has a poor overall survival after diagnosis. Molecularly targeted drugs have offered a novel treatment option for patients left with few alternatives. Over the past 20 years, investigators have gained a better understanding of the redundant pathways that exist in cell signaling, resulting in tumor growth and proliferation. This has enabled researchers to target pathways thought to be involved in cancer development and, more recently, has translated to better outcomes for the cancer patient. These novel drugs have substantial cost and potential serious risks; therefore, it is essential that we develop better methods to determine which patients are likely to derive benefit from these drugs and how best to deliver them (alone or in combination).

Antiangiogenics may potentially improve therapeutic options for women with ovarian cancer, but more research needs to be carried out in order to understand the best patients to receive these drugs, when best to administer them in the overall treatment plan and how best to control side effects. Combinations of antivascular agents with chemotherapy are presently being tested in clinical studies in the first-line setting and it is hoped that this approach may significantly improve patient outcome.

Future perspective

There have been key changes in how we manage ovarian cancer in the past decade. Survival is improving and our treatment arsenal is growing. With the emergence of more molecularly targeted agents, including those targeting VEGF, clinicians are more able to offer patients a variety of treatment options. Over the coming years, as we learn more about the mechanism of action of the targeted agents, we can anticipate a more tailored treatment protocol based on a patient's specific tumor characteristics, hopefully resulting in improved response rates and a decrease in toxicity.

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Executive summary

- Ovarian cancer is the fifth leading cause of cancer deaths among women.
- Standard palliative options for platinum-resistant disease are limited.
- There is strong rationale for using antiangiogenic drugs in ovarian cancer.
- Bevacizumab is a humanized antibody that binds to all isoforms of VEGF-A.
- Bevacizumab and other VEGF-targeted agents have demonstrated activity in ovarian cancer, both as single agents and in combination.
- Side effects seen with this class of medications include hypertension, proteinuria, hemorrhage, thromboembolic events, impaired wound healing, neurologic complications and gastrointestinal perforation.

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