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Bevacizumab in the treatment of ovarian cancer

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Abstract: Despite advances in surgical cytoreduction and cytotoxic chemotherapy, ovarian cancer continues to be the leading cause of death in women with gynecologic malignancy. Our understanding of the treatment of ovarian cancer was revolutionized with the discovery of platinum- and taxane-based adjuvant chemotherapy regimens. Since that time however, overall survival has been stable. Given the above, an emphasis has been placed on exploring alternative therapeutics. Recent research efforts have improved our understanding of the molecular biology of ovarian cancer and novel targeted treatment strategies have emerged. The most studied of these agents has been the monoclonal anti-vascular endothelial growth factor antibody bevacizumab. The purpose of this review is to discuss management issues related to the treatment of ovarian cancer, with a focus on the utilization of bevacizumab, summarizing applicable clinical trials, its potential benefits, and reported adverse events.

Keywords: bevacizumab, ovarian cancer, molecular targeted therapy, VEGF, angiogenesis

Introduction

Epithelial ovarian cancer (EOC) accounts for 25% of all malignancies affecting the female genital tract, and is the most lethal gynecologic malignancy. In the United States alone, a projected 21,880 new cases will be diagnosed, with 13,850 deaths.¹ Advanced stage epithelial ovarian cancer is traditionally managed with surgery, followed by chemotherapy consisting of platinum and taxane.² Patients with advanced disease who undergo successful cytoreductive surgery have a median survival of just over 4 years after completion of adjuvant chemotherapy.³ Unfortunately, the majority of these patients develop recurrent cancer, with selection of chemotherapy resistant clones.⁴

More recently, targeted therapies have been explored in the treatment of ovarian cancer and various potential therapeutic pathways, and biologic therapies have emerged. Specifically, anti-angiogenic agents have been the most studied and effective in the treatment of ovarian cancer. Angiogenesis is essential for tumor invasion and metastasis, and is required for tumor growth beyond 1–2 mm.⁵ This process requires the recruitment of vasculature and circulating endothelial cells, and pro-angiogenic mediators including vascular endothelial growth factor (VEGF). Ovarian cancer patients with elevated VEGF levels have been shown to have poorer overall prognosis, with VEGF levels being independent indicators of survival.

To date, bevacizumab, a recombinant human monoclonal antibody to the VEGF ligand, has been the most studied anti-angiogenic agent. The immediate mechanism of action of bevacizumab is to bind and inactivate VEGF, thereby inhibiting endothelial, and possibly tumor, cell activation and proliferation.⁶ In addition to denying tumors of

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nutrients, VEGF inhibition has been shown to induce vascular normalization, and to restore normal structure, function, and flow to the disorganized, leaky vessels characteristic of malignant tumors. These changes result in improved delivery of oxygen, nutrients, and cytotoxic chemotherapy to the tumor.⁷

Bevacizumab was first studied in patients with clear cell renal cell cancer, because of its unique VEGF-driven biology, and 4 other common solid tumors with high therapeutic need; colon, prostate, lung, and breast cancers.⁸ Phase III bevacizumab trials were then conducted in metastatic colorectal cancer (mCRC),⁹ metastatic nonsmall cell lung cancer (mNSCLC),¹⁰ and metastatic breast cancer (mBC),¹¹ all of which met their primary endpoints, thus supporting Food and Drug Administration (FDA) approval of bevacizumab for these indications.¹² One of the next opportunities for approval will be in epithelial ovarian and primary peritoneal carcinomas.

Current treatment regimens in ovarian cancer

Currently, patients presenting with advanced stage ovarian cancer are managed with surgical resection followed by adjuvant platinum- and taxane-based chemotherapy. Our understanding of the therapeutic benefits of this regimen originated following the results of Gynecologic Oncology Group (GOG) protocol 111.¹³ This randomized trial illustrated an improvement in both progression free survival (PFS) and overall survival (OS) in patients treated with cisplatin and paclitaxel, in comparison to those treated using cisplatin and cyclophosphamide (PFS 18 vs 13 months, OS 38 vs 24 months, respectively). This study offered justification for a major change in the treatment of ovarian cancer.

Following completion of GOG 111, the GOG opened protocol 158.³ This was designed as a noninferiority trial comparing carboplatin and paclitaxel with cisplatin and paclitaxel. In previous nonrandomized trials the combination of carboplatin and paclitaxel was shown to be a less toxic and highly active combination regimen in the treatment of ovarian cancer. Ozols et al enrolled 792 eligible patients, with results showing decreased gastrointestinal, renal, and metabolic toxicities as well as decreased grade 4 leukopenia in the carboplatin-containing arm.³ Median PFS and OS did not differ significantly between study groups. The authors thus concluded that the combination of carboplatin and paclitaxel was less toxic, easier to administer, and not inferior to the previous standard of cisplatin and paclitaxel. Furthermore,

in patients who were optimally cytoreduced (residual disease at completion of surgery <1.0 cm) the median survival was nearly 5 years in the carboplatin-containing arm.

In addition to intravenous (IV) therapy, the GOG also investigated intraperitoneal (IP) treatment options. GOG protocol 172 was designed to compare IV paclitaxel (135 mg/m²) over 24 hours with IV cisplatin (75 mg/m²) on day 2, vs IV paclitaxel (135 mg/m²) over 24 hours, followed by IP cisplatin (100 mg/m²) on day 2 and IP paclitaxel (60 mg/m²) on day 8. A total of 6 courses would be administered every 3 weeks.¹⁴ All patients had optimally resected disease with residual tumor limited to less than or equal to 1 cm in size. The median survival for the IV and IP arms were 49.5 and 66.9 months respectively. The relative risk (RR) of death was 0.71 in the IP group ($P = 0.0076$). The authors however noted that tolerability for IP chemotherapy was a concern as grade 3 and 4 hematologic, metabolic, and gastrointestinal toxicities were significantly more common in the IP arm. In fact, only 42% of patients allocated to the IP arm completed 6 cycles of chemotherapy.

Unfortunately, despite the above advances in up-front adjuvant chemotherapy, disease recurrence continues to be problematic. Patients with recurrent disease are uncommonly cured, and thus comprise a population of patients for whom clinical trials and investigations into alternative therapies may be beneficial. Patients with disease recurrence 6 months after first-line therapy are termed “platinum sensitive”, and have response rates in the range of 30%–40% to second-line agents.¹⁵ These patients typically receive a platinum-based regimen, often in combination with paclitaxel, gemcitabine, or pegylated liposomal doxorubicin.¹⁶ On the other hand, patients with disease recurrence within 6 months of up-front therapy, termed platinum resistant, and those with disease persistence/progression while on first-line platinum therapy, termed platinum refractory, are typically treated with nonplatinum-based regimens.¹⁵ Agents that can be considered in this setting include liposomal doxorubicin, topotecan, gemcitabine, and oral etoposide.¹⁷

Bevacizumab

As described above, despite multimodal chemotherapy after surgical cytoreduction, the minority of women with ovarian cancer are actually cured. Thus, exploration of alternative therapeutics has been a priority. Specifically, the study of angiogenesis in ovarian cancer, and the role of potential modulators of angiogenesis in its treatment have emerged as a promising strategy.¹⁸ Angiogenesis is the process of new

blood vessel development and is essential for tumor growth beyond 100–200 μm . This process is mediated through the VEGF family of growth factors and receptors. The immediate action of bevacizumab, the first FDA-approved monoclonal anti-angiogenic antibody, is to bind and inactivate VEGF, inhibiting endothelial cell proliferation and activation. The utility of VEGF 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.¹⁹ Numerous retrospective clinical studies have shown that VEGF polymorphisms, and increased intra-tumoral VEGF gene expression correlates with poor prognosis.²⁰ Ovarian cancer tumor vasculature also tends to be structurally and functionally abnormal, leaky and tortuous, with immature endothelial cells. These cells have increased dependence on VEGF for survival in comparison to mature vasculature.^{21,22}

Two single-agent phase 2 bevacizumab trials have explored its utility in the treatment of recurrent, predominantly platinum-resistant, ovarian cancer. The first, GOG 170D, the largest single agent study, explored the use of bevacizumab at a dose of 15 mg/kg in patients with persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer after 1–2 prior cytotoxic regimens.²³ The study consisted of 62 eligible and assessable patients. Of these, 66.1% had received 2 prior cytotoxic chemotherapy regimens, and 41.9% were considered platinum resistant. Thirteen patients (21.0%) experienced clinical responses (2 complete, 11 partial; median response duration, 10 months), and 25 (40.3%) survived progression free for at least 6 months. Median PFS and OS were 4.7 and 17 months, respectively. The second was an industry-sponsored trial evaluating the efficacy and safety of bevacizumab in 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 liposomal doxorubicin.²⁴ Enrolled patients received single-agent bevacizumab 15 mg/kg every 3 weeks, and nearly 84% were platinum resistant. Partial responses were observed in 15.9% with median PFS of 4.4 months (95% CI: 3.1–5.5 months), and a median survival duration of 10.7 months at study termination. This was followed by 2 trials combining cytotoxic chemotherapy with bevacizumab in the treatment of recurrent disease. The trials showed response rates of 24% each and 6-month progression-free rates of 50% and 56%, respectively.^{25,26}

The above phase 2 trials were then followed by 4 randomized phase 3 trials, looking at bevacizumab as a first-line

agent and in disease recurrence. Three of these trials have completed accrual, namely GOG 218, International collaborative ovarian neoplasm (ICON) 7, and OCEANS. GOG 218 is a 3-arm placebo controlled study, with all patients receiving carboplatin and paclitaxel. In the first experimental arm, patients were treated with concurrent bevacizumab followed by placebo maintenance, while in the third experimental arm, patients received concurrent and maintenance bevacizumab (15 mg/kg every 3 weeks) for up to 16 doses.²⁷ A total of 1873 patients were enrolled. Of these patients, 34% were optimally cytoreduced, with 40% suboptimally debulked, and 26% being stage 4. Preliminary data, as presented at the 2010 meeting for the American Society of Clinical Oncology (ASCO), showed a significant improvement in PFS in patients treated with concurrent and maintenance bevacizumab, 14.1 months vs 10.3 months in the placebo arm. Relative to arm 1 of the trial, the hazard ratio for first progression in the maintenance arm of the trial was 0.717 (95% CI: 0.625–0.824, $P < 0.0001$). The OS data are not yet mature.

ICON-7 was a 2-armed trial comparing carboplatin and paclitaxel (6 cycles) against carboplatin + paclitaxel + bevacizumab (7.5 mg/kg) every 3 weeks for 6 cycles, followed by 12 cycles of maintenance bevacizumab or disease progression, whichever occurred earlier. Data from this trial were presented in abstract form at the 2010 meeting of the European Society of Medical Oncology (ESMO). A total of 1528 women were randomized from 263 centers. Adverse events were reported as consistent with previous bevacizumab trials. More importantly, relative to arm 1 of the trial, the hazard ratio for disease progression in the bevacizumab arm was 0.81 (95% CI: 0.70–0.94, $P < 0.0041$).

The remaining phase III trials target patients with recurrent disease. GOG 213, is a randomized trial comparing carboplatin and paclitaxel with or without bevacizumab in platinum sensitive relapsed ovarian cancer patients. It also includes a study of secondary cytoreductive surgery in eligible patients. OCEANS, an industry-conducted study, is a randomized, placebo-controlled trial, comparing carboplatin and gemcitabine with or without bevacizumab in the treatment of recurrent disease.⁷ This trial has completed accrual, but results are not available at this time (Table 1).

As with any new anti-tumor agent, the benefits of bevacizumab in the treatment of patients with ovarian cancer must be weighed against the side effects. Overall, bevacizumab is well tolerated, with a side effect profile unique to its mode of action. In a comprehensive review, Randall et al investigated

Table 1 Randomized clinical trials evaluating bevacizumab in ovarian cancer

Study	Trial design	Status
First-line adjuvant therapy		
GOG 218	Randomized, placebo-controlled, 3-arm, CT ± bev with 18-cycle bev maintenance	Completed accrual: HR 0.717 favoring the concurrent and maintenance bevacizumab arm
ICON-7	Randomized, 2-arm, CT ± bev with 12-cycle bev maintenance	Completed accrual: HR 0.80 favoring the concurrent and maintenance bevacizumab arm
Second-line therapy		
GOG 213	Randomized, CT ± bev	Open to accrual
OCEANS	Randomized, placebo-controlled, CG ± bev	Completed accrual July 2010: Results not yet available

Abbreviations: CT, carboplatin/paclitaxel; CG, carboplatin/gemcitabine; GOG, Gynecologic Oncology Group; ICON, International Collaborative Ovarian Neoplasm; bev, bevacizumab.

the toxicities of bevacizumab in ovarian cancer patients, and their management.⁷ Table 2 lists the adverse effects that were included in the FDA-approved bevacizumab package insert.²⁸

The most common toxicities include hypertension (grade 3–4 ranging from 0.3% to 14.8% of patients), proteinuria (usually grade 1–2), hemorrhage, arterial and venous thrombotic events, impaired wound healing, and gastrointestinal perforation.^{18,29} Treatment strategies for bevacizumab related hypertension have yet to be defined, but traditional anti-hypertensive agents including beta blockers, calcium channel blockers, and ACE inhibitors have successfully managed bevacizumab-related hypertension.

Bowel perforation is an additional feared adverse event and appears to be disease site-dependent, occurring in patients with mCRC and ovarian carcinoma. Ovarian cancer patients may be at increased risk due to the potential for bowel dysmotility and obstruction as a direct result of the disease process. Data from key phase II trials discussed previously indicated that patients who were heavily pretreated (3 or more previous cycles of cytotoxic chemotherapy) were at increased risk of bowel perforation. Although there were no reported gastrointestinal perforations (GIP) in GOG 170-D, eligible patients were limited to 1 or 2 previous chemotherapy regimens.²³ Conversely, the phase II study completed by Cannistra et al was terminated early due to the high rate of GIP in the patient population, 11.4% (5 of 44 patients).²⁴

Table 2 Adverse events associated with bevacizumab

Adverse events	
Common (mild)	Rare (serious)
Headache	Nongastrointestinal fistula formation
Hypertension	Arterial thromboembolic events (myocardial infarction, cerebrovascular accident)
Proteinuria	Gastrointestinal perforation
	Wound healing complications
	Reversible posterior leukoencephalopathy syndrome

Importantly, all GIP occurred in patients receiving 3 or more previous chemotherapy regimens. We are awaiting final data from GOG 218 and ICON-7 to help elucidate risk in up-front treatment with bevacizumab.¹⁸

The management of bevacizumab toxicity requires individualized decision making that weighs drug efficacy against adverse event severity (grade) and potential long-term consequences of both the adverse event and the disease. The goals of therapy (palliative vs curative), potential alternative therapies, cost, and patient quality of life should all be factored into these decisions. Communicating to the patient the complexity of issues that inform treatment decisions can aid in the management of expectations as well.

Conclusion

In summary, our understanding of the complex molecular pathways that control tumor angiogenesis continues to improve. The anti-VEGF agent bevacizumab has shown activity in the treatment of ovarian cancer, with an overall acceptable toxicity profile and is currently listed as an active treatment for recurrent ovarian and primary peritoneal cancers by the National Comprehensive Cancer Network, but it is not yet FDA-approved for these indications. Bevacizumab has been shown to exhibit a 15%–20% response rate with up to 50% PFS at 6 months in several phase II trials.^{23–26} Furthermore, the preliminary data from 2 phase III clinical trials, GOG 218 and ICON-7, show an improvement in PFS in the up-front treatment of ovarian cancer with the addition of bevacizumab. It is unclear, at this point in time, how these data will be applied clinically.

In the last decade, numerous biologic targets, including VEGF-inhibitors, epidermal growth factor receptor inhibitors, poly-ADP-ribose polymerase inhibitors, and anti-folate agents have been identified and studies are under way to determine their utility in the treatment of ovarian cancer. Future studies exploring potential biomarkers to aid in

predicting response to therapy (analogous to HER2 in breast cancer) are of utmost importance, as this will allow us to better select patients for therapy.

Disclosure

The authors declare no conflicts of interest.

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