Commentary (Denlinger/Meropol): The Horizon of Antiangiogenic Therapy for Colorectal Cancer

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Olszewski and colleagues review preclinical and clinical data regarding vascular endothelial growth factor (VEGF) inhibitors, with particular attention to the development of bevacizumab (Avastin) in patients with colorectal cancer. The translation from biologic concept to clinical proof of concept has been striking in its rapidity. However, many important questions remain, and this story is only beginning to unfold. In this commentary, we will highlight some of those questions that bear on the optimal use of VEGF inhibitors in patients with colorectal cancer.

A New Paradigm
VEGF inhibitory strategies represent a new paradigm for the treatment of cancer—namely, targeting of the tumor microenvironment rather than the cancer cell itself. Tumors rely on the development of new blood vessels to continue to grow and survive, as the diffusion capacity of oxygen and micronutrients is only approximately 200 mm. Cells that exceed this distance from a vascular source cannot survive. [1,2] Further convection of larger molecules requires a net pressure gradient between capillaries and interstitium. [3] VEGF is one of the most potent angiogenic growth factors identified to date; it is upregulated in normal conditions such as wound healing and bone growth, as well as in pathologic conditions such as rheumatoid arthritis and tumor growth. VEGF promotes angiogenesis, induces vascular leakage and fenestration of endothelial cells, and maintains existing blood vessels. [4] The angiogenic process involves dissolution of the existing basement membrane, endothelial cell proliferation, formation of a new basement membrane, and recruitment and investment of smooth muscle cells and pericytes around the new blood vessels. [2] The resulting tumor vasculature is disorganized, tortuous, and porous, leading to increased interstitial fluid pressure as plasma proteins diffuse out of the vessels, thereby equalizing the pressure gradient and potentially interfering with the delivery of cytotoxic chemotherapy. [2,3] As noted by Olszewski et al, VEGF and VEGF receptors are upregulated in colorectal cancer, and this upregulation is associated with a poor prognosis and increased metastatic potential.

Primary Mechanisms of VEGF Inhibitor Effect
Uncertainty exists regarding the primary mechanisms underlying the clinical activity of VEGF inhibitors such as bevacizumab. It is often presumed that antiangiogenic therapy will result in tumor cell "starvation." However, it is becoming increasingly clear that VEGF inhibitor effects on vascular permeability, resulting in reduced interstitial fluid pressure with the associated improved delivery of cytotoxic therapy, is of paramount importance for clinical activity. [5,6] For example, in preclinical models, inhibition of VEGF signaling results in normalization of the tumor vascular network, decreased interstitial fluid pressure, and restoration of a hydrostatic pressure gradient that allows for deeper penetration of larger molecules into the tumor. [3,5] Clinically, bevacizumab appears to have limited activity as a single agent, [7] or when coadministered with chemotherapy to which the tumor has already developed resistance. [8] If VEGF inhibitors act in large part to facilitate the chemotherapy effect, they may not bring us closer to an ultimate goal of therapeutic regimens that do not include small-molecule cytotoxics and their associated toxicities. On the other hand, recent data demonstrating antitumor activity with a combination of a VEGF inhibitor (bevacizumab) and an epidermal growth factor receptor (EGFR) inhibitor (erlotinib [Tarceva]) in patients with lung cancer [9] raise the possibility that combinations of relatively selective agents that target interrelated pathways (EGFR signaling results in VEGF upregulation [10]) can result in cooperative antitumor activity. However, if bevacizumab potentiates the activity of erlotinib via permeability mechanisms, this does not imply that a similar benefit would not be seen with antibody inhibitors of EGFR, given that their
bulky structures may limit the impact of changes in interstitial pressure on drug delivery.

**Second-Line Therapy?**

Bevacizumab is most commonly utilized as a component of front-line therapy for metastatic colorectal cancer. A key unanswered question is whether bevacizumab should be continued with the next line of cytotoxic treatment. One might hypothesize that if bevacizumab potentiates the delivery of chemotherapy to tumors, this should also hold for second-line therapy. Unfortunately, available data do not address this issue directly. Giantonio et al recently reported the results of Eastern Cooperative Oncology Group (ECOG) 3200, a randomized trial in which bevacizumab was associated with improved survival when added to the FOLFOX4 regimen (fluorouracil [5-FU], leucovorin, oxaliplatin [Eloxatin] after failure of initial treatment with irinotecan (Camptosar) and 5-FU.[7] However, the patients in this trial had not received bevacizumab as a component of first-line therapy. In the bevacizumab licensing trial reported by Hurwitz et al,[11] patients randomized to receive bevacizumab in combination with irinotecan/5-FU leucovorin were permitted to continue bevacizumab after progression on first-line therapy. However, it is difficult to define the impact of bevacizumab continuation in this trial, as this decision was not randomized, and is hence subject to selection bias. The hypothesis that continuation of bevacizumab after initial therapy will be of benefit is testable and should be pursued.

**Adjuvant Treatment**

Ongoing and planned clinical trials will address the use of bevacizumab in the adjuvant setting in colon cancer (National Surgical Adjuvant Breast and Bowel Project [NSABP] C-08, ECOG 5202) and rectal cancer (ECOG 5204). This is another context in which hypotheses regarding mechanism of action will guide clinical trial design and interpretation of results. It is unknown whether micrometastases in patients with clinically localized disease are of sufficient size to enable the angiogenic process, and hence be a target for anti-VEGF therapy. The NSABP trial was designed with continuation of bevacizumab biweekly for 6 months after the completion of a 6-month chemotherapy- plus-bevacizumab phase.[12] A question arises as to whether this design should be modified given the current data suggesting a lack of activity for single-agent bevacizumab,[7] as well as the potential for arterial thromboembolic events[13] with prolonged use in this potentially cured population. The current designs of ECOG 5202 and ECOG 5204 also call for bevacizumab use concurrently with chemotherapy, and for 6 months thereafter.

**Other Unanswered Questions**

At this time, no clinical parameters associated with response or resistance to bevacizumab have been identified.[14] In addition, little is known with regard to risk factors for potentially severe adverse events such as thrombosis,[13] hypertension, or gastrointestinal perforation.[11] The optimal dose of bevacizumab is not certain, as both the 5- and 10-mg/kg doses biweekly have resulted in improved survival.[7,11] In vivo pharmacodynamic studies (eg, using vascular imaging) are being pursued as a potential surrogate to help define dose and schedule.[6] Furthermore, the VEGF gene is polymorphic, and the functional relevance of these variations is currently undetermined. It is plausible that polymorphisms in VEGF or VEGF-receptor genes will contribute to tumor behavior as well as to the clinical activity of VEGF inhibitors.[15,16] Definition of the clinical activity of other VEGF inhibitory strategies (eg, receptor antagonists) is also eagerly awaited. Clinical success with bevacizumab has provided proof of principle regarding the tumor microenvironment as a target in general, and the VEGF pathway in particular. These advances should stimulate further efforts to understand the relationship between tumor and stroma, permitting refinement and identification of strategies that exploit this interdependence as a therapeutic target.

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**References:**


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