Review

Sequencing of Antiangiogenic Agents in the Treatment of Metastatic Colorectal Cancer☆

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Abstract

Significant advances have been made with respect to our understanding of the critical role of agents targeting angiogenic pathways in the treatment of metastatic colorectal cancer (mCRC). The approval of 3 agents that target angiogenic signaling, bevacizumab, ziv-aflibercept, and regorafenib, provides strong evidence that angiogenesis is an important process in mCRC. The addition of bevacizumab to combination chemotherapy in the first- and second-line treatment of mCRC has resulted in meaningful improvement in overall and progression-free survival. The standard of care for mCRC has evolved to incorporate cytotoxic chemotherapy as the backbone regimens (eg, FOLFOX [folinic acid, 5-fluorouracil, and oxaliplatin], FOLFIRI [folinic acid, 5-fluorouracil, and irinotecan]) with or without bevacizumab, and epidermal growth factor receptor–targeted therapies (eg, cetuximab, panitumumab) in the setting of wild-type *KRAS*. The development of ziv-aflibercept in combination with FOLFIRI has improved clinical efficacy in the second-line treatment of mCRC. Regorafenib, a small-molecule multikinase inhibitor, has recently been approved by the US Food and Drug Administration as single-agent therapy in the treatment of refractory and progressive mCRC. Each of these agents has been integrated into an evidence-based—albeit, still evolving—treatment continuum for initial treatment, treatment after first progression, and treatment after second progression. However, the most effective strategy for the use of these agents, and others in development remains unclear. This review provides an overview of the current clinical evidence for the use of antiangiogenic agents targeting in the treatment of mCRC.

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Introduction

Colorectal cancer (CRC) remains a major public health problem in the United States with an annual incidence of nearly 150,000.[1] Worldwide, it is estimated that more than 1 million new cases of CRC will be diagnosed each year. Approximately 20% of newly diagnosed CRC is metastatic at the time of initial presentation, and more than 50% of patients with early-stage CRC at initial diagnosis will eventually present with metastatic disease. Despite significant progress in the treatment of metastatic CRC (mCRC) over the past 2 decades, the prognosis of mCRC is still quite poor. Although median overall survival (OS) has improved to the point where it is now in the range of 24 to 28 months, 5-year OS remains less than 10%.

Systemic chemotherapy has been the main treatment modality for patients with mCRC. For nearly 40 years, the fluoropyrimidine 5-fluorouracil (5-FU) was the only agent approved by the US Food and Drug Administration (FDA) for the treatment of mCRC. However, since the mid-1990s, considerable advances have been made with 3 new cytotoxic agents and 5 targeted agents approved by the FDA. The cytotoxic agents include irinotecan, a topoisomerase I inhibitor, oxaliplatin, a third-generation platinum analogue, and capecitabine, an oral fluoropyrimidine. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, was approved in 2004, along with cetuximab, a chimeric anti-epidermal growth factor receptor (EGFR) antibody. In 2006, panitumumab, a fully human anti-EGFR antibody, was approved for use in the disease-refractory setting, and in the fall of 2012, the anti-VEGF recombinant fusion protein, ziv-aflibercept, and regorafenib, a multikinase small molecule inhibitor, were approved as second- and third-line treatment options, respectively.[2] The combinations of a fluoropyrimidine (5-FU or oral capecitabine) with either oxaliplatin (FOLFOX [folinic acid, 5-FU, and oxaliplatin] or XELOX [capecitabine and oxaliplatin]) or irinotecan (FOLFIRI [folinic acid, 5-FU, and irinotecan] or XELIRI [capecitabine and irinotecan]) have been widely accepted as standard cytotoxic chemotherapeutic regimens for the first- and second-line treatment of patients with mCRC.[3-7]

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With several recent new developments in antiangiogenic therapy for mCRC, including the introduction of ziv-aflibercept and regorafenib, there is a clear need to determine how best to sequence and integrate these agents along with bevacizumab, the first-generation anti-VEGF antibody. Herein, we review the current clinical recommendations for the treatment of mCRC with a particular focus on patients with disease progression after first-line antiangiogenic therapy in combination with chemotherapy. We also review the clinical evidence for the potential role of sequencing of these antiangiogenic agents.

The Biology of Angiogenic Pathways

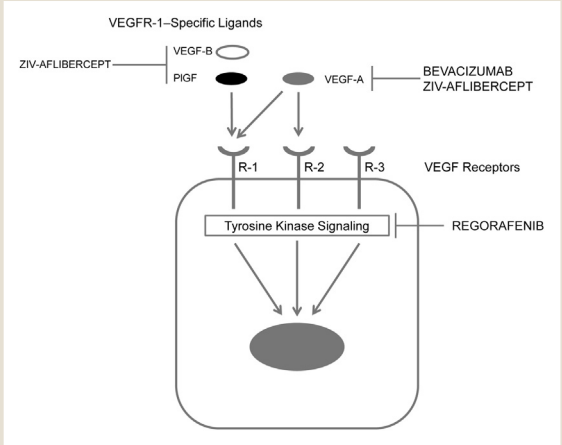
Vascular Endothelial Growth Factors and VEGF Receptors

The VEGF family of ligands and receptors is one of the best-characterized pathways for its role in pathologic angiogenesis. VEGF-A and the structurally related VEGF ligands, VEGF-B, -C, -D, and placental growth factor (PlGF) mediate their respective biological effects through at least 3 different cellular receptors, VEGF receptor (VEGFR)-1, -2, and -3, each of which have tyrosine kinase activity (Fig. 1).[8-16] The interaction of VEGF-A, which has 6 alternatively spliced isoforms, with VEGFR-2 is believed to account for the main angiogenic activities of VEGF-A in stimulating tumor angiogenesis.[8] The specific function of VEGFR-1 in angiogenesis has not been fully defined, and its specific ligands, VEGF-B and PlGF, are known to play a role in the maintenance of tumor blood vasculature without a significant role in the formation of new tumor blood vessels.[17,18]

Antiangiogenic Agents for the Treatment of mCRC

Bevacizumab is a humanized immunoglobulin (Ig)-G 1 monoclonal antibody directed against VEGF-A. It binds all isoforms of VEGF-A and blocks the subsequent binding of VEGF-A to its cognate receptors, thereby inhibiting its biologic activity.[11,12]

Figure 1 Antiangiogenic Agents and Their Targets



Abbreviations: PlGF = placental growth factor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

Ziv-aflibercept is a soluble decoy receptor molecule composed of the critical ligand-binding domains of human VEGFR-1 and -2 fused with the Fc portion of IgG.[16,19] As such, it acts as a multiple angiogenic factor trap that inhibits the binding of VEGF-A to its cognate receptors (VEGFR-1 and VEGFR-2) and in contrast to bevacizumab, it also inhibits the binding of 2 additional factors—VEGF-B and PlGF—to their cell-surface receptor, VEGFR-1 (Fig. 1).[9] Ziv-aflibercept binds VEGF-A, VEGF-B, and PlGF at low picomolar concentrations, such that multiple pathways, including VEGFR-2–mediated angiogenesis and VEGFR-1–mediated tumor growth, endothelial cell proliferation, and/or bone marrow myeloid progenitor recruitment, might be inhibited by ziv-aflibercept.[20,21]

Regorafenib is a small-molecule multikinase inhibitor that targets a wide range of tyrosine kinases involved in oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. These kinases include VEGFR-1, -2, and -3, fibroblast growth factor receptor, platelet-derived growth factor receptor, RET, TIE-2, DDR2, RAF-1, BRAF, and BRAF V600E.[13,15] Thus, regorafenib hits a much broader range of key cellular targets that go beyond the VEGF-signaling pathway.[13,15]

Preclinical Data on Antiangiogenic Agents

The currently available antiangiogenic therapies for mCRC differ in their underlying mechanisms of action. Bevacizumab targets only VEGF-A, and ziv-aflibercept targets VEGF-A and other VEGF ligands, VEGF-B and PlGF. Regorafenib acts through the more broad-spectrum action of tyrosine kinase inhibition, thereby inhibiting the activity of all VEGFRs and other receptors (Fig. 1). However, to date, it is unclear as to whether these differences in mechanisms of action ultimately account for different levels of clinical efficacy in selected groups of patients.

There is preclinical evidence suggesting that differences between bevacizumab and ziv-aflibercept might be clinically relevant. The more efficient and potent binding of ziv-aflibercept to VEGF-A, by up to 3 logs, when compared with bevacizumab, has been well documented in cell-free systems, and this enhanced ligand binding has been associated with more potent biologic activity.[16,22] In fact, in directly comparative in vitro studies, the binding of ziv-aflibercept to VEGF-A has been reported to be between approximately 10-fold and more than 100-fold more efficient than that of bevacizumab.[16,22] The differences in VEGF-A binding between these 2 agents, using cell-free systems, have also been reflected in the more potent biologic activity of ziv-aflibercept, at least in the assay systems that were studied.[16,22] The human umbilical vein endothelial cell assay showed that ziv-aflibercept at subnanomolar concentrations nearly completely inhibited cell migration in response to exogenously administered VEGF-A, and treatment with bevacizumab, at the same concentrations, resulted in only 50% inhibition, with greater drug concentrations required for complete inhibition.[16,22] This study showed that approximately 5-fold greater concentrations of bevacizumab when compared with ziv-aflibercept were needed for an equivalent level of inhibition of human endothelial cell migration induced by VEGF-A.[16] A different assay system demonstrated 27-fold greater inhibition of VEGFR-1/VEGFR-2 signaling (calcium mobilization) induced by VEGF-A with ziv-aflibercept compared with bevacizumab.[22] It is