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Review Article

Exploring the Therapeutic Rationale for Angiogenesis Blockade in Cervical Cancer

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ABSTRACT

Purpose: This review highlights the molecular and pathologic evidence that cervical cancer is driven by angiogenesis and presents a summary of the recent clinical research in antiangiogenesis therapy for advanced cervical cancer with a focus on the use of bevacizumab.

Methods: The articles chosen for this review reveal the rationale for antiangiogenesis agents in cervical cancer from 3 perspectives: pathologic, molecular, and clinical data.

Findings: Several translational investigations have revealed that proangiogenic signaling cascades are active in cervical carcinogenesis and can be used to improve patient outcomes in advanced disease. For example, in a recently published study of patients with recurrent and metastatic cervical cancer, bevacizumab was the first targeted agent to improve overall survival in a gynecologic cancer when successfully combined with 2 different chemotherapy regimens.

Implications: Because of recent advances in screening, aggressive management of cervical intraepithelial neoplasia, and human papillomavirus vaccination, cervical cancer is preventable and curable with radical surgery plus lymphadenectomy surgery or chemoradiation plus brachytherapy if detected early. Unfortunately, for patients with metastatic or recurrent disease, effective therapeutic options are limited for this aggressive life-threatening condition. However, molecularly targeted agents have provided a critical opportunity to improve patient outcomes beyond optimizing cytotoxic chemotherapy regimens so that they may benefit from other agents or emergent therapies in the future. (*Clin Ther*. 2015;37:9–19)

Key words: angiogenesis, bevacizumab, recurrent cervical cancer, therapeutic rationale, anti-angiogenesis therapy.

INTRODUCTION

Since the 1950s widespread use of cervical cytologic testing has been successful in markedly reducing the incidence and mortality of cervical cancer in developed countries and is recognized as one of the greatest cancer prevention achievements to date. In patients with abnormal cervical cytologic test results, one of the hallmarks of invasive disease is vascular aberrations. Mosaicism, punctuations, and atypical vessels are all vascular markings that can be identified colposcopically and are indicative of angiogenesis. Angiogenesis is the process of formation of new blood vessels in the body, which is fundamental in the growth of new tissues, wound healing, and embryogenesis, but is also essential for tumor proliferation, invasion, and metastasis.[1] Neovascularization in cervical tumors is indicative of aggressive clinical behavior and poor prognosis.[2]

PATHOLOGIC EVIDENCE IN SUPPORT OF ANGIOGENESIS-DRIVEN CERVICAL CARCINOMA

Several key translational studies have reported the association between markers of angiogenesis and prognosis in cervical cancer. Cooper et al[3] assessed

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intratumoral microvessel density (MVD) in 111 patients with locally advanced cervical cancer and found that higher tumor vascularity was associated with lower overall survival (OS) and locoregional control after treatment with pelvic irradiation. Similarly, Obermair et al[4] reported enhanced 5-year survival with lower MVD ($\leq$20 per high-power field) of approximately 90% compared with 63% with higher MVD in 166 patients with stage IB cervical cancer; MVD identified patients with early-stage disease with negative nodes at high-risk for relapse. Angiogenesis appears to be an early event in premalignant changes of the cervix from high-grade cervical intraepithelial neoplasia, and MVD increases significantly with malignant transformation, suggesting it is a prerequisite for the development of invasive cancer.[5–7] Other authors have confirmed that cervical carcinomas characterized by strong staining for the endothelial marker CD31 (immunohistochemistry [IHC] marker used to measure degree of tumor angiogenesis) and increased MVD are correlated with worse survival.[8,9]

In contrast to earlier studies, a prospective analysis performed 10 years later examined CD31 MVD in patients who received cisplatin-based chemotherapy along with adjuvant radiation after radical hysterectomy in high-risk patients. Increased tumor angiogenesis as reflected by CD31 MVD was an independent prognostic factor for improved progression-free survival (PFS) and OS. This observation was attributed to improved delivery of oxygen, nutrients, and cytotoxic chemotherapy to well-vascularized and oxygenated tumors.[10] The vasculature associated with $CD31^+$ endothelial cells tends to be more organized and may result in less tumor hypoxia, whereas endoglin, or CD105 (coreceptor for transforming growth factor-β), enriched endothelial cells are disorganized and $CD105^+$ MVD is associated with an increased relative risk of treatment failure.[11] Observed differences in survival and pathologic tumor features may be related to the progression and stages of angiogenesis.

Investigation of several other pathologic features and IHC staining of cervical tumors led to the description of other potentially clinically relevant biomarkers that may be correlated with prognosis and metastatic spread (**Table I**). For example, there is evidence that CD40 is overexpressed in cervical cancers positive for human papillomavirus (HPV)-16 and -18 and is associated with neovascularization via vascular endothelial growth factor (VEGF)–induced angiogenesis. CD40 expression also correlates with lymphatic metastasis.[12] Researchers have proposed that CD40 staining is a useful biomarker for evaluating the risk of developing cervical malignant tumors and better understanding the immune response against these tumors and may provide a potential target for future research in immunotherapy. In addition, maspin is another example of a clinicopathologic biomarker that has been studied and is predictive with regard to the correlation between tissue expression of maspin and prognosis in squamous cell cervical carcinomas. Maspin (a member of the serine protease inhibitors) has an inhibitory effect on angiogenesis and is thought to be potentially implicated in lymphangiogenesis in cervical cancer. Liu et al[13] found that cytoplasmic and nuclear expression of maspin is significantly weaker in squamous cell carcinomas compared with high-grade dysplasia and normal cervical specimens. Subcellular expression of maspin was significantly decreased or absent in the presence of high-lymphatic MVD, advanced clinical stage, and lymph node metastases.

Therefore, given the prominence of vascular aberrations and prognostic significance in cervical cancer, active agents that mediate angiogenesis were expected to aid in the development of more effective treatments. However, a more thorough molecular characterization of cervical cancer remains crucial to the development of tolerable and effective biologic therapies.

A MOLECULAR CASCADE LINKING VIRAL ONCOGENE EXPRESSION AND VEGF-DEPENDENT ANGIOGENESIS

One frequently studied candidate for biologic therapies involves the VEGF signaling pathway because it is one of the major drivers of angiogenesis in cervical cancer. Dobbs et al[5] established that VEGF receptor expression is correlated with MVD in cervical carcinomas. In addition, persistent infection with the oncogenic subtypes of HPV increases angiogenic potential in tumors through upregulation of VEGF. By all accounts, this is an early event in the stages of carcinogenesis from chronic HPV infection or cervical intraepithelial neoplasia to invasive cancer.[15,25] There is a wide range of cellular factors and pathways that have been linked to HPV genomic integration and downstream effects on targets that promote angiogenesis in cervical tumors, thus permitting neovascularization and enabling tumors to acquire the blood supply required for permissive growth and spread.[26]

Table I. List of candidate genes and proteins of interest related to angiogenesis and endothelial cell markers as prognostic indicators in cervical carcinoma.

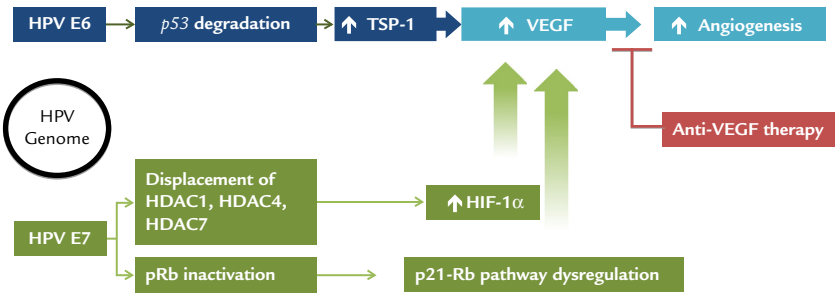
Molecular Target (Gene/Protein/Biomarker)	Pathologic and/or Prognostic Significance in ICC
Adrenomedullin	Proangiogenic peptide upregulated in ICC, target of miR-126
CD31	Endothelial marker associated with MVD in ICC and prognostic for PFS/OS[10]
CD40	Endothelial marker overexpressed with HPV-16/18+ ICC, associated with lymphatic metastasis and neovascularization[12]
CHI3L1	Overexpression of secreted glycoprotein correlates with prognosis and metastasis in ICC[14]
Colony-stimulating factor receptor	Proto-oncogene present in most ICC and absent in normal cervix, stimulates VEGF-mediated angiogenesis, and involved in carcinogenesis[15]
COX-2	COX-2 inhibition attenuated VEFG-C expression, potent mediator of lymphangiogenesis[16]
Endoglin (CD105)	Angiogenesis marker, highest in peritumoral areas, and correlated with VEGF and EGFR overexpression[17]
Fibulin-4	Glycoprotein upregulated in ICC, promotes angiogenesis and associated with poor clinicopathologic characteristics[18]
Maspin	Tumor suppressor implicated in lymphangiogenesis and metastasis[13]
miR-126	Micro-RNA involved in angiogenesis and vascular integrity, downregulated[19]
Tc17 (cytotoxic T cells and IL-17)	Infiltration by IL-17–producing T cells in ICC correlated with lymph node metastasis and MVD[20]
TSP-1	Antiangiogenesis factor that may regulate the angiogenic switch between CIN and ICC, mixed data on prognostic significance[10,21,22]
Tissue factor pathway inhibitor	Serine protease inhibitor implicated in apoptosis, angiogenesis, and progression of ICC[23]
Transforming growth factor-β1	Prognostic marker, strong expression associated with worse survival in $CD105^{+}$ tumors[11]
Vasohibin	Angiogenesis inhibitor and potential marker, endothelial cell expression correlated with VEGFR-2 in ICC[24]

CIN = cervical intraepithelial neoplasia; COX = cyclooxygenase; EGFR = epidermal growth factor receptor; HPV = human papillomavirus; ICC = invasive cervical cancer; IL = interleukin; MVD = microvessel density; OS = overall survival; PFS = progression-free survival; TFPI = tissue factor pathway inhibitor; TSP = thrombospondin; VEGFR = vascular endothelial growth factor receptor.

HPV-16 and -18 are responsible for the overwhelming majority of cervical cancer, and one of the key steps in carcinogenesis involves integration of the HPV genome and host DNA. The responsible intermediaries, E6 and E7, are the only HPV gene products that are consistently retained in invasive cervical cancers and are responsible for the transformation and maintenance of the immortalized malignant phenotype caused by ongoing infection.[27] E6 and E7 code for proteins that knock out cellular (host) tumor suppressor gene products, leading to several alterations in molecular signaling cascades that ultimately induce VEGF-dependent angiogenesis. The transcriptional repression of these viral oncogenes by E2, an HPV-related

gene product, is disrupted during the process of viral integration. Consequently, E6 and E7 are expressed, permitting transcription of certain oncoproteins that interact with other gene products to have 2 important effects: *p53* degradation and pRb inactivation, respectively. The proangiogenic signals that result from these molecular signaling changes after integration of high-risk HPV genomes into host cellular chromosomes are given in Figure 1. After DNA damage, HPV E6 proteins block the induction of *p53*, preventing the cell from going into cell cycle arrest to allow DNA repair and aborting programmed cell death or apoptosis and thus allowing continued cellular proliferation. E6 expression can promote ubiquitination of *p53*, leading to rapid proteasomal protein degradation. In some cases, certain polymorphisms bind more ardently with oncogenic HPV E6.[2] Individuals with HPV who carry the Arg variant (Arg 72) are an example of how this particular polymorphism increases the likelihood of progression from cervical intraepithelial neoplasia to invasive cancer compared with the Pro variant (Pro72).[28] E7-driven cell cycle progression that results from abrogation of pRb function has the opposite effect from E6 by potentiating apoptosis through upregulation of the *p53* pathway. The induced changes in several angiogenesis mediators that are regulated by *p53* are differentially affected by the expression of E6 and E7. Thromobospondin-1 and maspin are angiogenesis inhibitors that are normally positively regulated by *p53* but are decreased in cells that express E6 and E7. Conversely, VEGF (angiogenesis inducer), which is usually negatively regulated by *p53* via the transcription factor hypoxia inducible factor (HIF)-1α, is upregulated.[26] In addition, HPV E6 and E7 independently enhance the induction and stabilization of HIF-1α in *in vivo* models.[29] The oncogenes again have different mechanisms of achieving similar effects. HPV E7 increases HIF-1 transcriptional activity, but E6 counteracts the repression of HIF-1 through the *p53* pathway.[30] Furthermore, E7 enhances HIF-1–mediated transcription by inhibiting binding of histone deacetylases and promoting angiogenesis.[30] HIF-1α is a transcription factor that controls the expression of >40 different genes that encode various cytokines and growth factors involved in angiogenesis, including VEGF. Induction and stabilization of HIF-1α can be accomplished by viral oncogenes, as described here, through dysregulation of tumor suppressor genes or invoked by other mechanisms in response to environmental stressors such as hypoxia. As tumors grow beyond their existing blood supply and decreased oxygen tension is encountered, changes in gene expression are triggered which support angiogenesis and may be independent of the effects of HPV E6 and E7.

Both oncogenes have a wide range of other targets that are not completely understood. However, the cumulative results of these modifications in gene transcription, protein function, and the tumor microenvironment



Abbreviations: HDAC, histone deacetylase; HIF1α, hypoxia-inducible factor 1-alpha; HPV, human papilloma virus; pRb, retinoblastoma protein; TSP1, thrombospondin 1; VEGF, vascular endothelial growth factor.

Figure 1. Proposed mechanism of human papillomavirus (HPV) infection and the rationale behind angiogenesis inhibitor therapy. HDAC = histone deacetylase; HIF-1α = hypoxia-inducible factor-1α; TSP-1 = thrombospondin-1; VEGF = vascular endothelial growth factor.

ultimately lead to increased VEGF and increased angiogenesis potential. Overexpression of VEGF has been associated with cancer progression and poor prognosis in many malignant tumors, including cervical carcinoma. Therefore, the rationale for antiangiogenesis therapy in cervical cancer stems from the association of VEGF, pathologic neovascularization, and the development of invasive disease.

However, other molecular alterations contribute to the progression of cervical carcinogenesis beyond HPV infection alone because only a small proportion of these cases will progress to invasive cancer. Other genetic and environmental factors must play an important role in the balance between activating oncogenes and inhibiting the function of tumor suppressor genes. For example, researchers have been able to characterize several polymorphisms within the VEGF gene that not only affect angiogenesis but also influence survival and susceptibility to cervical cancer. This study compared 4 different VEGF genetic polymorphisms in the promoter region that could affect VEGF protein production or function (−2578C>A, −460 T>C, +405 G>C, and +936 C>T) in 215 patients without cervical cancer and 199 patients with cervical cancer who underwent surgery.[31] The VEGF −2578 C>A genotype was associated with a decreased risk of cervical cancer (adjusted odds ratio = 0.39; 95% CI, 0.16–0.96). CD31 MVD was used as a marker for angiogenesis and was significantly decreased in patients with the VEGF +405C/C genotype. In addition, decreased CD31 MVD was an independent risk factor for disease recurrence, and CD31 MVD was significantly associated with disease-free survival (adjusted hazard ratio [HR] = 0.23; 95% CI, 0.06–0.92). After controlling for other clinical prognostic factors, such as stage, tumor size, depth of invasion, lymphovascular space invasion, and adjuvant treatment, VEGF +405 G>C played a detrimental role in patients with cervical cancer based on Cox regression analysis. The VEGF +405C/C and VEGF −2578C, −460 T, +405C haplotypes were significantly related to shorter disease-free survival (adjusted HR = 3.18; 95% CI, 1.13–8.94) and OS (adjusted HR= 8.86; 95% CI, 1.40–56.08). These findings suggest that genetic polymorphisms are capable of modulating angiogenesis in tumors and thus may affect response to treatment and survival in early cervical cancers.

In summary, translational investigations have found that proangiogenic signaling cascades are active in cervical carcinogenesis. Molecular alterations that upregulate proangiogenic factors, such as VEGF, platelet derived growth factor, and other small molecules, have been correlated with advanced refractory disease and poor survival but also present exciting opportunities for the development of therapeutic interventions.

CLINICAL RAMIFICATIONS OF ANGIOGENESIS INHIBITION IN ADVANCED DISEASE

This body of translational work has established biological plausibility to justify the investigation of angiogenesis inhibitors in cervical cancer on both a molecular level and a clinicopathologic basis. VEGF-mediated angiogenesis is so critical to carcinogenesis in cervical cancer it follows therefore that disruption of this pathway with molecularly targeted agents may be useful in retarding tumor growth, progression, and metastasis or perhaps even eliminating small volume residual disease. Furthermore, antiangiogenesis agents are efficacious in other solid malignant tumors with similar tumor biology, such as non–small cell lung cancer. Bevacizumab is the most studied agent in gynecologic neoplasms and other solid tumors.

Bevacizumab is an anti-VEGF monoclonal antibody that blocks tumor angiogenesis by binding and inactivating VEGF and thereby inhibiting endothelial cell activation and proliferation, thus denying tumors the ability to recruit new vessel development. Bevacizumab also counteracts the survival (antiapoptotic) signaling that supports the immature vasculature usually associated with neoplastic growth and prevents constant endothelial remodeling required for local tumor spread, thus restoring normal structure and function to disorganized, highly permeable vessels typically seen in malignant tumors.[32] It is currently approved by the US Food and Drug Administration (FDA) for use in the management of non–small cell lung cancer, renal cell carcinoma, colorectal cancer, and, most recently, recurrent cervical cancer.

On the basis of the available literature, the use of cisplatin-based combination chemotherapy has been widely adopted as the standard treatment backbone in cervical cancer. Unfortunately, responses to chemotherapy are usually temporary, with median durations typically lasting 3 to 6 months.[33] More than 90% of the deaths attributed to cervical carcinoma occur within 5 years after diagnosis. Chemotherapy for recurrence is essentially palliative because effective

salvage therapies are lacking. This finding underscores the need for more effective treatment strategies for this clinical scenario. To improve the current management paradigm, researchers have developed therapeutic strategies that incorporate biologic agents with standard treatments. In a small case series, bevacizumab exhibited activity in patients with recurrent cervical carcinoma when combined with cytotoxic chemotherapy.[34]

The first prospective Phase II trial of bevacizumab in cervical cancer was conducted through the cooperative research network led by the Gynecologic Oncology Group (GOG). GOG 227C was a multicenter Phase II study of bevacizumab monotherapy that revealed the tolerability and efficacy of the drug in heavily pretreated patients with recurrent cervical cancer—bevacizumab performed even better than expected particularly compared with other historical control groups in this setting.[35] Subsequently, other agents with antiangiogenic activity have also been studied in advanced and recurrent cervical cancer, including oral tyrosine kinase inhibitors. Pazopanib (targets VEGF receptor, platelet-derived growth factor receptor, and c-kit) and lapatinib (dual anti–epidermal growth factor receptor and anti-HER2/neu) were studied in a Phase II trial comparing pazopanib (800 mg/d) or lapatinib (1,500 mg/d) monotherapy versus combination therapy with both drugs; however, the combination therapy treatment arm was closed for futility and imbalanced toxic effects after the first interim analysis.[36] This head-to-head comparison revealed the superiority of antiangiogenesis over anti-EGF therapy. Pazopanib improved PFS compared with lapatinib (4.5 vs 4.3 months; HR = 0.66; 90% CI, 0.48–0.91; $P < 0.013$) but did not result in an OS benefit (12.4 vs 11 months; HR = 0.67; 90% CI, 0.46–0.99; $P = 0.045$). The study provides additional support for pursuing further investigations of anti-VEGF treatments in cervical cancer, but unfortunately epidermal growth factor receptor–based therapies, such as cetuximab and erlotinib, have resulted in several negative clinical trials (data not shown).

The newest Phase II study of another angiogenesis inhibitor was recently presented at the annual meeting of the European Society for Medical Oncology in September, 2014. Cediranib is a once-daily oral tyrosine kinase inhibitor that was used in combination with a conventional chemotherapy in patients with metastatic or recurrent cervical cancer. Sixty-nine patients were randomized to receive carboplatin (AUC = 5) and paclitaxel (175 mg/m^2) every 21 days plus either 20 mg of cediranib or a placebo daily.[37] The results revealed a statistically significant improvement in median PFS with chemotherapy plus cediranib compared with placebo (35 vs 30 weeks; HR = 0.61; 80% CI, 0.41–0.89; $P = 0.046$). The median change in serum VEGF inhibition was also significantly improved with cediranib, and toxic effects appeared on par with other similar biologic agents. Overall, on the basis of reported results, cediranib appears tolerable and active in advanced cervical cancer. The study was not intended or powered to assess OS, but further investigation with a larger Phase III trial is warranted. Table II provides a summary of 3 prospective Phase II clinical trials that feature VEGF-based therapies in advanced or recurrent cervical cancer.

The first Phase III randomized clinical trial of antiangiogenesis therapy in cervical cancer was initiated by the GOG and cosponsored by the National Cancer Institute to study the combination therapy of bevacizumab and standard cytotoxic chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer. GOG 240 was designed to address 2 critical issues in this setting—the effectiveness of antiangiogenesis therapy and the effectiveness of nonplatinum-based chemotherapy doublets. A 2 × 2 factorial design was used to answer the biologic/antivascular hypothesis and the chemotherapy question of whether a nonplatinum doublet would have greater activity in the recurrent disease population. This was an important question because of the concern for possible platinum drug resistance given the widespread adoption of platinum-based chemoradiation in the primary treatment of locally advanced cancer with >70% of the patients in each group having had prior exposure to cisplatin.

Consequently, patients were randomized to receive 1 of 4 regimens: cisplatin (50 mg/m$_2$) plus paclitaxel (135 or 175 mg/m^2) with or without bevacizumab (15 mg/kg) or topotecan (0.75 mg/m^2 on days 1 through 3) plus paclitaxel (175 mg/m^2) with or without bevacizumab (15 mg/kg) with cycles repeated every 21 days until disease progression or unacceptable toxic effects occurred. The results confirmed that the topotecan/paclitaxel chemotherapy doublet was not superior to cisplatin/paclitaxel (median OS of 12.5 vs 15 months; HR = 1.20; 99% CI, 0.82–1.76;

Table II. Phase II studies of VEGF-based therapies in metastatic or recurrent cervical malignant tumors.

Study	Design	Response Rate	PFS, Median (Range)	OS, Median (Range)	Toxic Effects
GOG 227C[35]	Bevacizumab monotherapy 15 mg/kg q21d (n = 46)	PR = 10.9% PFS ≥6 mo = 23.9%	3.4 mo (2.5–4.5 mo)	7.3 mo (6.1–10.4 mo)	Common grade 3/4 AEs: HTN (n = 7), VTE (n = 5), and GI (n = 4); grade 5 infection (n = 1)
VEG105281[36]	Pazopanib monotherapy 800 mg once daily (arm P; n = 74)	Arm P = 9%	18.1 wk (4.5 mo)	50.7 wk (12.7 mo)	Common AEs: diarrhea (54% vs 58%; grade 3 = 11% vs 13%); nausea (36% vs 33%), HTN (30% vs 3%), anorexia (28% vs 32%), any grade 4 (12% v 9%) for arm P vs arm L
	Lapatinib monotherapy 1500 mg once daily (arm L; n = 78)	Arm L = 5%	17.1 wk (4.3 mo)	39.1 wk (9.8 mo)	
	Combination therapy (discontinued for futility and unacceptable toxic effects)		HR = 0.66 (95% CI, 0.48–0.91)	HR = 0.67 (95% CI, 0.46–0.99)	
CIRCCa[37]	Carboplatin/paclitaxel and cediranib 20 mg/d (arm C; n = 34)	Arm C = 66%	35 wk (8.8 mo)	59 wk (14.8 mo)	Grade 2 to 4 AEs: diarrhea (50% vs 18%), HTN (34% vs 12%), any grade (19% vs 9%) for arm C vs arm Z
	Carboplatin/paclitaxel and placebo (arm Z; n = 35)	Arm Z = 42%	30 wk (7.5 mo) HR = 0.61 (95% CI, 0.41–0.89)	63 wk (15.8 mo) HR = 0.93 (95% CI, 0.64–1.36)	

AE = adverse event; CIRRCa = cediranib for advanced cervical cancer; GI = gastrointestinal; GOG, Gynecologic Oncology Group; HR = hazard ratio; HTN = hypertension; OS = overall survival; PFS = progression-free survival; PR = partial response; VEGF = vascular endothelial growth factor; VTE = venous thromboembolism.

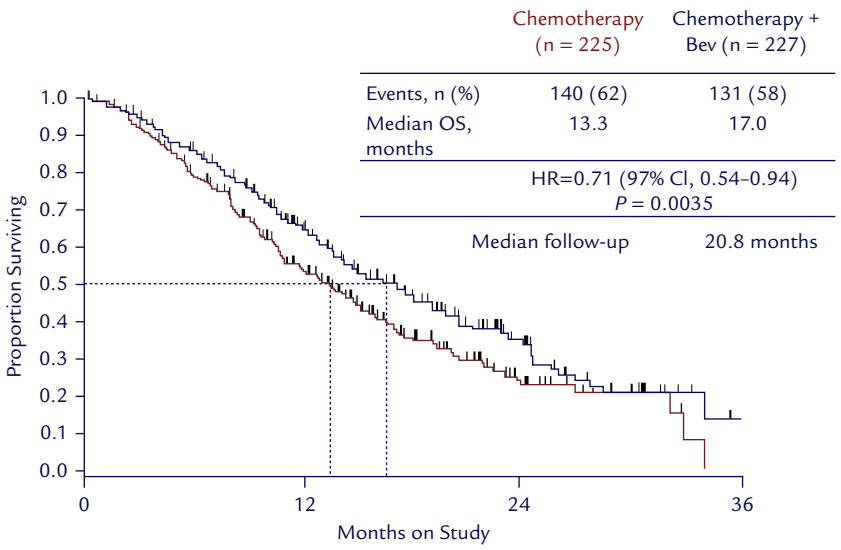


Figure 2. Gynecologic Oncology Group 240 results: overall survival curve. HR = hazard ratio; OS = overall survival. Copyright Massachusetts Medical Society. Adapted with permission from the New England Journal of Medicine.[28]

$P = 0.88$).[38] The final analysis revealed superior outcomes when bevacizumab was added to either chemotherapy regimen, leading to an HR for death of 0.71 (97.6% CI, 0.54–0.94; $P = 0.0035$). The survival curves are given in Figure 2. The median OS for patients who received cisplatin plus paclitaxel was 14.3 months, significantly less than the 17.5 months for those who received cisplatin, paclitaxel, and bevacizumab ($P = 0.0348$). In parallel, the median OS for those who received topotecan plus paclitaxel was lower compared with when bevacizumab was added to that regimen (12.7 months compared with 16.2 months respectively; $P = 0.09$). GOG 240 is a landmark trial because it is the first time that a targeted agent has reached its primary end point of improving OS in a gynecologic malignant tumor.

Bevacizumab was also established as a triple-threat after publication of GOG 240. In addition to achieving the clinical benefit gold standard in oncology trials (prolonged OS), patients who received bevacizumab also had improved PFS (HR = 0.67; 95% CI, 0.54–0.82; $P = 0.0002$) and higher response rates than controls (48% vs 36%; $P = 0.008$). Twenty-eight patients who received bevacizumab had complete responses compared with 14 in the control groups. Even patients with disease contained within a previously irradiated pelvis experienced sustained clinical benefit from bevacizumab.[38]

As with any other experimental regimens, the benefits must outweigh the risks of treatment. Bevacizumab was associated with a reasonable toxicity profile that is similar to previous studies with this drug. The overall rate of serious adverse effects associated with bevacizumab-containing regimens was <10% in GOG 240. As expected from previous reports, treatment-related toxic effects observed with the incorporation of bevacizumab included mainly thromboembolism (8%) gastrointestinal or genitourinary fistulas (6%), and hypertension (25%). No new toxic effects of bevacizumab were identified, and no deterioration in health-related quality of life was reported by patients receiving bevacizumab.[38] After GOG 240 it is critical that all health care professionals and patients are educated about these findings to ensure that all women with persistent, recurrent, or metastatic cervical cancer who may benefit from bevacizumab are appropriately counseled about the risks and benefits of adding bevacizumab to standard chemotherapy. Individual treatment decisions should be made on a case-to-case basis and take into account prior treatment history, medical comorbidity, functional status, predisposition to certain toxic effects, and quality of life. Appropriate patient selection, close clinical monitoring, and cautious attention to the management of treatment-related adverse effects will optimize efficacy and tolerability.

The National Cancer Institute issued a practice changing press release after the initial results from GOG 240 were presented at the American Society of Clinical Oncology annual meeting in June 2013 in support of bevacizumab for late-stage cervical cancer.[39] In July 2013, the National Comprehensive Cancer Network updated their practice guidelines for cervical cancer treatment to include the cisplatin-paclitaxel-bevacizumab triplet as Category 2A (and would ultimately list both triplet regimens as Category 1 in August 2014).[40] Attaining expeditious FDA approval was a crucial step in enhancing the care of women with invasive cervical cancer because this regulatory milestone is required for coverage under Medicare and Medicaid. In less than 4 months after filing under the FDA's priority review program, in August 2014 bevacizumab became the first biologic agent approved for use in patients with late stage cervical cancer and was the first drug approved in this patient population since 2006.[41] This overwhelming and rapid response is a reflection of the importance of successfully addressing a historically unfulfilled clinical need.

FUTURE DIRECTIONS

The excitement created with publication of GOG 240 will promote the continued study of other classes of antiangiogenesis inhibitors in recurrent or even front-line therapy for cervical cancer. The observed benefits associated with several antiangiogenesis agents in the aforementioned Phase II and Phase III trials merit additional investigation to further refine the most appropriate regimen for this population with tolerable toxic effects. Moving forward, confirmatory Phase III clinical trial proposals should include multifactorial study designs that combine conventional chemotherapy backbones with known active biologic agents, including carboplatin or cisplatin/paclitaxel/bevacizumab with or without cediranib or pazopanib.

Unfortunately, despite the proven efficacy of antiangiogenesis therapy in cervical cancer, disease recurrence is still problematic for these women. Most patients diagnosed as having locally advanced or metastatic cervical cancer will experience disease recurrence. Historically, this disease is often refractory to chemotherapy, resulting in disappointing responses to salvage therapies. However, if patients are living longer with antiangiogenesis therapy, there will be an increasing demand for second- and third-line therapies moving forward, resulting in an unmet clinical need for alternative agents and new treatment paradigms for this disease in the future. Molecularly targeted drugs are needed to exploit other relevant signal transductions pathways to disrupt the highly integrated tumor microenvironment, and immune system modulation will be critical to achieving improved oncologic outcomes for women affected by invasive cervical cancer.

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CONFLICTS OF INTEREST

Dr Tewari has reported working as a consultant for Roche/Genentech, Caris, and Advaxis; serving on the advisory board of Roche/Genentech, Caris, Advaxis, Vermillion; serving on the speaker's bureau of Vermillion; and performing contracted research for Genentech, Amgen, Endocyte, and Astra-Zeneca. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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