Overcoming Antiangiogenic Resistance

James C. Yao and Alexandria Phan

The success of drugs targeting angiogenesis is tempered by the transient duration of disease control and modest survival improvement. The very hypoxic stress produced by successful therapy may lead to upregulation of multiple pathways that promote angiogenesis and invasive behavior. Overcoming this evasive resistance may further improve outcome. Clin Cancer Res; 17(16); 1–3. ©2011 AACR.

In this issue of Clinical Cancer Research, Allen and colleagues (1) suggest that cotargeting of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) signaling pathways can improve efficacy and overcome adaptive resistance to VEGF inhibition in a transgenic model of pancreatic neuroendocrine tumor. Although the field of antiangiogenic therapy has seen tremendous advances since Judah Folkman (2) proposed that angiogenesis plays a critical role in sustained growth of cancer, further work in understanding the mechanisms of resistance and identifying ways to overcome them is clearly needed.

Tumor angiogenesis results from the disequilibrium between pro- and antiangiogenic signaling pathways. The most important regulatory factor is VEGF. During the last 7 years, the U.S. Food and Drug Administration has approved 5 different agents that inhibit the VEGF/VEGFR signaling pathway (bevacizumab, sunitinib, sorafenib, pazopanib, and vandetanib) for 9 different malignancies (gastrointestinal stromal tumor; glioblastoma; hepatocellular carcinoma; medullary thyroid cancer; neuroendocrine cancers of pancreatic origin; renal cell carcinomas; and breast, colon, and lung cancers). Nonetheless, resistance to antiangiogenic therapy eventually develops, resulting in modest overall survival benefit in many malignancies.

In the authors’ prior work using the same transgenic model, Casanovas and colleagues (3) showed that VEGF inhibition and hypoxia can lead to the upregulation of multiple proangiogenic molecules, including VEGF, FGF, and angiopoietin, which can contribute to eventual resistance. The current work, published in this issue of Clinical Cancer Research, suggests that dual targeting of VEGF and FGF signaling can overcome this resistance mechanism.

Although these experiments were conducted with the use of a transgenic model of pancreatic neuroendocrine tumor, the suggestion that hypoxic stress may lead to upregulation of multiple proangiogenic molecules can generally be applicable to a variety of solid malignancies. Although large tumors often already have a hypoxic center, successful VEGF inhibition will lead to a further increase in this hypoxic stress. Hypoxic stress will then trigger upregulation of transcription factors that control multiple proangiogenic and survival pathways (Fig. 1). For example, bevacizumab therapy in xenograft models of human cancer has been shown to increase the expression of hypoxia inducible factor-1α (HIF-1α) (4) and specificity protein 1 (Sp1) (5). Upregulation of these transcription factors in turn leads to the expansion of a variety of molecules, including VEGF and FGF, that may promote angiogenesis and tumor growth, ultimately leading to resistance.

Proposed strategies to overcome this resistance mechanism include targeting of key transcription factors and multiple downstream pathways with the use of multiple agents or a single drug that inhibits multiple kinases (Fig. 1). Findings from preclinical works suggest that dual targeting of VEGF and HIF-1α or Sp1 leads to increased therapeutic efficacy (4, 5); however, this remains to be validated in human studies. A number of multikinase inhibitors, including brivanib targeting both VEGF and FGF, are also currently in development for patients who have failed prior therapy with a VEGF inhibitor. One limitation of these ongoing human studies is that it would be difficult to isolate the specific benefit of FGF inhibition, because a tumor may indeed respond to a second VEGF inhibitor after developing resistance to initial treatment. For example, partial responses have been observed in patients receiving pazopanib after failing sunitinib, sorafenib, or bevacizumab (6). The work of Allen and colleagues (1) in this issue of Clinical Cancer Research is critical for understanding the relative roles of VEGF and FGF in this resistance mechanism. The use of DC101, a monoclonal antibody against VEGF-R2, and FGF-trap, which binds multiple FGF ligands to inhibit FGF signaling, allowed the investigators to test their hypothesis that dual inhibition of VEGF and FGF can overcome adaptive resistance to VEGF inhibitors in this model system.
There has been considerable interest in antiangiogenic therapy within the field of neuroendocrine tumors. A recent phase III study reported that sunitinib delayed progression compared with placebo in patients with advanced pancreatic neuroendocrine tumors (7). Although the study failed to achieve statistical significance due to unplanned analyses, a 5.9-month improvement in median progression-free survival was observed (7). The role of VEGF inhibition in pancreatic neuroendocrine tumors is also supported by results of multiple phase II studies using other VEGF tyrosine inhibitors (8, 9). A separate phase III study comparing bevacizumab with interferon in advanced carcinoid tumors is also ongoing through the cooperative group SWOG (http://www.swog.org; Protocol Abstract 0518).

Although specific studies designed to evaluate strategies for overcoming resistance to VEGF inhibition have not been conducted in neuroendocrine tumors, intriguing observations have been made about the effect of interferon on angiogenesis. Interferon has been used in the past for the control of hormonal syndrome from neuroendocrine tumors. Although interferon is no longer used for this purpose due to the availability of less-toxic agents for symptom control, it is also thought to have antitumor activity, possibly through an antiangiogenic mechanism. In one study, investigators reported that interferon decreased microvessel density and VEGF expression through a Sp1/Sp3-dependent mechanism (10). The same investigators also reported that interferon treatment reduced VEGF mRNA expression and circulating plasma VEGF in a small number of neuroendocrine patients who had undergone pre- and postinterferon treatment biopsies (10).

In a previous study (11), we used perfusion computed tomography to evaluate the vascular effects of antiangiogenic agents in patients with advanced neuroendocrine tumors. In this random-assignment, run-in study, patients received bevacizumab or pegylated interferon-α2b until progression or completion of 18 weeks, and they subsequently received the combination of both drugs. We observed that bevacizumab therapy led to a rapid and sustained decrease in tumor blood flow. Treatment with pegylated interferon was associated with a significant reduction in circulating βFGF. Compared with baseline measurements, the relative reductions in mean βFGF at weeks 9 and 18 were 57% (P = 0.04) and 52% (P = 0.01), respectively (11). Reductions in βFGF, however, did not translate to any notable change in tumor blood flow parameters. The addition of pegylated interferon to bevacizumab also resulted in no appreciable changes in tumor blood flow (12). Several explanations could account for the lack of change in tumor blood flow. First, a greater degree of FGF inhibition may be needed. Second, the changes induced by FGF inhibition may not be readily measurable by perfusion computed tomography. Finally, the role of FGF in resistance to VEGF

Figure 1. Successful inhibition of the VEGF signaling pathway leads to hypoxic stress, which leads to the upregulation of transcription factors. Transcription factors, such as HIF and SP1, regulate multiple proangiogenic and prosurvival pathways. Upregulated by hypoxic stress, transcription factors lead to increased expression of multiple proangiogenic molecules, including VEGF, FGF, and Ang, which may lead to the development of resistance to initial VEGF inhibition. Strategies to overcome resistance include concurrent targeting of VEGF and transcription factors or concurrent targeting of multiple angiogenic pathways, such as VEGF and FGF.
inhibition may be mediated by the change to a more invasive phenotype with vascular cooption rather than angiogenesis.

Pancreatic neuroendocrine tumor has now joined renal cell carcinoma, hepatocellular carcinoma, and glioblastoma on the list of malignancies in which VEGF inhibitors have shown effective single-agent antitumor activity. Whether an approach of dual FGF and VEGF inhibition using one or multiple agents can prevent or overcome resistance in human pancreatic neuroendocrine tumors will have to be investigated in future clinical trials.

Disclosure of Potential Conflicts of Interest

J.C. Yao is a consultant for Pfizer and Novartis. A. Phan is a consultant for Novartis.

Received May 26, 2011; accepted June 8, 2011; published OnlineFirst August 9, 2011.

References
