Normalization of Tumor Vasculature and Microenvironment

A Potential Mechanism of Action of Antiangiogenic Therapies

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Summary

Solid tumors require blood vessels for growth, and many new cancer therapies are targeted against the tumor vasculature. The widely held view is that these antiangiogenic therapies destroy the tumor vasculature, thereby depriving the tumor of oxygen and nutrients. Indeed, that is the ultimate goal of antiangiogenic therapies. However, emerging preclinical and clinical evidence support an alternative hypothesis, that judicious application of agents that block angiogenesis directly (e.g., bevacizumab and cediranib) and indirectly (e.g., trastuzumab) can also transiently “normalize” the abnormal structure and function of tumor vasculature. In addition to being more efficient for oxygen and drug delivery, the normalized vessels are fortified with pericytes, which can hinder intravasation of cancer cells, a necessary step in hematogenous metastasis. Drugs that induce vascular normalization can also normalize the tumor microenvironment—reduce hypoxia and interstitial fluid pressure—and thus increase the efficacy of many conventional therapies if both are carefully scheduled. Reduced interstitial fluid pressure can decrease tumor-associated edema as well as the probability of lymphatic dissemination. Independent of these effects, alleviation of hypoxia can decrease the selection pressure for a more malignant phenotype. Finally, the increase in proliferation of cancer cells during the “vascular normalization window” can potentially sensitize tumors to cytotoxic agents. Results from our recent phase II clinical trial of cediranib, an oral, pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI) in glioblastoma
patients, show that the normalization window—identified using advanced magnetic resonance imaging (MRI) techniques—can last 1–4 months, and the resulting changes in tumor vasculature correlate with blood circulating molecular and cellular biomarkers in these patients. Antiangiogenic therapies may provide benefit for cancer patients by working through different mechanisms at different points in time. Normalization may be an early consequence of antiangiogenic therapy and offers an opportunity for optimizing delivery and facilitating the cytotoxic effects of chemotherapy and radiation. However, additional consequences of antiangiogenic therapies may include vessel “pruning” and nutrient deprivation of tumors.

**Key Words:** Angiogenesis; biomarker; MRI; normalization; VEGF; tumor

### 1. INTRODUCTION

After nearly four decades of basic research and clinical development of antiangiogenic therapy for cancer, two anti-vascular endothelial growth factor (VEGF) approaches have yielded survival benefit in patients with metastatic cancer in randomized phase III trials (1). In one approach, the addition of bevacizumab, a VEGF-specific antibody (Genentech Inc., South San Francisco, CA), to standard therapy improved overall survival (OS) in colorectal and non-small cell lung cancer patients and progression-free survival (PFS) in breast cancer and renal cell cancer patients (2, 3). In the second approach, multi-targeted tyrosine kinase inhibitors (TKIs) that block not only VEGF receptor kinases but also other kinases in both endothelial and cancer cells demonstrated a survival benefit in gastrointestinal stromal tumor and renal cell cancer patients (sorafenib; Bayer AG, Leverkusen, Germany and Onyx Pharmaceuticals; Emeryville, CA, and sunitinib, Pfizer, New York, NY). By contrast, bevacizumab failed to increase survival with chemotherapy in patients with previously treated and refractory metastatic breast cancer or pancreatic cancer. Furthermore, the addition of vatalanib (Novartis International AG, Basel, Switzerland), a multitargeted TKI developed as a VEGF receptor-selective agent, to conventional cytotoxic therapy did not produce a survival benefit in metastatic colorectal cancer patients. Finally, several agents—that target oncogenic signaling pathways (such as HER2 by trastuzumab; Genentech Inc.)—may indirectly inhibit angiogenesis and have yielded increased OS with chemotherapy in clinical trials.

These contrasting responses raise critical questions about how these agents work in patients and how to combine them optimally. There are multiple potential mechanisms of action of antiangiogenic agents, but the focus of this chapter is on normalization of tumor vasculature for improved delivery and efficacy of therapeutics (1, 4). After summarizing preclinical evidence in support of vascular normalization, clinical evidence from two trials, treatment of rectal carcinoma patients receiving bevacizumab (5, 6) and recurrent glioblastoma patients receiving cediranib (7), will be reviewed. A discussion of potential biomarkers of anti-VEGF agent efficacy in humans—molecular and cellular parameters obtained from tissue biopsies, interstitial fluid pressure, blood circulating endothelial cells (CECs), protein levels in bodily fluids and physiological parameters—measured with various imaging techniques will be highlighted followed by comments on the potential avenues of further investigation.