Review Article

Role of vascular endothelial growth factor inhibitors in the treatment of gynecologic malignancies

Robert A. Burger

Department of Surgical Oncology, Section of Gynecologic Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

This article reviews the history and current status of vascular endothelial growth factor targeted therapy for the most common gynecologic malignancies - epithelial ovarian, endometrial and cervical cancers. The biologic rationale for targeting vascular endothelial growth factor (VEGF) for these disease sites is well-founded, and pre-clinical studies have supported the development of anti-VEGF agents. Their classification, known mechanisms of action, unique toxicities and clinical development are herein explored, the latter including issues related to study design, disease site and disease setting.

Key Words: Vascular endothelial growth factor, Ovarian neoplasms, Endometrial neoplasms, Cervical neoplasms, Angiogenesis, Bevacizumab

RATIONALE FOR MOLECULAR TARGETED THERAPY

A plateau in the mortality statistics for the common gynecologic malignancies underscores limitations of surgical resection, cytotoxic therapy and regional radiation in the management of these diseases and suggests a role for continued research on novel therapeutics. Table 1 stratifies the 2009 American Cancer Society estimated incidence and mortality for major neoplastic sites in women in order of lethality. Ovarian cancers (the majority being epithelial in origin and including fallopian tube and primary peritoneal carcinomas), are tied with lung cancers as the second most lethal cancer site in women and represent the most lethal site of gynecologic malignancy in the United States, with an estimated 21,550 new cases and 14,600 deaths per year.[1] Despite somewhat effective primary preventive approaches and advances in cytotoxic therapeutics, incidence and mortality rates have yet to decline convincingly. Endometrial carcinoma is the most common gynecologic malignancy, representing the vast majority of the 42,160 new cases of uterine cancer and most of the 7,780 uterine cancer deaths estimated in the US for 2009.[1] Failure of preventive measures, such as weight control and management of chronic anovulation, is the most likely ex-

planation for the continued rise in incidence for endometrial cancers. Although the majority of patients present with symptoms of abnormal vaginal bleeding and are found to have early stage disease that can be controlled with standard therapeutic modalities, according to 2006 estimates, at diagnosis 16% are diagnosed with locally advanced disease (including regional lymphatic spread) and 8% are found to have distant metastases; the corresponding 5-year survival rates for these two groups are 66% and 25% respectively.[1] Carcinoma of the uterine cervix is the leading cause of cancer mortality in women world-wide, attributed mostly to the lack of broadly applied cytology screening programs in less industrialized regions. Despite the implementation of effective prevention, early detection and therapeutic methods in the US, however, the American Cancer Society estimates 4,070 cervix cancer deaths for 2009.[1] According to 2006 estimates by the American Cancer Society, 32% of cancers are locally advanced or associated with regional nodal metastases, and 8% are as-

Correspondence to **Robert A. Burger**
Department of Surgical Oncology, Section of Gynecologic Oncology, Fox Chase Cancer Center, Room C312, 333 Cottman Avenue, Philadelphia, PA 19111, USA
Tel: 1-215-728-3150, Fax: 1-215-728-2773
E-mail: robert.a.burger@fccc.edu

Table 1. US Incidence and mortality for female solid tumors: 2009[1]

Disease site	New cases	Deaths	Lethality (Deaths/New cases)
Pancreas	21,420	17,210	0.80
Ovary	21,550	14,600	0.68
Lung	103,350	70,490	0.68
Uterine cervix	11,270	4,070	0.36
Colorectal	71,380	24,680	0.35
Breast	192,370	40,170	0.21
Uterine corpus	42,160	7,780	0.18

sociated with distant metastases. The corresponding 5-year survival rates are 55% and 17% respectively.[2]

Recent studies have suggested that molecular targeted therapeutics may represent an important solution to the current barriers in gynecologic cancer control. Broadly speaking, in contrast to systemic cytotoxic drugs, molecular targeted agents are developed by first identifying key biological pathways driving tumor progression and potential targets therein.

VASCULAR ENDOTHELIAL GROWTH FACTOR SIGNALING IN PATHOGENESIS OF GYNECOLOGIC CANCERS

There is abundant evidence that vascular endothelial growth factor (VEGF) signal transduction plays a central role in disease progression and prognosis for carcinomas of the ovary, endometrium and cervix. From a molecular mechanistic standpoint, multiple cell types in the tumor microenvironment, including endothelial cells, stromal cells and tumor cells themselves may express functional VEGF receptors. The synthesis and release of VEGF by tumor cells may trigger these receptors and promote a phenotype conducive to tumor proliferation, invasion and metastasis. This is predominantly, though not exclusively, through induction of angiogenesis, characterized initially by the development of immature, abnormally permeable, micro-vascular networks from existing blood and lymphatic vessels. In epithelial ovarian cancer (EOC) and primary peritoneal cancer, VEGF expression is thought to be the key promoter of malignant ascites and pleural effusions.[3-9]

The degree of tumor angiogenesis within individual gynecologic tumors appears to have prognostic importance. Micro-vessel density (MVD) in primary epithelial carcinomas of the ovary,[10-14] endometrium[15-19] and cervix[20-22] has correlated with extent of disease and has inversely correlated with overall survival (OS) or progression free survival (PFS) after initial therapy. Often this relationship to clinical outcome has been found to be independent of important clinical and pathologic prognostic factors.[13,14,16-22] In addition VEGF has demonstrated prognostic value[23-25] in accordance with its known functional relationship to angiogenesis.

In addition to correlative clinical studies cited above, pre-clinical investigations have provided a strong rationale for clinical trials of anti-VEGF therapeutics in gynecologic malignancies. There is ample evidence in human ovarian cancer xenograft models that direct blockade of VEGF activity alone can result in decreased tumor growth, metastasis and malignant ascites formation.[3,7,26-29] Multiple mechanisms may explain the observed "anti-tumor" effect in these pre-clinical models of VEGF inhibition. In the most widely accepted model, the anti-angiogenic effect involves both blockade in the formation of new vessels and maturation of existing immature vessels. The latter process, initially described by Jain et al.[30] involves normalization of the primitive tumor microvasculature through endothelial cell maturation, restoration of pericyte continuity, decrease in micro-vascular permeability and interstitial pressure, and re-establishment of normal flow. Vascular normalization is thought to result in decreased metastatic potential and enhanced delivery of other systemic anti-tumor agents such as cytotoxic drugs. Indirect evidence of an anti-neoplastic effect independent of tumor angiogenesis has also been described for some solid tumors. Functional VEGF receptors are expressed on tumor cells in multiple solid tumor types, including colon, breast and ovarian carcinomas.[31-35] Studies of breast carcinoma cells *in vitro* have demonstrated that stimulation with exogenous VEGF may increase invasive potential and stimulate growth factor signaling.[31]

CLINICAL TRIALS OF VEGF INHIBITORS FOR GYNECOLOGIC MALIGNANCIES

1. General considerations

Two broad classes of anti-VEGF agents have been developed for clinical application - those which directly neutralize VEGF (ligand-specific) and those which bind to and inactivate functional VEGF receptors. The first class is comprised of large molecules which tend to be administered systemically. These include bevacizumab, a humanized monoclonal antibody (mAb) which neutralizes VEGF-A, the predominantly active species of VEGF;[36] and VEGF-TrapR1R2 (aflibercept, AVE 0005), a soluble decoy receptor generated by fusing the constant region of IgG1 with the ligand binding domains of two principle anti-VEGF receptors, then optimized for VEGF binding affinity and pharmacokinetics.[37] The second class is comprised mostly (but not exclusively) of orally administered small molecules which tend to block tyrosine kinase activity located in the cytoplasmic domain of VEGF receptors. The exception to this is the drug ramucirumab, a monoclonal antibody which specifically recognizes the predominantly active VEGF receptor, VEGFR-2.[38]

It is worth discussing relative advantages and disadvantages of small molecular inhibitors (Ibs) and monoclonal antibodies (mAbs). Ibs are orally bio-available, but often require daily administration due to their relatively short half-lives. In addition, based on the route of administration, systemic levels may be more highly variable than for mAbs. While some of the Ibs (e.g. cediranib,[39] pazopanib[40]) are almost exclusively specific for VEGFR, others target multiple signal transduction pathways in addition to that for VEGF. Examples of the latter agents include sorafenib[41] and sunitinib,[42] which target both VEGFR and the platelet-derived growth factor receptor (PDGFR). PDGF signal transduction appears to stimulate later phases of tumor angiogenesis involving vessel maturation (see discussion of PDGF inhibition below). MAb therapy is systemic in nature but requires less frequent administration due to longer clearance times; they are in principle more uniformly bio-distributed than Ibs. Due to affinity for single tar-

gets, they are associated with a more limited range of potential anti-tumor effects. Recent strategies have involved combinations with both mAbs and Ibs, for example the phase I/II trial of bevacizumab and sorafenib discussed later in this article.

VEGF inhibitors have demonstrated unique toxicities, some which appear to be related to interference with known physiologic effects of VEGF, and others whose mechanisms have yet to be elucidated. The largest database comes from studies of bevacizumab[36,43] in clinical trials utilizing the US National Cancer Institute (NCI) Common Toxicity Criteria (CTC),[44] though the spectrum of adverse effects appears to be consistent across most VEGF inhibitors. Proteinuria is common but fortunately mild and self-limited in the vast majority of patients; nephrotic range proteinuria has been observed in only 0.5% of the treated population. Hypertension is also common, and though 8% to 18% develop grade 3 or higher blood pressure elevation, the majority of such patients can be stabilized with single agent anti-hypertensive therapy. Mucosal hemorrhage can be seen, most commonly in the form of low grade epistaxis; however, patients with central bronchogenic non-small cell lung cancers are at risk for high grade hemoptysis. Interference with wound healing has been a source of concern in the treatment of patients in the peri-operative period. Fortunately, wound dehiscense has been limited to 1% patients at potential risk. In large-scale randomized control trials of bevacizumab, the incidence of arterial thrombotic events (ATE) has been approximately 4.4% in treated subjects, compared with 1.9% in controls; risk factors include advanced age and pre-existing arterial vascular disease. Other rare but unique toxicities include reversible posterior leu-

koencephalopathy syndrome (RPLS), occurring in fewer than 0.1% of patients and characterized by a variety of central nervous system manifestations such as mental status changes, seizures, visual disturbance, usually with hypertension. Perhaps the most concerning adverse effect is the development of gastrointestinal perforation (GIP) or fistula. This complication has been reported in approximately 2.4% overall, and in 5% of patients with epithelial ovarian cancer. The mechanisms of GIP have not yet been elucidated; however, proposed risk factors include intestinal obstruction, ischemia, trans-mural tumor infiltration, infectious or non-infectious inflammatory bowel diseases - unlikely dose or duration of therapy.

While it is important to recognize the contribution of published historical experience, for succinctness, and in order to concentrate on the highest levels of evidence, the current article reviews only prospective clinical research. Needless to say, the integration of VEGF targeted therapeutics into clinical trials for gynecologic malignancies has been pursued enthusiastically, yet the knowledgebase generated from gynecologic cancer trials pales in comparison to that produced through research on non-gynecologic tumors. A review of the current US NCI database[45] identified 51 registered trials in at least phase II development, 37 examining VEGF neutralizing agents and 15 investigating VEGFR inhibitors (one trial evaluates a combination of both drug classes). Of these 51, only 20 have been closed and published final results are available for only four studies. When one takes into account the epidemiologic aspects of gynecologic malignancies discussed earlier, it is not surprising that the 41 of these 51 clinical trials utilizing VEGF inhibitors have been focused on the treatment

Table 2. US NCI registered single agent phase II trials of VEGF inhibitors in recurrent gynecologic cancers

Site	Trial	Agent	Class	Target	PI	Status
Ovarian	AVF 2949	Bevacizumab	Mab	VEGF	Cannistra[48]	Completed
Ovarian	GOG 170-D	Bevacizumab	Mab	VEGF	Burger[47]	Completed
Ovarian	CP12-0711	Ramucirumab	Mab	VEGF-R2	Not listed	Active
Ovarian	ARD6122	VEGF Trap	Receptor	VEGF	Tew[51]	Closed
Ovarian	ARD6772	VEGF Trap	Receptor	VEGF	Not listed	Closed
Ovarian	DFCI-05170	Cediranib	TKI	VEGF-R	Matulonis	Closed
Ovarian	PMH-PHL-037	Cediranib	TKI	VEGF-R	Hirte	Closed
Ovarian	GOG 170-L	Motesanib	TKI	VEGF-R + PDGF-R	Schilder	Closed*
Ovarian	VEG104450	Pazopanib	TKI	VEGF-R	Friedlander	Closed
Ovarian	GOG 170-F	Sorafenib	TKI	VEGF-R + PDGF-R + Raf-K	Matei	Closed
Ovarian	AGO-OVAR 2.11	Sunitinib	TKI	VEGF-R + PDGF-R	Wagner	Active
Ovarian	DF 08-056	Sunitinib	TKI	VEGF-R + PDGF-R	Campos	Active
Ovarian	CAN-NCIC-IND185	Sunitinib	TKI	VEGF-R + PDGF-R	Biagi	Closed
Endometrial	GOG 229-E	Bevacizumab	Mab	VEGF	Aghajanian[49]	Completed
Endometrial	GOG 229-F	VEGF Trap	Receptor	VEGF	Coleman	Suspended[†]
Endometrial	PHL-062	Sunitinib	TKI	VEGF-R + PDGF-R	Oza	Active
Cervical	GOG 227-C	Bevacizumab	Mab	VEGF	Monk[50]	Completed

NCI: National Cancer Institute, VEGF: vascular endothelial growth factor, PI: principal investigator, MAb: monoclonal antibody, TKI: tyrosine kinase inhibitor.
*Secondary to toxicity, [†]Suspended after 1st stage, interim analysis pending.

of EOC (including primary peritoneal and fallopian tube carcinomas).

The remainder of this article is focused on the assessment of this group of clinical trials. The information is organized first by design, then by disease site, with consideration of what has been learned, the design and rationale for investigation in progress, and future directions.

2. Single agent VEGF inhibitor trials: standard phase II studies

As demonstrated in Table 2, 17 NCI registered trials have evaluated single agent anti-VEGF activity in patients with recurrent ovarian, endometrial and cervical carcinomas. Most of these have utilized two-stage designs in patients with NCI Response Evaluation Criteria in Solid Tumor (RECIST)[46] measurable disease and have evaluated primary endpoints of response rate, PFS, or the combination. Thus far, the only completed, published (or accepted for publication) trials are those involving bevacizumab; these have demonstrated single agent activity in EOC,[47,48] endometrial[49] and cervical carcinoma.[50]

For EOC, the design and results of three, phase II trials of VEGF neutralizing agent monotherapy have been reported, two examining bevacizumab[47,48] and one investigating VEGF-Trap (preliminary results published in abstract form only).[51] As shown in Table 3, all three trials enrolled patients with RECIST measurable recurrent or persistent disease, yet demonstrated variable clinical activity of single agent therapy, with response rates ranging from 8% to 21% and 6-month PFS rates ranging from 4% to 40%. A recent report from the sponsor stated that the VEGF-Trap trial failed to achieve its primary endpoint of demonstrating either dose level to achieve a RECIST response rate statistically greater than 5%.[52] Although it is unscientific to draw conclusions upon comparisons among separate phase II trials (and only preliminary data are available for the VEGF-Trap trial), one may hypothesize that clinical activity may be more favorable for patients with a longer interval from the completion of last platinum-containing chemotherapy, fewer prior cytotoxic regimens, and better performance status. In contradistinction, in the Gynecologic Oncology Group (GOG) trial[47] an internal exploratory regression analysis failed to demonstrate any relationship of these known prognostic factors (or age) with PFS. To date there are no published pre-clinical or clinical studies prospectively comparing the anti-tumor activities of bevacizumab and VEGF-Trap.

With regard to adverse effects, when taken together, these trials demonstrated that single agent anti-VEGF therapy was tolerable in general, with the expected frequency of events. The exception to this was higher than expected rate of GIP in the third line Genentech AVF 2,949 trial of bevacizumab in platinum-resistant patients.[48] This trial was terminated prematurely because of 5 GIPs reported out of the first 44 patients enrolled. In October 2005, the US FDA released an

Table 3. Phase II trials of VEGF neutralizing single agent therapy in patients with epithelial ovarian and primary peritoneal cancer

Trial	GOG 170-D[47]	AVF2949[48]	Sanofi-Aventis[51]
Agent	Bevacizumab	Bevacizumab	VEGF-Trap
Dose/schedule	15 mg/kg q 21 d	15 mg/kg q 21 d	2 or 4 mg/kg q 14 d
Primary endpoint	RR + 6 mo PFS	RR	RR
Eligibility			
Measurable disease	RECIST	RECIST	RECIST
Platinum DFI	Unrestricted	$1°$ or $2°$ <6 mo	$1°$ or $2°$ <6 mo
Prior regimens	1-2	2-3	3-4
PS	0-1	0-1	0-2
Target sample size	60	53	200
Enrollment	62	44*	162[‡]
$1°$ platinum DFI <6 mo	36%	84%	47%
% prior regimens (1/2/3/4)	34/66/0/0	0/52/48/0	0/0/46/46
% GOG/ECOG PS (0/1/2)	73/27/0	59/41/0	60/33/7
RR	13 (21%)	7 (16%)	13 (8%)
6 mo PFS	40%	27%	4-15%
≥G3 GIP	0	5 (11%)	2 (1.2%)
≥G3 Arterial TE	0	3[†] (8%)	1
≥G3 HTN	6 (10%)	6[†] (14%)	18%
≥G3 CNS	0	1[†]	1
≥G3 Proteinuria	1	0	7%

RR: response rate, PFS: progression free survival, RECIST: Response Evaluation Criteria in Solid Tumor, PS: performance status, DFI: disease-free interval, GOG: Gynecologic Oncology Group, ECOG: Eastern Cooperative Oncology Group, GIP: gastrointestinal perforation, TE: thrombo- embolism, CNS: central nervous system.
*Trial terminated prematurely secondary to unacceptable frequency of gastrointestinal perforations, [†]Event fatal in one case, [‡]Preliminary analysis.

Action Letter[53] alerting investigators and patients to this risk, even though a black box warning was already present on the package insert. At that time, the rates of GIP were highly variable among trials, (as a distinct example, there were no events in 62 patients treated on the GOG phase II bevacizumab trial). As mentioned previously, a 2007 review of GIP by Han et al.[54] the aggregate number of events reported in published bevacizumab clinical trials and institutional off-label case series of EOC was 16 (5.2%) events in 308 patients. Based on this and other historical analyses, the risk factors for GIP remain unclear; clearly large scale prospective investigation would more reliably answer this question.

3. Consolidation therapy trials

Despite the fairly obvious rationale for such an approach, the investigation of VEGF inhibitors for their potential to extend PFS or OS in high risk patients considered to be in complete remission following standard therapies has been quite limited. To date there are only two registered trials of this nature. These are active phase II randomized trials in patients with EOC. One is a placebo controlled trial of single agent sorafenib; the other is a trial of bevacizumab +/- erlotinib (an epidermal growth factor receptor 1 Ib).

4. Combinations with cytotoxic regimens

The rationale for combining cytotoxic drugs with anti-VEGF therapy stemmed initially from additive and in some cases synergistic interaction in pre-clinical models. While an additive effect might be explained by complementary, independent anti-tumor activity, multiple purported mechanisms exist to promote synergistic interaction, including sensitization to apoptosis, reversal of cytotoxic drug resistance, and increased

tumor access to chemotherapeutics secondary to vascular normalization (see above).[30] It has also been hypothesized that combining VEGF targeted agents with frequently administered low dose, so called metronomic chemotherapy may have additive or synergistic anti-angiogenic or anti-tumor effects.

Given the results of pre-clinical studies referenced above and multiple positive phase III trials (all with bevacizumab) in non-gynecologic cancers,[55-58] it is not surprising that trials investigating anti-VEGF and cytotoxic therapy combinations in patients with gynecologic tumors have been pursued with vigor. These are listed in Table 4 and Table 5.

While it would appear reasonable for cytotoxic agents considered active in gynecologic cancers to be combined with anti-VEGF agents in phase II trials, many such trials have perhaps been initiated without evidence of safety or preclinical evidence of benefit, in a "cart before horse" fashion. This enthusiasm has also been reflected in multiple published multi-institutional historic cohort studies of VEGF inhibitors in recurrent EOC, endometrial and cervical cancer reflecting the utilization of VEGF inhibitors in combination with cytotoxic agents in routine clinical practice.[59-66] It is unclear whether combination therapy is a better choice than single agent therapy in this setting without controlled clinical trials data.

Perhaps the first phase II trial of combined cytotoxic and anti-VEGF bevacizumab and low dose oral cyclophosphamide in 70 patients with recurrent or persistent EOC.[67] Patients were treated with bevacizumab at 10 mg/kg every 14 days with 50 mg of daily oral cyclophosphamide. Based on similar eligibility criteria, patient and disease characteristics were similar to that of the GOG 170-D population. This regimen was associated with a toxicity profile similar to the single agent bev-

Table 4. National Cancer Institute registered trials of VEGF inhibitors in combination with cytotoxic agents for recurrent gynecologic cancers

Site	Trial	Agent	Phase	Regimen	PI	Status
Ovarian	CCC PHII45	Bev	II	Metronomic Cyclophosphamide + Bev	Garcia	Completed[67]
Ovarian	GOG 0213	Bev	III	Carboplatin + Paclitaxel +/- Bev	Coleman	Active
Ovarian	2008-000878-20	Bev	II	Carboplatin + Bev	Jakobsen	Active
Ovarian	OCEANS	Bev	III	Carboplatin + Gemcitabine +/- Bev	Aghajanian	Active
Ovarian	2005CO073	Bev	II	Carboplatin + Gemcitabine + Bev	Copeland	Active
Ovarian	DF 04-356	Bev	II	Oxaliplatin + Gemcitabine + Bev	Horowitz	Active
Ovarian	CR015094	Bev	II	Carboplatin + Liposomal Doxorubicin + Bev	J&J	Active
Ovarian	MCC-14920	Bev	II	Docetaxel + Bev	Wenham	Active
Ovarian	ALSSOPR0501	Bev	II	Abraxane + Bev	Schwartzberg	Closed
Ovarian	MDA-2006-0329	VEGF Trap	II	Docetaxel + VEGF Trap	Coleman	Active
Ovarian	AVF3648s	Bev	II	Topotecan + Bev	McGonigle	Active
Ovarian	MDA 2007-0368	Bev	II	High Dose Combination Chemotherapy + Bev	Nieto	Active
Ovarian	GYN06-111	Sorafenib	II	Sorafenib + Topotecan	Matei	Active
Ovarian	SCRI GYN 19	Sorafenib	II	Carboplatin + Paclitaxel +/- Sorafenib	Hainsworth	Active
Ovarian	CASE-CWRU-2804	Sorafenib	II	Sorafenib +/- (Carboplatin + Paclitaxel)	Von Grunigen	Closed
Ovarian	MRC-NCRI-ICON6	Cediranib	III	Carboplatin + Paclitaxel +/- Cediranib	Ledermann	Active
Cervical	Wash U 06-1098	Bev	II	Cisplatin + Topotecan + Bev	Rader	Active
Cervical	GOG 240	Bev	III	Topotecan + (Cisplatin v Paclitaxel), +/- Bev	Tewari	Pending

VEGF: vascular endothelial growth factor, PI: principal investigator, Bev: bevacizumab.

Table 5. US National Cancer Institute registered front-line trials of VEGF inhibitors in combination with cytotoxic agents for gynecologic cancers

Site	Trial	Agent	Phase	Regimen	PI	Status
Ovarian	GOG 0218	Bev	III	Carboplatin + Paclitaxel +/- Bev	Burger	Active
Ovarian	MREC-ICON7	Bev	III	Carboplatin + Paclitaxel +/- Bev	Perren	Active
Ovarian	AV53206s	Bev	II	Carboplatin + Paclitaxel + Bev	Micha	Closed
Ovarian	MGH 04-247	Bev	II	Carboplatin + Paclitaxel + Bev	Penson	Active
Ovarian	TEACO	Bev	II	Oxaliplatin + Docetaxel + Bev	Nagarwala	Closed
Ovarian	AVF3953	Bev	II	IP Cisplatin + IV Paclitaxel + Bev	McMeekin	Active
Ovarian	MSK 06-064	Bev	II	IP Cisplatin + IP/IV Paclitaxel + Bev	Konner	Active
Cervical	AVF3963s	Bev	II	Carboplatin + Bev, Neoadjuvant, + RT	Gay	Active
Cervical	RTOG-0417	Bev	II	Radiotherapy + Cisplatin + Bev	Schefter	Active

VEGF: vascular endothelial growth factor, PI: principal investigator, Bev: bevacizumab.

acizumab trial with the exception of 2 cases of G4 cerebral ischemia, 2 cases of pulmonary hypertension, 4 GI perforation events and 3 treatment related deaths. With regard to efficacy, 56% of patients were progression-free as of 6 months and 24% had partial clinical responses. These findings provide rationale for a phase II randomized trial of combination versus single agent therapy, but early stopping rules for excessive toxicity in such trials would be important.

Additional reports of outcomes for patients with epithelial ovarian and primary peritoneal cancers treated with bevacizumab include at least three historical case series of patients treated outside clinical trials with single agent therapy or in combination with cytotoxic drugs, suggesting activity in more heavily pre-treated patients with recurrent disease[61,63,66] and two single arm phase II studies demonstrating the feasibility of the combination of traditional carboplatin-paclitaxel chemotherapy combined with bevacizumab in front line therapy.[68,69]

Taken together, these results support the need for randomized trials to determine relative efficacy and toxicity. As shown in Table 4, four such studies are in progress for recurrent EOC. One example is GOG 213, a phase III trial of second line therapy with carboplatin and paclitaxel, with or without bevacizumab, in patients with initial platinum-free intervals of at least 6 months, with a primary endpoint of overall survival. To address the potential added benefit of secondary cytoreductive surgery, in this study, patients who are deemed to be "surgical candidates" undergo secondary randomization to surgery versus no surgery. Another is a placebo controlled trial of carboplatin and gemcitabine with or without bevacizumab in a similar population, with primary endpoint of PFS.

As demonstrated in Table 5, currently, two phase III trials of bevacizumab in front-line therapy are in progress - GOG 0218, activated September 2005 and ICON7, activated October 2006. Both trials include six cycles of standard platinum-taxane chemotherapy, but there are important differences between the two trials which should be noted. GOG 218 is a three-arm, placebo-controlled trial, whose primary objective is to determine whether the addition of bevacizumab (15 mg/kg every 21 days) to standard cytotoxic therapy, when ad-

ministered concurrently, or concurrently plus extended for an additional 16 cycles, will produce an improvement in PFS. It is limited to patients with stage III or IV disease. In contrast, ICON-7 is a two-arm trial without a placebo, with the experimental arm containing bevacizumab (7.5 mg/kg every 21 days) concomitantly with cytotoxic therapy, then extended for 12 cycles, also with the primary endpoint of PFS. The patient population for the ICON trial includes all patients with at least high risk early stage disease. As far as secondary endpoints are concerned, both trials will systematically examine quality of life, and while translational research will be performed in the context of GOG 218 and a pharmaco-economic analysis is planned for ICON-7.

Clinical trials combining anti-VEGF agents with cytotoxic drugs in the treatment of endometrial and cervical cancers are relatively scarce when compared with those for EOC. Only one trial is currently active in the NCI Database, a GOG phase III randomized trial of cisplatin plus paclitaxel with or without bevacizumab vs. the non-platinum doublet, topotecan plus paclitaxel, with or without bevacizumab.

With respect to endometrial cancer, the reason for the paucity of phase III trials has mostly to do with impact on public health in industrialized nations, but there may be other explanations - relatively few indications for systemic therapy, and the observation that epithelial ovarian cancers and advanced endometrial cancers appear to be similar with respect to histologic cell types (endometrioid, serous, clear cell) and biologic behavior. Hence, the development of systemic therapy for patients with advanced endometrial cancers has tended to shadow the development of systemic therapy for patients with epithelial ovarian cancers.

The situation for carcinomas of the cervix is even more pronounced, with only 4,070 cancer deaths estimated for 2009.[1] Again, in 2006, of the 9,710 annual cases of cervical cancer in the U.S., over half were classified as localized, with over 90% of patients cured using standard modalities.[2] However, given that this disease is a major cause of morbidity and mortality in less industrialized regions, novel approaches to systemic therapy are still needed. Given the potential for anti-VEFG inhibitors to restore microcirculation, phase I and II trials are in

progress to explore the interaction between such agents and standard chemo-radiation in the management of patients with advanced disease.

5. Combinations with other biologic targeted agents

Although conceptually attractive, the evaluation of rational combinations of anti-VEGF and other biologic agents is in its infancy. One avenue of pursuit has been cross-talk between the VEGF and EGFR-1 pathway. However, thus far preliminary data suggest lack of additional benefit for anti-EGFR-1 drugs.[70] Another trial is evaluating the combination of bevacizumab with Sorafenib, attempting to exploit simultaneous blockade of VEGF and its receptors, as well as other pathways potentially involved in ovarian cancer progression.

SUMMARY AND FUTURE DIRECTIONS

In summary, VEGF appears to be a driving force in the biology of tumor progression for the most common gynecologic malignancies, likely related to multiple mechanisms. VEGF neutralizing therapy has demonstrated clinical benefit in phase II trials for all three disease sites. The addition of these agents to standard therapy is now being explored in phase II randomized and phase III trials, with results from those in patients with EOC maturing within the coming year. Said with cautious optimism, VEGF-targeted therapeutics might one day represent another standard modality to complement surgery, cytotoxic chemotherapy, and radiotherapy in the control of these diseases.

There are several future directions which should be considered to be of high priority within the next ten years. These include both clinical-pathologic and pre-clinical investigation on the mechanisms of gastrointestinal perforation in order to identify true predictors of this complication; hypothesis driven correlative laboratory research in the context of phase III trials in order to identify factors predictive of efficacy for anti-VEGF agents; studies to determine mechanisms resistance or escape from anti-VEGF therapy; and clinical trials to determine the potential utility of continuing versus discontinuing anti-VEGF therapy after disease progression.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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