The Context of Blood Vessels and Response to VEGF-Targeted Therapy

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Although therapy directed against VEGF has produced clinical benefit, an understanding of responsive tumor characteristics is lacking. Blood vessel location relative to tumor cells and stromal factors may influence tumor susceptibility to VEGF-targeted therapy. Clinical validation of this potential biomarker is needed to influence clinical practice. Clin Cancer Res; 19(24); 6647–9. ©2013 AACR.

In this issue of Clinical Cancer Research, Smith and colleagues report on the association of vascular architecture and stromal elements to (i) historic response to VEGF blockade in human tumor types, (ii) response to a VEGFR-2–blocking antibody in preclinical models, and (iii) outcome to bevacizumab plus chemotherapy in a cohort of patients with metastatic colorectal cancer (1). Therapy targeting tumor-associated blood vessels, to date largely directed against the VEGF pathway, has produced a spectrum of success and failure in oncology therapeutics. Inhibition of VEGF ligand or receptor has resulted in antitumor effects across a wide variety of solid tumors, with single-agent activity noted in renal cell carcinoma, hepatocellular carcinoma, thyroid cancer, and glioblastoma multiforme. Additional tumor types are minimally susceptible to VEGF inhibition alone, but clinical benefit is observed in combination with standard chemotherapy as in colorectal cancer and lung cancer. However, the hypothesis that targeting tumor angiogenesis would produce vast and durable control in all malignancies is not supported by the clinical data. No antiangiogenic therapy is currently considered curative, and thus ongoing therapy producing ongoing toxicity is required. Furthermore, innate or adaptive resistance is ultimately observed in all tumors. The mechanisms of this resistance and the most beneficial clinical action in this circumstance are undefined.

Attempts to select tumors for sensitivity to VEGF-targeted therapy emerged almost simultaneously with drug development (2). Initial attempts to look at tumor and/or circulating VEGF/related proteins did not find clinically relevant associations, outside of the adverse prognostic value of high VEGF levels (3). Additional retrospective analyses have identified treatment-induced hypertension as associated with outcome after VEGF inhibition across a wide variety of tumor types, but this does not help the practicing clinician select tumors for responsiveness before therapy (4). Pharmacogenomic alterations have also been studied, which in theory may allow for pretreatment selection for or against a specific therapy, but to date no associations have been reported that have meaningfully altered the clinical approach to patients (5). Similarly, tumor enhancement changes on contrast computed tomography have been associated with outcome in retrospective series (6), but again this requires treatment of all patients initially and makes a determination of “sensitivity” after a period of treatment, often when a patient’s clinical status or tumor size compared with baseline is already revealing.

The authors examined human and xenograft tumors and characterized different vascular phenotypes using hematoxylin and eosin (H&E) and CD31 staining of both full tumor sections and tissue microarrays. They defined a tumor-vessel phenotype as a tumor in which vessels are embedded throughout the tumor cells, and defined a stromal-vessel phenotype as one in which the stromal areas contained the majority of vessels and are distinct from tumor cell nests (Fig. 1). Characterization of human tumor types (from primary tumor samples) revealed that tumors with demonstrated sensitivity to single-agent VEGF-targeted therapy (renal cell carcinoma, hepatocellular carcinoma, thyroid cancer, and glioblastoma multiforme) were predominantly of the tumor-vessel phenotype, whereas tumor types in which single-agent VEGF-targeted therapy had limited activity (colorectal cancer, non–small cell lung cancer, prostate cancer, and breast cancer) were predominantly of the stromal-vessel phenotype. A panel of human tumor xenografts was then analyzed with 30 of 31 xenografts exhibiting the tumor-vessel phenotype, and the lone stromal-vessel phenotype xenograft (Calu-3) enriched in genes associated with stromal cell recruitment such as fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF). Anti-VEGFR-2 antibody administered to different xenografts demonstrated effects on endothelial cells in both...
phenotypes (as evidenced by endothelial cell gene changes in the stroma in both models), but differential effects on the tumor (as evidenced by different human/tumor gene changes and different tumor growth curves). Thus, a hypothesis is generated that the effect on the endothelial cell of blocking VEGF is relatively constant across tumor types, but the anatomic distribution of blood vessels relative to tumor cells (embedded vs. not) and other stromal factors (e.g., pericytes and myofibroblasts) do not allow for the antivessel effect of VEGF blockade to meaningfully affect the tumor cell kinetics in stromal-vessel tumors. It is notable that a single xenograft displayed an stromal-vessel phenotype. This may in part explain the plethora of positive preclinical data supporting an antitumor effect of VEGF-targeted therapy (because most xenografts were of the tumor-vessel phenotype and thus more sensitive to VEGF inhibition), but a much smaller number of the corresponding human tumor types sensitive to single-agent VEGF blockade.

The clinical implication of these data is that tumor-associated blood vessels may need to be embedded within a tumor (and with fewer associated stromal cells such as pericytes) to respond to single-agent therapy targeting VEGF. With further investigation and validation of this hypothesis in clinical/tumor datasets, examination of tumors before starting therapy could allow for choosing VEGF therapy for a specific tumor (and not just tumor type). Additional investigation, however, is needed to answer several lingering questions before these data can be applied to clinical practice. It would be useful to know if the stromal-vessel phenotype correlates with primary refractory disease, as the authors suggest in a small cohort of patients with colorectal cancer treated with bevacizumab plus chemotherapy, so that futile therapy can be avoided. Also, will the association of vessel phenotype and response persist in the clinic with single-agent anti-VEGF therapy or with anti-VEGF agents other than a VEGFR-2–blocking antibody? Intratumoral vessel phenotype heterogeneity and differences in the vessel phenotype of the primary tumor versus metastatic sites are of high interest. Furthermore, whether the vessel phenotype can change over time and thus signify a potential mechanism of resistance is unknown. Of special note is the previously reported association of treatment-induced hypertension and clinical outcome of VEGF-targeted therapy in this context. One hypothesis to explain that association is that the “susceptibility” of blood vessels to hypertension is a reflection of blood vessel susceptibility to VEGF blockade. The present study identifies the physical location of vessels and stromal elements as influencing the antitumor effects of VEGF blockade, and thus the association of vessel/stromal characteristics and a hypertensive response to VEGF blockade and could be tested in mouse models and humans to link these phenomena.

Multiple factors influence the antitumor effect of a given therapy. The ideal biomarker is easily tested, unambiguous and clearly directs therapy toward or away from a particular agent or class of agents. Although not at present ready for utility in the routine care of patients with cancer, the data by Smith and colleagues provide intriguing insight into a new potential biomarker for response to VEGF-targeting therapy. Application of this technology to larger data sets from prospective clinical trials of VEGF-targeted agents across a variety of malignancies is the next logical step to validate these hypotheses about the mechanism of tumor susceptibility to VEGF-targeted therapy.

**Disclosure of Potential Conflicts of Interest**

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Figure 1. A, a tumor-vessel phenotype is characterized by blood vessels embedded in tumor cells with high vascular density and little pericyte coverage of vessels. There are less myofibroblasts and greater macrophage infiltrate. These characteristics may make the tumor cells more susceptible to the antivascular effects of single-agent VEGF blockade. B, a stromal-vessel phenotype is characterized by blood vessels embedded in stroma outside tumor cell nests with less vascular density and greater pericyte/myofibroblasts coverage of vessels. There is less macrophage infiltrate. These characteristics may make the tumor cells less susceptible to the antivascular effects of single-agent VEGF blockade.
References

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