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]