Antivascular Endothelial Growth Factor Monoclonal Antibody Therapy: A Promising Paradigm in Colorectal Cancer

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Angiogenesis plays an important role in tumor growth and development. Vascular endothelial growth factor (VEGF) is one of the most potent proangiogenic factors and therefore is an ideal target in colorectal cancer therapy. Bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA) is a humanized monoclonal antibody, designed to directly target VEGF. The agent has shown promising activity in preclinical and phase I and II studies and is well tolerated compared with conventional cytotoxic chemotherapy. The U.S. Food and Drug Administration recently approved bevacizumab in combination with 5-fluorouracil–based chemotherapy as first-line therapy for patients with metastatic colorectal cancer. The approval was based on phase III data demonstrating that patients treated with bevacizumab plus chemotherapy survived approximately five months longer compared with patients treated with chemotherapy alone. This article will focus on the role of VEGF in tumorigenesis and summarize the available data on the use of bevacizumab in the treatment of metastatic colorectal cancer.

Colorectal cancer is the third most common malignancy in men and women in the United States. The American Cancer Society (2004) estimated that, in 2004, 147,000 new cases were diagnosed and 57,000 died from the disease, accounting for about 10% of cancer deaths. Approximately 30% of patients with colorectal cancer have metastatic disease at the time of diagnosis, and 50% of those with limited disease will develop advanced disease (Coutinho & Lima, 2003). The five-year survival rate for patients with distant metastatic disease is 9% (American Cancer Society).

Currently, chemotherapy-based regimens are first-line treatment for patients with metastatic colorectal cancer, and 5-fluorouracil (5-FU) has been the standard treatment since the 1960s. However, newer chemotherapeutic agents recently have been added to therapies based on 5-FU in an attempt to improve response rates and survival. Irinotecan, oxaliplatin, and capecitabine, in a variety of combinations, have been approved for the treatment of colorectal cancer (Goldberg et al., 2004; Hoff et al., 2001; Saltz et al., 2000; Van Cutsem et al., 2001). A new targeted agent, bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA) recently was approved for the treatment of metastatic colon cancer. Bevacizumab, also known as a recombinant human monoclonal antibody vascular endothelial growth factor (VEGF), is a monoclonal antibody that targets VEGF, a ligand that attaches to the VEGF receptor (VEGFR), stimulating angiogenesis (i.e., the formation of new blood vessels). The U.S. Food and Drug Administration approval of first-line therapy for patients with metastatic colorectal cancer was based on positive results from a phase III study of bevacizumab in combination with irinotecan, bolus fluorouracil, and leucovorin (IFL) (Hurwitz, Fehrenbacher, Novotny, et al., 2004). This article describes the impact of VEGF on tumorigenesis and the role of bevacizumab in treating advanced colorectal cancer.

Vascular Endothelial Growth Factor in Tumorigenesis

Vasculogenesis is the process of new vessel formation during embryo development, and angiogenesis is the process by which new vessels develop in preexisting vessels. In general, angiogenesis is quiescent in adults, but it is activated during wound healing, menstruation, hypertrophic growth of muscle after strenuous exercise, and bone growth. However, once activated, angiogenesis ceases after one to two weeks (Gaiso, 1999). Angiogenesis also occurs in several pathologic processes, including rheumatoid arthritis, atherosclerosis, and chronic inflammatory diseases. In cancer, angiogenesis allows the delivery of oxygen and nutrients to the tumor cells (Volker, 2001).

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