

Therapeutic advances in women's cancers

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1. ABSTRACT

Cytotoxic therapy and surgery have improved outcomes for patients with gynecologic malignancies over the last twenty years, but women's cancers still account for over ten percent of cancer related deaths annually. Insights into the pathogenesis of cancer have led to the development of drugs that target molecular pathways essential to tumor survival including angiogenesis, DNA repair, and apoptosis. This review outlines several of the promising new biologically targeted drugs currently being tested to treat gynecologic malignancies.

2. INTRODUCTION

Gynecologic malignancies including cancers of the uterus, ovaries, cervix, fallopian tubes, vagina, and vulva carry an estimated incidence of 80,720 cases per year (>11% of all malignancies in women), and estimated mortality rate of 28,120 women per year (>10% of all cancer related deaths) (1). While endometrial cancer is the most common gynecologic malignancy, ovarian cancer causes more deaths than all other gynecologic cancers combined. The reason for this discrepancy is attributed in large part to advanced stage at the time of diagnosis, frequent recurrence, and emergence of drug resistance. Advances in the utilization of surgery and chemotherapy have improved survival for gynecologic malignancies, but survival rates appear to have plateaued. Overall cure rates for ovarian cancer, for example, are limited to a mere 30% (2). Therefore, new therapies are urgently needed to improve the outlook for women with ovarian or other gynecologic cancers.

Recent advances in genomic and proteomic research have identified cancer of any organ site to be quite heterogeneous. Based on these observations, there is a growing emphasis on developing "personalized" therapies focused on specific molecular relationships to guide therapy. The investigative environment is anchored in discovery from which a wide array of therapeutic approaches including antibodies, small molecule antagonists, vaccines, and RNA interference offer hope for improving the outcome of women with gynecologic and other malignancies. These therapies represent attempts to target relevant and, most importantly, critically vulnerable biologic processes that drive or define cancer growth and progression. As such, features required for all solid tumors to grow, including the ability to replicate without control, evade host anti-growth signals, avoid apoptosis, and promote angiogenesis provide the greatest opportunities for effective intervention (3).

3. ANGIOGENESIS INHIBITORS

Development of a new blood supply or angiogenesis is essential to the development and maintenance of any living tissue (4, 5). Normal vasculature is architecturally structured to bring oxygen and nutrients to cells, allow for specific exchange of contents, and remove waste in a streamlined, efficient fashion. Diffusion of nutrients over small distances is sufficient for cellular function, but in order for tumor growth to exceed 1mm³ in volume, new vessels must be recruited (5). Tumor cells generate angiogenic factors that promote new vessel

formation and recruit supporting cells. The resulting vasculature, however, is disorganized and heterogeneous with tortuous blood flow (6). The supporting endothelial cells, pericytes, and basement membrane surrounding the tumor vessels are also abnormal, resulting in increased permeability (7). The vessel density and circulating tumor levels of many pro-angiogenic proteins such as VEGF and platelet-derived growth factor (PDGF) are poor prognostic factors for many solid tumors, including ovarian, endometrial and cervical carcinoma (8-12).

Since the early 1970's, angiogenesis has been a proposed target for the control of tumor growth and as an adjunct to chemotherapy in the treatment of solid tumors (13). It is a logical conclusion that if cancer cells cannot recruit vessels to bring nutrients, then cellular proliferation, transformation and metastasis will be limited. Cytotoxic therapies kill a proportion of abnormal cells, but the remaining cells adapt and employ evasive maneuvers to avoid cell death. Over the last ten years, there is increasing evidence that tumors capable of upregulating pro-angiogenic factors in response to chemotherapy and radiation are more resistant to treatment (14). Agents that block pro-angiogenic factors may enhance drug delivery by lowering interstitial pressure in the tumor and sensitize the tumor vasculature to cytotoxic agents.

3.1. VEGF and VEGF receptor

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF), is one of the most well characterized angiogenesis mediators (15, 16). VEGF comprises a family of proteins, of which VEGFA (often implied by the term "VEGF") is the dominant factor in tumor angiogenesis (17). There are three tyrosine kinase receptors for VEGF, of which VEGFR2 appears to have the most significant effects on angiogenesis (17). VEGF is ubiquitous in most human tissue and is upregulated in response to injury or stress (18, 19). Interaction of VEGFR2 with its ligand causes homo- or heterodimerization of the receptors resulting in activation of a cascade of downstream signaling pathways. VEGF activation also results in increased production of nitric oxide and prostaglandin I₂, both vasodilators (20). Increased production of VEGF as well as other growth factors is frequently observed in regions of hypoxia or inflammation and in the presence of activated oncogenes or down-regulated tumor suppressor genes (21-23). Human papillomavirus (HPV), for example, is the root cause of virtually all cervical cancers. HPV's E6 protein increases VEGF production by down-regulating the tumor suppressor gene p53 and enhancing induction of hypoxia-inducible factor (HIF) 1- α (24). Overexpression of VEGF results in increased endothelial cell proliferation, decreased apoptosis, and increased fenestration of endothelial cells (21, 25). High VEGF expression has been shown to be associated with poor prognosis in most gynecologic malignancies including cervical, endometrial, ovarian, and vulvar cancers (26-31).

3.1.1. Bevacizumab

Bevacizumab (Avastin[™] (Genentech, San Francisco, CA)) is a humanized monoclonal antibody

against VEGFA that is approved by the U. S. Food and Drug Administration (FDA) for the treatment of metastatic colorectal, non-small cell lung, renal cell, and breast cancers (32). Several phase II trials of this VEGFA antibody have been performed to assess its activity in gynecologic cancers. Bevacizumab has been most extensively studied in recurrent ovarian cancer patients where response rates have ranged from 16-24% and median overall survival is 10.7 to 17 months, when administered either as a single agent or in combination with metronomic cyclophosphamide (33-35). In patients with recurrent or persistent endometrial cancer, bevacizumab showed a 15.1% response rate (one complete response) and a median PFS of 4.2 months (GOG 229-E) (36). GOG 227-C examined single agent bevacizumab in patients with progressive or recurrent cervical cancer and also demonstrated a promising response rate (11%) and median survival (7.3 months) in this population (37). Table 1 presents the outcome measures of bevacizumab and other targeted therapies in these and other trials in gynecologic oncology patients.

Most studies of bevacizumab in gynecologic cancer have been conducted in patients with recurrent or progressive disease. A recent phase II trial by Penson *et al* evaluated bevacizumab in combination with carboplatin and paclitaxel as first-line chemotherapy in patients with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. All three agents were given every 21 days for six to eight cycles followed by bevacizumab every three weeks for one year. All patients had a computed tomography (CT) scan after surgery and before chemotherapy and 45% of the study population had suboptimal cytoreduction (>1cm residual disease). In this study, women experienced an overall response rate of 76% (21% with complete response) and a median progression-free survival of 29.8 months (38). These efficacy characteristics appear quite favorable compared to historical control data of the combination without bevacizumab (39). GOG 218 (NCT00262847) and ICON-7 (NCT00483782) are two randomized phase III studies that include an experimental arm mimicking this strategy (combination therapy plus maintenance). While the latter trial is awaiting the accumulation of sufficient events, GOG 218 has reported that the arm including bevacizumab maintenance therapy demonstrated superior clinical activity (hazard for progression) over control and combination paclitaxel, carboplatin and bevacizumab followed by placebo maintenance. Of interest, progression-free survival of this "winning" arm is substantively less than that reported by Penson and colleagues despite a similar proportion of suboptimal stage IIIC patients.

Toxicities associated with bevacizumab in phase II trials include hypertension, proteinuria, hemorrhage, neutropenia, venous thromboembolism, pulmonary embolus, congestive heart failure, myocardial infarction, and cerebrovascular ischemia (Table 2). Hypertension is the best characterized and most common side effect of the drug. It is thought to be caused by blocking nitric oxide production *via* inhibiting activation of VEGFR2 and by endothelial dysfunction in normal tissue (19). The severity

Table 1. Activity of targeted therapies

			SD	PR	CR	Median PFS*	Median OS*
Burger <i>et.al.</i> (33)	Bev	Persistent or recurrent epithelial ovarian and peritoneal CA	32 (52%)	11 (18%)	2 (3%)	4.7	16.9
Cannistra <i>et.al.</i> (34)	Bev	Platinum-resistant epithelial ovarian and peritoneal CA	27 (61%)	7 (16%)	0	4.4	10.7
Aghajanian <i>et.al.</i> (36)	Bev	Persistent or recurrent Endometrial CA	19 (36%)	7 (13%)	1 (2%)	4.2	10.5
Monk <i>et.al.</i> (37)	Bev	Persistent or recurrent squamous cell cervical CA	11 (24%)	5 (11%)	0	3.4	7.3
Garcia <i>et.al.</i> (35)	Bev + CPM	Persistent or recurrent epithelial ovarian and peritoneal CA	44 (63%)	17 (24%)	0	7.2	16.9
Nimeiri <i>et.al.</i> (43)	Bev + erlotinib	Persistent or recurrent epithelial ovarian, peritoneal, and FT CA	7 (54%)	1 (8%)	1 (8%)	4.1	11
Azad <i>et.al.</i> (54)	Bev + sorafenib	Advanced ovarian CA	5 (38%)	6 (46%)	0		
Matei <i>et.al.</i> (49)	Sorafenib	Persistent or recurrent epithelial ovarian and peritoneal CA	20 (34%)	2 (3%)	0		
Nimeiri <i>et.al.</i> (50)	Sorafenib	Persistent or recurrent uterine CA	21 (44%)	2 (5%)	0	3.2	11.4
		Persistent or recurrent uterine carcinosarcoma	4 (25%)	0	0	1.8	5
Welch <i>et.al.</i> (48)	Sorafenib + GCB	Recurrent ovarian CA	26 (60%)	2 (5%)	0	5.4	13.3
Biagi <i>et.al.</i> (51)	Sunitinib	Recurrent epithelial ovarian, peritoneal, and FT CA	10 (63%)	2 (13%)	0		
Welch <i>et.al.</i> (52)	Sunitinib	Recurrent or metastatic uterine CA	2 (13%)	2 (13%)	0	2.5	6.2
Mackay <i>et.al.</i> (53)	Sunitinib	Advanced or recurrent cervical CA	16 (84%)	0	0	3.5	
Matulonis <i>et.al.</i> (58)	AZD2171	Recurrent epithelial ovarian and peritoneal CA	6 (13%)	8 (17%)	0	5.2	
Hirte <i>et.al.</i> (57)	AZD2171	Persistent or recurrent epithelial ovarian, Peritoneal, and FT CA	5 (26%)	2 (11%)		4.1	11.9
Friedlander <i>et.al.</i> (59)	Pazopanib	Advanced epithelial ovarian Peritoneal, and FT CA	4 (27%)	7 (47%)	0		
Tew <i>et.al.</i> (61)	VEGF Trap	Recurrent platinum-resistant epithelial ovarian CA		5 (11%)			
Townsley <i>et.al.</i> (63)	VEGF Trap	Recurrent or metastatic uterine LMS	8 (32%)	0	0		15.1
		Recurrent or metastatic uterine carcinosarcoma	0	0	0		3.1
Secord <i>et.al.</i> (74)	Cetuximab+CBP	EGFR positive platinum-sensitive recurrent epithelial ovarian and peritoneal CA	8 (31%)	6 (23%)	3 (12%)	9.4	
Konnor <i>et.al.</i> (75)	Cetuximab + CBP + PTX	Stage III or IV EGFR positive epithelial ovarian, peritoneal, and FT CA				14.4	
Kurtz <i>et.al.</i> (77)	Cetuximab + CDDP + TPT	Advanced cervical CA	6 (32%)	6 (32%)	0	5.7	7.3
Oza <i>et.al.</i> (78))	Erlotinib	Advanced or metastatic uterine CA	15 (47%)	4 (12%)	0		
Schilder <i>et.al.</i> (79)	Erlotinib	Persistent or recurrent squamous cell cervical CA					
Goncalves <i>et.al.</i> (80)	Gefitinib	Advanced or recurrent cervical CA	6 (20%)	0	0	1.2	3.6
Monk <i>et.al.</i> (91)	Pazopanib lapatinib	Advanced or recurrent cervical CA					13.6
Fong <i>et.al.</i> (100)	Olaparib	BRCA deficient persistent ovarian CA	1 (7%)	8 (53%)	0		
Carden <i>et.al.</i> (99)	AZD2281	BRCA deficient ovarian CA	5 (11%)	19 (41%)	0		
Oza <i>et.al.</i> (109)	Temsirolimus	Advanced or recurrent uterine CA	12 (44%)	2 (7%)	0		
Slomovitz <i>et.al.</i> (110)	Everolimus	Recurrent uterine CA	29 (100%)	0	0		

* months Abbreviations: SD - stable disease; PR - partial response; CR - complete response; PFS - progression-free survival; OS - overall survival; CA - cancer; FT - fallopian tube; bev - bevacizumab; CPM - cyclophosphamide; GCB - gemcitabine; LMS - leiomyosarcoma; CBP – carboplatin; PTX paclitaxel; CDDP – cisplatin; TPT - topotecan

of hypertension is directly correlated with the dose of bevacizumab and the baseline blood pressure of the patient before initiating therapy (18). The degree of hypertension may also be a biomarker for response to therapy. In a study of patients with metastatic breast cancer, individuals with grade 3 or 4 hypertension after receiving bevacizumab had a longer median survival than those with no elevation in blood pressure during therapy (25.3 vs 38.7 months) (40). This same trend was observed for patients with non-small-cell lung and colorectal cancer (41, 42). Though a potential bioresponse marker of treatment effect, bevacizumab-induced hypertension should be treated in order to avoid cardiovascular morbidity and mortality.

One of the most alarming potential adverse events associated with bevacizumab is gastrointestinal (GI) perforation. Two phase II trials of bevacizumab in treatment of ovarian cancer were stopped early due to a high rate of GI perforation (11% and 15%) (34, 43). A retrospective review at Memorial Sloan-Kettering Cancer Center of patients with ovarian carcinoma receiving bevacizumab either in combination or as monotherapy revealed a GI perforation rate of 4% (6/160). This is comparable to a compilation of published ovarian cancer trials of bevacizumab that estimates a GI perforation risk of 5.4% (16/298) (32, 44). Many of the enrolled patients were heavily pre-treated. Some studies have suggested that

bowel involvement with ovarian carcinoma, bowel wall thickening or bowel obstruction on CT imaging, prior radiation therapy, and recent surgery may predispose patients to GI perforation, but strong evidence of association with these factors is still lacking. There are also reports of GI perforations associated with diverticulitis, ulcers, recent anastomosis, or bowel stricture or ischemia (18). The etiology of these events is not fully understood, but may be related to vascular compromise following VEGF blockade. Although a proforma has yet to be validated in whom bevacizumab administration is without safety concerns, it is prudent to consider these known toxicities relative to benefit and in the context of pre-existing medical infirmity prior to treatment.

There are currently at least 57 studies underway to evaluate bevacizumab in the treatment of gynecologic cancer, 45 of which focus on ovarian carcinoma (45). Furthermore, there are two recently completed phase III trials (GOG 218 and ICON7) evaluating bevacizumab in combination with carboplatin and paclitaxel as first line treatment for advanced ovarian cancer (Table 3). As mentioned, the initial observations for GOG 218 show improved progression-free survival in the cohort receiving bevacizumab in the consolidation phase, but full details remain to be reported (46). In addition, two phase III trials (GOG 213, NCT00565851 and OCEANS, NCT00434642) are evaluating chemotherapy and bevacizumab combinations (paclitaxel/carboplatin and gemcitabine/carboplatin, respectively) in patients with recurrent platinum sensitive disease (47). GOG 213's experimental arm also includes a bevacizumab maintenance arm to assess disease progression. The AURELIA trial (NCT00976911) is appraising the addition of bevacizumab to paclitaxel, topotecan, and liposomal doxorubicin in patients with platinum-resistant ovarian cancer (45). Two new trials in front-line disease are open (GOG 252, NCT00951496) or poised to open soon (GOG 262), which will continue this investigative theme of combining bevacizumab with chemotherapy and continuing single agent bevacizumab as maintenance therapy. Further, the Gynecologic Cancer Intergroup (GCI) will be addressing two different chemotherapy backbones in combination with bevacizumab for women with primary advanced stage and recurrent mucinous ovarian cancer. GOG 240 (NCT00803062) is a four-arm trial comparing paclitaxel/cisplatin or paclitaxel/topotecan with or without bevacizumab in patients with primary stage IVB or recurrent/persistent cervical carcinoma (24, 47). These studies will broaden our understanding of the overall safety and utility of bevacizumab in the treatment of malignant gynecologic disease.

3.1.2. Other therapeutics against VEGF and the VEGFR

Sorafenib and sunitinib are two tyrosine kinase inhibitors that block the activity of VEGFR, both approved by the FDA for targeted cancer therapy in renal cell carcinoma. Sorafenib inhibits several proteins including VEGFR-1, VEGFR-2, VEGFR-3, and platelet derived growth factor receptor (PDGFR)-alpha. It has been evaluated in a phase II trial in combination with

gemcitabine and found to provide a high rate of stable disease (60%) with 4.7% achieving a partial response (Table 1) (48). It has also been tested as a single agent (GOG 170-F) in patients with recurrent or persistent epithelial ovarian cancer and 20% of patients were found to have stable disease for six months or more (49). A phase II trial of single agent sorafenib in patients with advanced uterine carcinoma and carcinosarcoma showed 5% partial response and 43% stable disease in the carcinoma group and 25% stable disease in the carcinosarcoma group with overall median survival of 7.0 and 5.0 months, respectively (50). Sunitinib is also a multi-kinase inhibitor that blocks VEGFR and PDGFR, and has been found to promote stable disease in 59% of recurrent ovarian cancer patients and in 21% of patients with recurrent or metastatic endometrial cancer (51, 52). In a phase II study of patients with metastatic/advanced cervical carcinoma, 84% experienced stable disease with single agent sunitinib (median duration 4.4 months), but no objective responses were observed (53). Sorafenib and sunitinib have a similar side effect profile to bevacizumab with the addition of hand-foot syndrome, which occurs as grade 3 or higher in approximately 13% of recipients (Table 2) (50).

Combination of anti-angiogenic agents may further improve the anti-tumor activity of monotherapy. An analysis of sorafenib with bevacizumab in patients with ovarian cancer yielded an impressive 43% response, however dose reductions of sorafenib were required in 74% of patients due to toxicities (54). Eighty-four percent of the ovarian cancer patients in this study experienced grade 1-3 hypertension and grade 1-2 hand-foot syndrome occurred in 95%. The toxicities experienced with the drugs in combination were greater than the additive effects of each drug alone. Similar trends of increased response with increased toxicity requiring dose reduction or discontinuation have been observed using bevacizumab with sunitinib or sorafenib in renal cell carcinoma (55, 56).

Other small molecule tyrosine kinase inhibitors that target VEGFR include AZD2171, pazopanib and BIBF-1120. AZD2171 (cediranib) is an oral tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR-alpha, and c-kit that has been evaluated in phase II trials for patients with recurrent epithelial ovarian cancer, fallopian tube carcinoma, or peritoneal cancer. The partial response rate in this population was 10-17% and stable disease was achieved in 13-34% (57, 58). ICON-6 (NCT00544973) is currently evaluating AZD2171 in a randomized placebo-controlled phase III trial in patients with recurrent ovarian cancer. Pazopanib is an inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR-alpha, PDGFR-beta, and c-kit, and has been tested in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Response rate as measured by CA-125 decline, was seen in 47% of patients and 27% had stable disease (59). Pazopanib is currently being evaluated as a maintenance therapy in a double-blind, placebo-controlled phase III clinical study in women who have achieved a partial or complete response to primary platinum-based adjuvant chemotherapy (NCT00866697). BIBF-1120, an inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR-alpha, PDGFR-beta, and

Table 2. Reported number of patients with \geq grade 3 toxicities receiving agents targeting VEGF

	Disease	GI Perf	HTN	TE	Heme	Bleed *	Pain	Wound†	
Bevacizumab monotherapy									
Burger <i>et.al.</i> (33)	persistent or recurrent epithelial Ov/P CA	0	6 (10%)	2 (3%)	1 (2%)	0	3 (5%)		
Cannistra <i>et.al.</i> (34)	platinum-resistant epithelial Ov/P CA	5 (11%)	4 (9%)	1 (2%)			2 (5%)	2 (5%)	
Aghajanian <i>et.al.</i> (36)	persistent or recurrent endometrial CA		4 (8%)	2 (4%)	1 (2%)	1 (2%)	4 (8%)		
Monk <i>et.al.</i> (37)	persistent or recurrent SC cervical CA	0	7 (15%)	5 (11%)	8 (17%)	1 (2%)	6 (13%)		
Bevacizumab combination therapy									
Garcra <i>et.al.</i> ((35)	persistent or recurrent epithelial Ov/P CA	3 (4%)	11 (16%)	1 (1%)	8 (11%)	1 (1%)	13 (19%)	1 (1%)	
Nimeiri <i>et.al.</i> (43)‡	persistent or recurrent epithelial Ov/P/FT CA	2 (15%)	1 (8%)		1 (8%)		0		
Azad <i>et.al.</i> (54)•	advanced solid tumors	1 (3%)	5 (13%)	1 (3%)	1 (3%)			0	1 (3%)
Sorafenib monotherapy									
Matei <i>et.al.</i> (49)	persistent or recurrent epithelial Ov/P CA		‡2 (3%)						
Nimeiri <i>et.al.</i> (50)	persistent or recurrent uterine carcinoma or carcinosarcoma		7 (13%)	2 (4%)	4 (7%)	3 (5%)		1 (2%)	7 (13%)
Sorafenib combination therapy									
Welch <i>et.al.</i> (48)	recurrent ovarian CA		9 (21%)		≥ 14 (32%)				
Sunitinib									
Welch <i>et.al.</i> (52)	recurrent or metastatic uterine CA		5 (31%)						
Mackay <i>et.al.</i> (53)	advanced or recurrent cervical CA		2 (11%)		≥ 8 (42%)				
Cediranib									
Matulonis <i>et.al.</i> (58)	recurrent epithelial Ov/P/FT CA	0	21 (46%)			3 (7%)	3 (7%)	0	0
Hirte <i>et.al.</i> (57)	persistent or recurrent epithelial Ov/P/FT CA		16 (33%)						
Pazopanib									
Friedlander <i>et.al.</i> (59)	advanced epithelial Ov/P/FT CA								
VEGF Trap									
Tew <i>et.al.</i> (61)	recurrent platinum-resistant epithelial Ov CA	2 (1.2%)	15 (9%)	2 (1%)					
Townsend <i>et.al.</i> (63)	recurrent or metastatic uterine LMS and carcinosarcoma	7 (18%)		3 (8%)					

includes any hemorrhage, † wound complications including fistulas, ** includes cardiac, renal, GU, hepatic, and pulmonary toxicities; cerebrovascular events; GI, neurologic, and constitutional complaints; and metabolic disturbances, ‡ bevacizumab in combination with erlotinib, • bevacizumab in combination with sorafenib, † unspecified cardiovascular toxicity, Abbreviations: Ov - ovarian; P - peritoneal; FT - fallopian tube; CA - cancer; SC - squamous cell; GI perf - gastrointestinal perforation; HTN - hypertension; TE - thromboembolism; heme - hematologic toxicities; HFS - hand-foot syndrome; LMS – leiomyosarcoma

FGF, has been investigated as a single agent in the maintenance setting. Eighty-four patients with best outcome to one or two previous lines of chemotherapy of either partial or complete response were randomized to either placebo or BIBF-1120. The primary endpoint was progression-free survival (PFS). Overall, patients on placebo had a PFS of 2.8 months compared to 4.8 months in those treated with BIBF-1120 (60). These data have prompted a larger phase III trial (NCT01015118) and exploration of chemotherapy combinations as primary therapy for women with ovarian cancer. Each of these agents have similar side effects, the most frequent being hypertension, fatigue, and gastrointestinal complaints (Table 2).

VEGF Trap, or aflibercept, is a protein containing the VEGF binding regions of VEGFR-1 and 2 fused to the Fc region of a human IgG1. This inhibitor resulted in a partial response rate of 11% in women with recurrent platinum resistant epithelial ovarian carcinoma

(61). VEGF Trap was also studied as a single agent in women with refractory ascites. In this trial, the agent was significantly associated with reduced need for paracentesis (62). In patients with uterine sarcoma, a phase II trial of aflibercept showed 16% of patients with leiomyosarcoma experienced stable disease for over 6 months, but no response and no stable disease were observed in those with carcinosarcoma (63). Similar to bevacizumab, aflibercept is also associated with fatigue, hypertension, and GI complaints. A comparison of the two is shown in Table 4.

3.2. Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR), like VEGFR, is a tyrosine kinase receptor in the cell membrane. Its ligand, epidermal growth factor (EGF), binds EGFR which then dimerizes and initiates signal transduction pathways that affect cellular proliferation, motility and invasion, apoptosis, and angiogenesis. EGFR is overexpressed in 60-80% of endometrial cancers, 73% of cervical carcinomas, and 68% of vulvar malignancies and

Table 3. Recently completed, ongoing, and future phase III trials evaluating bevacizumab in treatment of gynecologic cancers

Trial	Site of disease	Drug regimens	Date
GOG 218(NCT00262847)	Primary advanced epithelial ovarian, peritoneal, and FT cancer	CBP + PTX vs CBP + PTX + bev vs CBP + PTX + bev then maintenance bev	Sept 2005 to Oct 2008
ICON-7 (NCT00483782)	Primary epithelial ovarian, peritoneal and FT cancer	CBP + PTX with and without bev then maintenance bev	Opened Apr 2006
GOG 213 (NCT00565851)	Platinum-sensitive recurrent ovarian peritoneal, and FT cancer	CBP + PTX with and without bev then maintenance bev	Opened Dec 2007
OCEANS (NCT00434642)	Platinum-sensitive recurrent ovarian cancer	CBP + GCB with and without bev	Opened Apr 2007
AURELIA (NCT00976911)	Platinum-resistant epithelial ovarian cancer	PTX + TPT + LD with and without bev	Opened Oct 2009
GOG 252 (NCT00951496)	Primary stage II-IV epithelial ovarian, peritoneal, and FT cancer	IV vs IP platinum + PTX with IV bev then maintenance bev	Opened Aug 2009
GOG 262	Epithelial ovarian cancer	Dose dense PTX with bev	Awaiting NCI clearance
GCIG (NCT01081262)	Stage II-IV or recurrent mucinous Epithelial ovarian and FT cancer	CBP + PTX with and without bev then Maintenance bev vs OX + CAP with and without bev then maintenance bev	Opened Jan 2010
GOG 240 (NCT00803062)	Stage IVB, recurrent or persistent Cervical cancer	CDDP + PTX with and without bev vs TPT/PTX with and without bev	Opened Apr 2009

Abbreviations: FT - fallopian tube; CBP - carboplatin; PTX - paclitaxel; bev - bevacizumab; GCB - gemcitabine; TPT - topotecan; LD - liposomal doxorubicin; IV - intravenous; IP - intraperitoneal; CDDP - cisplatin; OX - oxaliplatin; CAP - capecitabine

Table 4. Comparison of bevacizumab with VEGF Trap

Characteristic	Bevacizumab	Aflibercept
Molecule	Chimeric murine/human mAb	Fusion protein
Target	VEGF	VEGF, placental growth factor (PlGF)
T _{1/2}	21 days	25 days
FDA approval?	Yes, but not for gynecologic malignancies	No

is associated with advanced stage and poor prognosis (64-69). Initial *in vivo* studies of EGFR inhibitors showed increased chemo- and radiosensitivity of tumors (70, 71).

Cetuximab is a monoclonal antibody against EGFR that has improved survival in patients with head and neck and colorectal carcinoma (72, 73). This antibody has been tested in combination with carboplatin in patients with EGFR-positive recurrent epithelial ovarian cancer with a response rate of 35% (12% with complete response; Table 1) (74). A trial of cetuximab in combination with carboplatin and paclitaxel in patients with advanced ovarian or peritoneal cancer achieved a complete response of 70%, but 18 month progression-free survival was 38.8% and was not considered a meaningful improvement in outcome over expected activity of carboplatin and paclitaxel alone (75). GOG 76DD was a phase II trial that evaluated the addition of cetuximab to standard cisplatin therapy in women with advanced stage, persistent or previously untreated recurrent cervix cancer. Despite completing both stages of accrual, the combination was associated with increased toxicity and no additional survival benefit (76). Another phase II trial was stopped early due to toxicity while assessing the combination of cisplatin, topotecan, and cetuximab in patients with advanced squamous cell and adenocarcinoma of the cervix. Most of the patients receiving this therapy experienced grade 3 or 4 myelosuppression and three of nineteen patients died from treatment related toxicity (77). Erlotinib and gefitinib are tyrosine kinase inhibitors that block the EGF receptor. Erlotinib was tested as a single agent in patients with recurrent or metastatic endometrial cancer and found to have a 12.5% partial response rate. Forty-seven percent of the patients in this trial had stable disease for a median duration of 3.7 months (78). In GOG 227D,

erlotinib was tested in patients with recurrent squamous cell carcinoma of the cervix and found to be ineffective in stabilization or regression of disease (79). Gefitinib also yielded no objective response as a single agent in patients with advanced/recurrent cervical carcinoma (80). On the other hand, two case reports of single agent Tarceva, a small molecule EGFR inhibitor, in patients with vulvar carcinoma showed interesting clinical results (81).

Human epidermal growth factor receptor 2 (HER2) is also a membrane bound tyrosine kinase receptor in the same family as EGFR. Like EGFR, HER2 dimerizes upon activation to mediate cell survival, proliferation and angiogenesis. Approximately 5-23% of epithelial ovarian cancers and up to 44% of endometrial cancers overexpress HER2 (82-84). HER2 gene amplification has been found to directly correlate with poor clinical outcomes in many malignancies including breast and ovarian cancer (85). Trastuzumab is a humanized monoclonal antibody against HER2 that has been effective for the treatment of many patients with HER2 positive breast cancer (86, 87). In patients with recurrent or progressive epithelial ovarian cancer positive for HER2 overexpression, 7.3% achieved a clinical response with single agent trastuzumab, but only 95 of 837 patients screened positive for HER2 and only 41 patients were eligible for the study (88). The combination of trastuzumab with paclitaxel and carboplatin for patients with progressive advanced ovarian cancer had a complete response rate of 43%, however, only seven patients were included in the trial and only 22 of 321 patients screened showed positive HER2 gene amplification (89). Another recent trial observed no clinical response with single agent trastuzumab in patients with advanced or recurrent endometrial cancer and HER2 gene amplification (90).

VEGF targeted agents appear to have greater activity against cervical cancer than EGF, EGFR, and HER2 blocking agents. A phase II trial compared the two approaches head to head utilizing pazopanib, a tyrosine kinase inhibitor that blocks VEGFR and PDGFR, versus lapatinib, a tyrosine kinase inhibitor that targets EGFR and HER2 activity. Pazopanib was superior to lapatinib with improved progression-free and overall survival with minimal toxicity (91). In a multicenter phase II trial of bevacizumab in combination with erlotinib in patients with recurrent ovarian cancer, a response rate of 15% was noted, consistent with the response rate observed with bevacizumab alone (43). A randomized phase II clinical trial of vandetanib (dual VEGFR/EGFR inhibitor) followed by docetaxel *versus* vandetanib plus docetaxel is being launched through the Southwest Oncology Group (SWOG, S0904, NCT00872989).

Despite the apparent lack of activity of EGFR inhibitors in gynecologic cancer, there is rationale for further evaluation of these drugs. Given the high expression of EGFR in gynecologic malignancies and the increased sensitivity of tumors to other cytotoxic therapies when given in combination with EGFR inhibitors, further studies may prove highly beneficial. As illustrated by the discovery that KRAS mutations in colorectal tumors made them resistant to EGFR inhibition, continued strides toward effective oncologic treatment require a better molecular understanding of carcinogenesis.

4. POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS

There are a total of seventeen members of the poly (ADP-ribose) polymerase (PARP) family, of which PARP-1 and PARP-2 orchestrate repair of single-stranded breaks in DNA (92-94). These enzymes bind to DNA at the site of damage then initiate repair by ribosylation of nearby proteins, leading to base-excision repair at the site of damage and downstream effects on transcription and differentiation. Inhibition of PARPs *via* competitive blockade of the catalytic domain results in accumulation of DNA damage and cell death. BRCA1 and BRCA2 are tumor suppressor genes also important in DNA repair at sites of double-stranded breaks. Homologous recombination at DNA damaged sites is a high fidelity method of DNA repair mediated by Rad51, which is dependent on normal BRCA function (95). Mutations of BRCA genes force the cellular machinery to rely on lower fidelity methods of DNA repair and thus promote genomic instability. The initial studies of PARP inhibitors in BRCA deficient tumors noted that, though mutations in BRCA increased tumor sensitivity to certain cytotoxic therapies, PARP inhibition causes cell death in this population approximately three-fold over traditional treatment (96). By leaving single-stranded breaks unchecked by PARP inhibition, double-stranded DNA breaks are promoted in cells already lacking DNA repair capability, a process known as synthetic lethality. Normal cells with intact BRCA function will be able to repair their double-stranded DNA breaks, making tumor cells more susceptible to this treatment than normal tissue. Additionally, PARP

inhibition, itself, has been found to suppress expression of BRCA1 and Rad51 (97). Since the discovery of synthetic lethality in 2005, inhibitors of PARP have been studied in BRCA positive breast cancer and found not only to enhance the cytotoxic effects of chemotherapy and radiation, but also to improve outcomes when used as single agents (98).

PARP inhibitors are now being tested in patients with BRCA positive ovarian cancer. AZD2281 (olaparib) is an oral small molecule PARP-1 and PARP-2 inhibitor that was tested in two phase I trials. Among patients with BRCA mutations and ovarian carcinoma treated with olaparib, a response rate of 41-53% was noted (Table 1) (99, 100). A phase II study of AZD2281 in patients with BRCA positive recurrent ovarian cancer yielded a response rate of 33% at a dose of 400mg BID and 12.5% at a dose of 100mg BID (101). Side effects of olaparib include GI complaints, fatigue, and myelosuppression. Continued trials of AZD2281 and other PARP inhibitors alone and in combination with chemotherapy are ongoing in patients with BRCA positive and negative ovarian and primary peritoneal cancer. There are also newly developed PARP inhibitors such as ABT-888, MK4827 and BSI-201 currently being tested in gynecologic and non-gynecologic tumors.

The activity of PARP inhibitors may not be limited to patients with germline BRCA mutations. Approximately 50% of undifferentiated and high-grade serous ovarian cancers have loss of BRCA1 function (102). Many tumors have BRCA-like functional losses such as inactivation of BRCA genes or defects in other genes needed for BRCA-associated DNA repair that yield a clinical outcome similar to cancers with BRCA mutations (94, 103). There is also increasing evidence that PARP inhibitors enhance the cytotoxic effects of chemotherapy and radiation without regard to BRCA function (104-106). These alternative mechanisms of propagating cytotoxic DNA damage may expand the utility of PARP inhibitors to a substantial number of malignancies. PARP inhibitors are currently being tested in alone and in combination with chemotherapeutic agents, which may induce a vulnerable tumor homologous recombination phenotype, to evaluate the potential risks and benefits of these drugs among patients with impaired and normal BRCA function.

5. PTEN PATHWAY

The tumor suppressor gene PTEN (phosphate and tensin homolog detected on chromosome ten) is important for normal cellular function. Mutations in PTEN result in decreased apoptosis and are found in up to 83% of endometrioid carcinomas of the uterus (69). Decreased transcription due to mutation leads to decreased phosphatidylinositol 3-kinase (PI3K) inhibition, increased activity of Akt, and uncontrolled function of mTOR. Elevated activity of mTOR is seen in a vast majority of endometrial cancers as well as approximately 50% of cervical adenocarcinomas and 55% of ovarian carcinomas (107, 108).

Mammalian target of rapamycin (mTOR) is a kinase that regulates cell growth and apoptosis (64). Temsirolimus, deforolimus and everolimus are mTOR inhibitors that have been tested as single agents in phase II studies and found to promote stable disease in 44% of patients with metastatic or recurrent cancer of the endometrium (109, 110). Side effects of these drugs consisted mostly of myelosuppression, hyperlipidemia and fatigue. There are several trials of these and other mTOR inhibitors in combination with chemotherapeutic and hormonal therapies currently underway in endometrial cancer (64). GOG 170I, a phase II evaluation of temsirolimus in persistent or recurrent epithelial ovarian cancer, has also recently closed and results are pending (111). Several phase II trials have also been initiated in ovarian and cervical cancer to evaluate efficacy of these novel drugs.

6. EMERGING TARGETS

Greater appreciation and understanding of the tumor microenvironment and the interactions that provide a survival advantage for developing malignancy has sparked an explosion of investigation into novel drug targeting and tumor profiling. Some of the most interesting emerging targets function critically at convergent points of activated pathways or are expressed as treatment-evasive adaptations. Two promising molecular pathways, which may mediate cancer stem cell function and are implicated in many malignancies, are the Notch and hedgehog pathways. Each of these pathways regulates nuclear transcription and each is regulated by many different mediators (112, 113). Initial studies show overexpression of the Notch1 receptor in ovarian and endometrial cancer and the Notch3 receptor in squamous cell carcinoma of the cervix (114-117). The Hedgehog pathway, like the Notch pathway, is important to cellular proliferation and differentiation. Dysregulation of Hedgehog signaling components have been observed in ovarian, cervical and endometrial cancers (118-120). Several modulators of the Notch and Hedgehog pathways are currently under investigation in a variety of malignancies (121, 122). Further characterization of Notch and Hedgehog signaling is currently underway for gynecologic tumors and will likely identify several potential targets for cancer therapy.

Other drugs currently being studied that target tumor vasculature include AMG-386 and vascular disrupting agents. AMG-386 is an anti-angiogenic agent composed of an Fc bound peptide that interferes with normal angiopoietin interactions and was found to be well tolerated in phase I analysis (123). A phase II trial (NCT00479817) is currently underway to compare paclitaxel alone or in combination with AMG-386 in patients with advanced or recurrent epithelial ovarian, fallopian tube and peritoneal cancer. Vascular disrupting agents (VDAs) are drugs that occlude established tumor vessels by binding tubulin to alter cell shape, selectively inducing apoptosis in tumor endothelial cells leading to rupture of microvessels, and inducing chemotaxis of cytokines to cause vascular collapse (124). ASA404 (5,6-dimethylxanthone-4-acetic acid, DMXAA) is a VDA

flavonoid compound found in preclinical syngeneic colon cancer models to have a dose dependent reduction in perfusion up to 83% only four hours after treatment (125). Phase II trials in non-small cell lung cancer patients have shown improved response rates with ASA404 in combination with standard chemotherapy (126). Several trials are ongoing to evaluate ASA404 in patients with lung cancer and other solid tumors (NCT01031212, NCT00738387). Pre-clinical evaluation of AVE8062, also a VDA, showed decreased tumor growth and prolonged survival in ovarian cancer xenografts in nude mice (127). AVE8062 is currently undergoing phase I analysis as a single agent and in combination with standard chemotherapeutic treatments of solid tumors (NCT00968916, NCT00719524, NCT01021150, NCT01095302). Another VDA, combretastatin A-4 phosphate (CA4P), was tested in women with platinum-resistant ovarian cancer. When initiated within six months of last platinum chemotherapy, the combination of CA4P with carboplatin and paclitaxel showed a 32% partial response rate in this population (128). The response rate achieved in this phase II study was higher with the inclusion of CA4P than historically observed for treatment of platinum-resistant disease (129).

Several drugs that target the PI3K/Akt/mTOR pathway are being evaluated in gynecologic malignancies. NVP-BEZ235 and XL765 are dual PI3K and mTOR inhibitors, BKM120 and GDC-0941 are PI3K inhibitors and MK-2206 is an Akt inhibitor currently in phase I clinical trials (NCT00620594, NCT00485719, NCT01068483, NCT00876109, NCT00960960, NCT01071018, NCT00848718, NCT00670488) (130-132). There are also several tyrosine kinases, including ephrin type-A receptor-2 (EphA2), Src and focal adhesion kinase (FAK), that have been identified as poor prognostic indicators in gynecologic malignancies (133-137). Targeting these kinases has been found to significantly decrease tumor growth in pre-clinical models of ovarian cancer (138-140). Dasatinib is a multikinase inhibitor of EphA2, Src, FAK, c-kit and PDGFR-beta that has shown anti-tumor activity in patients with breast and prostate cancer (141). Dasatinib is currently being evaluated in combination with paclitaxel and carboplatin in a phase I trials of patients with advanced or recurrent ovarian, peritoneal, or fallopian tube cancer (NCT00672295).

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by decreasing mRNA expression. Over five hundred human miRNAs have been discovered (142). Given their alteration of mRNA levels in the cell, miRNAs are important to a diverse range of cellular processes and their aberrant expression is seen in many cancers. Numerous miRNAs have been found to have increased or decreased expression associated with histology, stage, response to chemotherapy, and survival in patients with gynecologic malignancies (143-149). Several preclinical studies in ovarian cancer have shown that regulation of miRNA expression can decrease tumor growth and sensitize tumor cells to chemotherapy (150). Targeting abnormalities in the miRNA transcriptome is currently a very exciting topic of cancer research.

Given the multitude and diversity of genetic abnormalities found in cancer cells, there are many potential molecular targets for therapy. Every year, new potential targets are identified and characterized. The pathways discussed in this review represent those most developed for targeted therapy of gynecologic malignancies. As our knowledge of tumorigenesis and the development of targeting agents grow, so will our ability to selectively kill tumor cells *in vivo*.

7. CONCLUSION

Over the last five to ten years, there has been rapid development and evaluation of molecularly targeted therapies in oncology. The goal of these endeavors is to identify agents against aberrant pathways common amongst specific tumors that can improve current treatments. Initial phase II trials show some promising results and large phase III trials are underway to confirm activity of these agents. There is concern that molecular targeting in treatment of cancer may provide evolutionary pressure to select for tumor cells that are highly resistant to therapy. Targeting multiple pathways of oncogenesis and using molecular inhibitors in combination with other cytotoxic treatments may overcome these selective processes to achieve higher cure rates for patients. Evolving knowledge regarding mechanisms of evasion of novel targeted treatments should lead to better combinations to surpass current standard therapy.

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permeability factor; VEGFR: vascular endothelial growth factor receptor; HPV: human papillomavirus; HIF: hypoxia-inducible factor; FDA: Food and Drug Administration; GOG: Gynecologic Oncologic Group; CT: computed tomography; GI: gastrointestinal; EGFR: epidermal growth factor receptor; EGF: epidermal growth factor; SWOG: Southwest Oncology Group; KRAS: v-Ki-ras2 Kristen rat sarcoma viral oncogene homolog; PARP: poly (ADP-ribose) polymerase; DNA: deoxyribonucleic acid; BRCA1: breast cancer susceptibility gene 1; BRCA2: breast cancer susceptibility gene 2; PTEN: phosphate and tensin homolog detected on chromosome ten; PI3K: phosphatidylinositol 3-kinase; mTOR: mammalian target of rapamycin; EphA2: ephrin type-A receptor-2; FAK: focal adhesion kinase; bev: bevacizumab; CPM: cyclophosphamide; GCB: gemcitabine; CBP: carboplatin; PTX: paclitaxel; CDDP: cisplatin; TPT: topotecan; LD: liposomal doxorubicin; OX: oxaliplatin; CAP: capecitabine

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Abbreviations: VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor; VPF: vascular