Antiangiogenic Therapy for Metastatic Colorectal Cancer

Edited by Axel Grothey, M.D., Mark Kozloff, M.D., and Lee Rosen, M.D.

Colorectal cancer remains the second leading cause of cancer-related death in the United States, with about 154,000 new cases and more than 52,000 deaths in 2007. Refinements to cytotoxic chemotherapy regimens have incrementally improved median life expectancy in patients with metastic colorectal cancer (mCRC), but these gains have generally come at the cost of increased toxicity. In 2004, the FDA approved the first specifically-designed antiangiogenic agent, **bevacizumab** (Avastin), a humanized monoclonal antibody, for first-line mCRC therapy in combination with 5-FU-based chemotherapy. Two other antibody therapies, **cetuximab** (Erbitux) and **panitumumab** (Vectibix), are approved for refractory mCRC treatment. These targeted agents, now validated in mCRC and other tumor types, interrupt critical cell-signaling pathways that stimulate tumor angiogenesis and growth.

Of the many endogenous growth factors employed in tumor angiogenesis, vascular endothelial growth factor (VEGF) has been the most studied. VEGF is overexpressed in most cancer cell types and is a potent stimulator of endothelial cell proliferation, migration, survival, vessel sprouting, and the recruitment of endothelial progenitor cells. VEGF also increases tumor vessel permeability, thereby allowing leakage of proangiogenic proteins into the tumor microenvironment. Increased VEGF production is initiated early in tumor development by hypoxia, genetic mutations, hormones, cytokines and other growth factors, and persists throughout disease progression.

Bevacizumab (BV) disrupts angiogenesis by binding to VEGF-A, reducing availability of this ligand to its receptors, thus preventing their activation. Epidermal growth factor receptor (EGFR), a receptor for EGF present on the surface of normal epithelium, is overexpressed in up to 80% of colorectal tumors. EGFR mediates cell differentiation, proliferation, migration, angiogenesis and apoptosis, all of which are deregulated in CRC. Cetuximab and panitumumab directly impede tumor growth and also exert antiangiogenic effects by blocking ligand-induced phosphorylation of EGFR on endothelial cells. EGF blockade also interferes with VEGF production by tumor cells.

In addition to disrupting blood flow to the tumor by interfering with growth factor/receptor signaling pathways, targeted therapies may also indirectly sensitize tumor cells to the effects of chemotherapy and radiation through respective normalization of tumor vasculature and improved tissue oxygenation.

Clinical Evidence for Monoclonal Antibodies

BV was approved for front-line mCRC therapy based on results from a randomized, phase 3 trial in combination with bolus 5-FU/leucorvin and irinotecan (IFL). Subsequently, in view of superior efficacy and tolerability compared with IFL, FOLFIRI[a] is now the preferred irinotecan-based regimen for the addition of BV. More recently, two randomized phase 3 trials (ECOG E3200, NO16966) showed that BV improves progression-free survival (PFS) when added to oxaliplatin-based chemotherapy. In the ECOG study in second-line mCRC, the addition of BV to FOLFOX4[b] increased median PFS and overall survival (OS) by 2.6 and 2.1 mo., respectively, versus FOLFOX4 alone in patients pretreated with irinotecan[1]. NO16966 was a double-blind study of FOLFOX4 or XELOX[c] plus BV or placebo as front-line mCRC therapy[2]. While the addition of BV to oxaliplatin-based regimens improved PFS in a pooled analysis (9.4 vs. 8 mo., P=0.0023), about 70% of BV-treated patients discontinued all treatment, primarily due to neurotoxicity related to oxaliplatin, thereby decreasing potential therapy benefits. For patients who remained on treatment, there was a continued PFS benefit in the BV/oxaliplatin arm (10.4 mo. vs. 7.9 mo., P<0.0001).

Important 'real world' data are now available from a U.S. community-based observational cohort study (BRiTE) involving more than 1,950 previously untreated mCRC patients who received BV in combination with various chemotherapy regimens[3]. Median PFS in BRiTE was 10.1 months and median OS 25.1 months, which exceeds median OS in the pivotal phase 3 trial (AVF2107) of BV plus IFL by almost 5 months. These data are among the first to show median OS beyond 2 years in front-line mCRC in a community-based population.

Cetuximab, a chimeric monoclonal antibody, was approved for second-line mCRC based on results from a phase 2 study (BOND) in 329 irinotecan-refractory/intolerant patients randomized to irinotecan plus cetuximab or cetuximab alone[4]. Patients who received the combination had significantly improved response rates (22.9% vs. 10.8%, P=0.007) and time-to-progression (TTP) (4.1 vs. 1.5 mo., P<0.001) compared with cetuximab alone, suggesting that cetuximab may resensitize some patients to irinotecan. As front-line therapy, cetuximab has not yet demonstrated improved OS when added to chemotherapy. In a phase 3 trial (CRYSTAL), the addition of cetuximab to FOLFIRI decreased risk of progression by 15% (median PFS: 8.9 mo. for cetuximab/FOLFIRI vs. 8 mo. for FOLFIRI alone, P=0.036)[5]. Cetuximab plus FOLFOX4 increased response rates by 10% in a smaller phase 2 study (OPUS)[6]. Thus, cetuximab will likely remain as salvage therapy for mCRC until improved survival is demonstrated in the front-line setting.

Antiangiogenic Escape and Treatment Strategies

Despite proven clinical benefit, virtually all mCRC patients receiving antiangiogenic therapy in the front-line setting eventually relapse. It is now recognized that tumors employ a number of mechanisms to escape (evade) anti-VEGF therapy, which are distinct from classic chemotherapy resistance. Proposed mechanisms of anti-VEGF escape include: 1) Increased production of VEGF by the tumor in response to treatment; 2) Upregulation of other proangiogenic growth factors (e.g., platelet-derived growth factor [PDGF], fibroblast growth factors [FGF], Ephrin-A1, angiopoietin-1) with concurrent downregulation of endogenous angiogenic inhibitors (e.g., endostatin, thrombospondin); 3) Cooption of existing blood vessels that are less susceptible to VEGF blockade; 4) Transformation of the tumor vasculature towards a more mature, less VEGF-dependent phenotype; 5) Contribution of VEGF and other growth factors by host stroma; and 6) Genetic selection for tumor cells exhibiting increased resistance to both hypoxia and chemotherapy.

Since most mCRC patients now receive BV in front-line therapy, a central treatment question is whether patients can benefit from continuation of anti-VEGF treatment in the context of disease progression. There is considerable evidence that anti-VEGF therapy induces a cytostatic effect characterized by reduction in tumor vascular density. Research has also shown that tumor vasculature can regrow aggressively soon after anti-VEGF therapy is halted. Therefore, discontinuing anti-VEGF therapy in the face of tumor growth could initiate even more rapid disease progression. Similarly, continuing therapy beyond progression may provide survival and quality-of-life benefits even in the absence of traditional tumor response.

Data from the non-randomized BRiTE study showed that patients who remained on BV beyond first progression had significantly prolonged median OS compared with patients who received no additional BV or no further treatment at all (31.8 vs. 19.9 vs. 12.6 mo., respectively)[7]. This suggests that tumor progression may have resulted from chemotherapy resistance rather than anti-VEGF evasion, but this hypothesis will need to be confirmed in randomized trials.

Other strategies being explored to combat anti-VEGF treatment evasion include the use of dual antiangiogenic agents that target different growth pathways, sequencing of drugs, and using single agents that target multiple pathways. BOND-2 was one of the first studies to combine VEGF- and EGFR-targeting agents for mCRC. This phase 2 trial, which replicated the BOND-1 design, showed that the addition of BV to either single-agent cetuximab or cetuximab/irinotecan improved TTP by 4.1 and 3.9 mo., respectively, vs. historical controls[8]. BOND-3 will compare cetuximab/BV/irinotecan vs. cetuximab/BV in mCRC patients refractory to BV. In surprising contrast to the BOND-2 results, the addition of panitumumab, a fully human anti-EGFR antibody, to BV and chemotherapy in front-line mCRC therapy resulted in significantly worse PFS vs. the control arm (BV/chemotherapy) in a randomized phase 3 trial (PACCE)[9]. In addition, there was an increased incidence of pulmonary embolism and grade 3 (severe) diarrhea, dehydration and infections in panitumumab-treated patients.

Thus far, single-agent, small molecule multi-targeting angiogenic inhibitors have shown mixed results for mCRC. In a randomized phase 3 trial (CONFIRM-2) in second-line mCRC, the combination of FOLFOX4 and **vatalanib** (PTK787/ZK), an agent that targets all three VEGF receptors, c-Kit, and PDGFR-ß, improved PFS compared to FOLFOX4 plus placebo (5.5 vs. 4.1 mo., P=0.026) but not OS (12.1 vs. 11.8 mo., P=0.51), the primary endpoint.[10] Data recently presented from a small phase 1 study of **sunitinib** (Sutent), a multi-kinase inhibitor, plus FOLFIRI in first-line mCRC showed that among 10 patients who received the MTD, 4 experienced PR and 6 had SD[11]. A multi-national, randomized phase 3 trial of sunitinib plus FOLFIRI in front-line mCRC has been initiated[11].

Side Effects of Antiangiogenic Therapy

Unlike cytotoxic chemotherapy, which is often discontinued due to side effects prior to disease progression, duration of antiangiogenic therapy is not typically limited by drug toxicities. Nonetheless, antiangiogenic agents exhibit distinct side effect profiles requiring special attention. Hypertension is the primary side effect of VEGF inhibition. Grade 3 hypertension occurs in approximately 10-18% of patients treated with BV and can usually be effectively managed with routine anti-hypertensive medications. Other serious but less frequent adverse events associated with BV include thromboembolic events (<5%), gastrointestinal perforations (1-3.5%), reversible posterior leukoencephalopathy (<0.1%), and case reports of hemorrhage and nasal septum perforation. Delayed wound healing has also been reported with BV therapy and is a concern for patients who may require surgery. In the neoadjuvant setting, BV was administered up to 5 weeks prior to resection of CRC liver metastases without adversely affecting wound healing or subsequent liver regeneration after surgery[12].

Skin reactions, associated with targeting of the epithelium, occur in >80% of people on EGFR inhibitors. EGFR-associated rash manifests aspustular-appearing lesions that can mimic acne but has a distinct pathology. Cutaneous reactions are most pronounced in the first 2-3 weeks of treatment and are managed empirically. Other adverse effects reported with anti-EGFR therapy include ocular toxicities, stomatitis and oral mucositis, hair changes such as elongated eyelashes, and hypersensitivity infusion reactions (primarily with cetuximab)[13]. More recently, hypomagnesemia has been observed in patients receiving EGFR inhibitors. Serum magnesium levels should be monitored routinely for patients on cetuximab or panitumumab therapy and hypomagnesemia should be considered in patients who develop fatigue and muscle weakness on therapy.

Future Directions

One of the important challenges in treating mCRC lies in selecting patients who could most benefit from antiangiognic therapy. While all tumors express VEGF, levels of growth factor and receptor expression vary greatly among patients, even within a single tumor over the disease course. Intensive research is underway to identify and validate biomarkers for selecting patients for therapy and gauging treatment response. Potential biomarkers under investigation include circulating endothelial progenitor cells (CEPs) – CEP levels decrease during anti-VEGF therapy, which may reflect shedding of non-viable tumor endothelial cells; angiopoietins – ligands that bind competitively to Tie-2 receptors, the activation of which promotes angiogenesis and vascular maturation; and tumor endothelial markers (TEMs), which are overexpressed in colorectal tumor cells[14].

Finally, antiangiogenic therapies that act on novel targets are in development. Some agents in early clinical trials include drugs that neutralize hepatocyte growth factor (HGF), selective angiopoietin antagonists that inhibit Tie-2-dependent stimulation of endothelial cells, an agent that blocks both VEGF and FGF-mediated signaling, and a thrombospondin-1 (TSP-1) mimetic. TSP is an endogenous inhibitor of angiogenesis, and loss of TSP-1 via the PI3K signaling pathway is one of the first steps of angiogenesis[15]. Whether these agents will demonstrate efficacy for mCRC remains to be seen, but the progress made to date is reason for optimism.

a. FOLFIRI = infusional 5-FU/leucovorin/irinotecan b. FOLFOX4 = oxaliplatin/5-FU/leucovorin c. XELOX (CAPOX) = capecitabine/oxaliplatin

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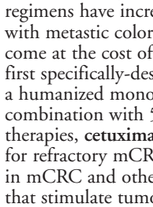
For complete references, please see www.angio.org and click on CME Information.



From the Editor-in-Chief

Furthering our commitment to advancing the field of angiogenesis-based medicine, the Angiogenesis Foundation is pleased to present this issue of *Targeting Tumor Angiogenesis* focused on new findings in mCRC. I have invited three preeminent experts, Drs. Axel Grothey, Mark Kozloff, and Lee Rosen, to discuss the latest evidence on antiangiogenic treatments for mCRC and what the future holds for new therapeutic targets under investigation.

– *William W. Li, M.D., President, The Angiogenesis Foundation*

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INTENDED AUDIENCE
Practicing oncologists and oncology nurses in the U.S.

EDUCATIONAL OBJECTIVES
- Describe angiogenesis targets and pathways in cancer
- Describe the paradigm shifts in cancer management accompanying antiangiogenic therapy
- Review clinical data regarding the use of antiangiogenic agents in treating metastatic colorectal cancer

METHOD OF PARTICIAPATION
Review the illustration and article(s) on this publication, and then visit www.angio.org and click on CME Information for additional content, CME registration and evaluation. There you can access additional program content, related articles, and detailed instructions to obtaining CME credits for this activity.

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DISCUSSION OF UNLABELLED USE
This CME activity contains discussion of published and/or investigational use of bevacizumab (approved for metastatic colorectal cancer in combination with 5-FU and advanced non-small cell lung cancer in combination with carboplatin and paclitaxel), cetuximab (approved as therapy for refractory metastatic colorectal cancer), vatalanib (PTK787/ZK), and sunitinib (approved as therapy for advanced renal cell carcinoma and gastrointestinal stromal tumors).

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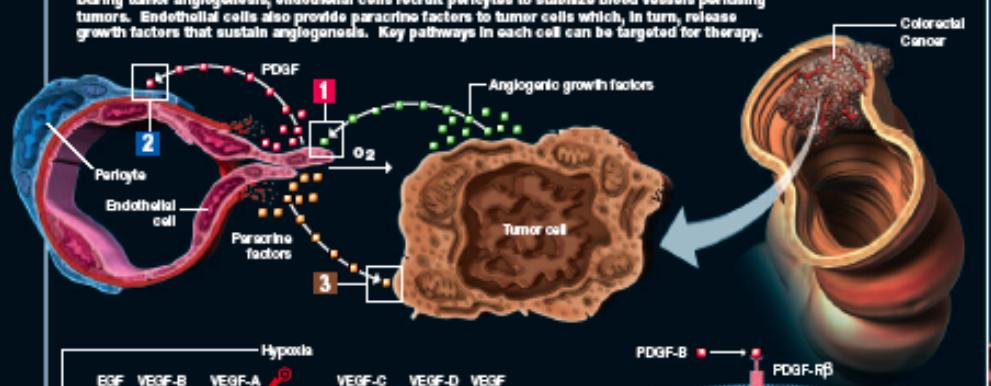
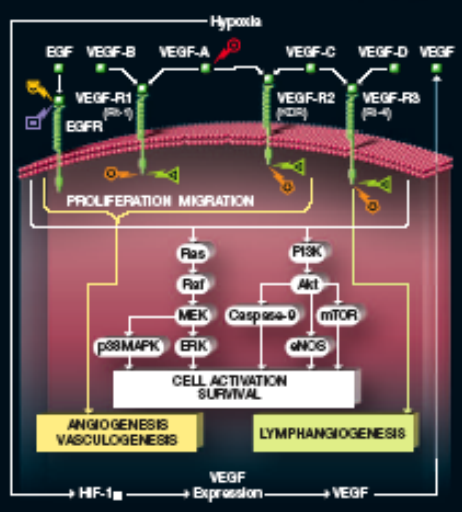
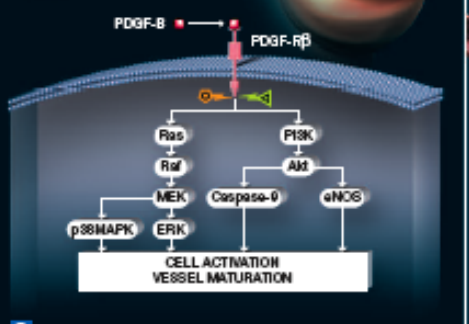
Targeting Cells and Pathways in Colorectal Cancer

During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells which, in turn, release growth factors that sustain angiogenesis. Key pathways in each cell can be targeted for therapy.

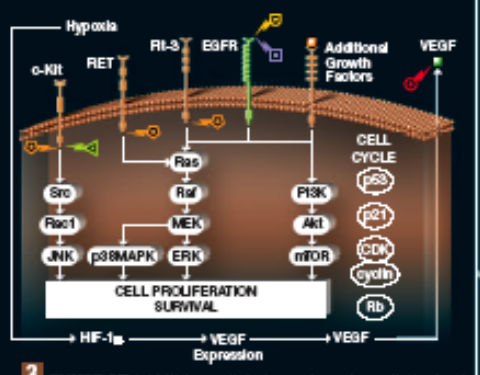




1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis, vasculogenesis, and lymphangiogenesis.



2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGF-Rβ mediate vessel maturation.



3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

Targeted Agents

(Targets shown in diagram above and to the right.)

- Bevacizumab (Avastin)
- Cetuximab (Erbitux)
- Panitumumab (Vectibix)
- Sunitinib (Sutent)
- Vatalanib (PTK787/ZK)

Targeting Tumor Angiogenesis

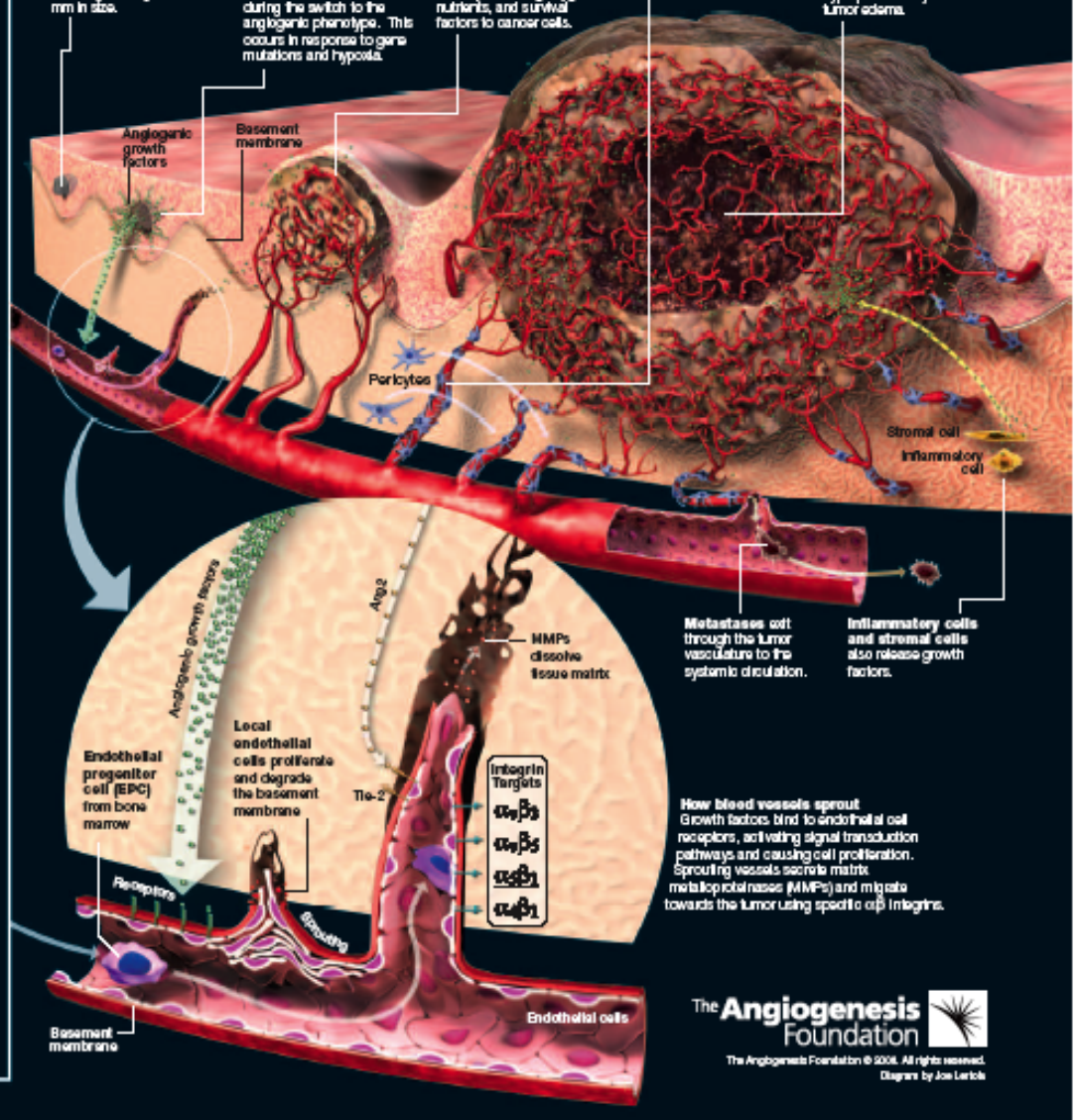
1 Incipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.

2 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. This occurs in response to gene mutations and hypoxia.

3 Angiogenic vessels form tubes and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.

4 Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.

5 Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to central hypoxia. Vessel hyperpermeability results in tumor edema.



How blood vessels sprout
Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation. Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific αβ integrins.

The Angiogenesis Foundation

Diagram by Joe Lertola