Antiangiogenic Therapy for Metastatic Colorectal Cancer

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tumor cancer remains the second leading cause of cancer-related death in the United States, with more than 50,000 deaths in 2007. Refinements to cytotoxic chemotherapy regimens have incrementally improved median life expectancy in patients with metastatic colorectal cancer, but there is significant room for additional gains to come at the cost of increased toxicity. In 2004, the FDA approved the first antiangiogenic agent approved for metastatic colorectal cancer (mCRC), a humanized monoclonal antibody, approved for first-line mCRC therapy in combination with 5FU/leucovorin chemotherapy. Two other monoclonal antibodies (Bevacizumab (Avastin), Zibotentumab (Sutent)), are approved for refractory mCRC therapy. These targeted agents, now validated in mCRC, are the latest in a long line of cell-signaling pathways that stimulate tumor angiogenesis and growth.

Of the many endogenous growth factors employed in tumor angiogenesis, vascular endothelial growth factor (VEGF) is hypoxia inducible factor-1α (HIF-1α) is a master regulator of genes that promote tumor angiogenesis and growth. VEGF is overexpressed in most cancer types and is a potent stimulator of endothelial cell proliferation, migration, survival, vessel sprouting, and the recruitment of pericytes around nascent blood vessels. VEGF increased permeability, thereby allowing leakage of proangiogenic proteins into the tumor microenvironment. Hypoxia is common early in tumor development by hypoxia, genetic mutations, cytokines and other growth factors, and persists throughout disease progression.

Bevacizumab is a monoclonal antibody, approved was for second-line mCRC therapy on the basis of a randomized, phase 3 trial in patients who progressed after fluorouracil or irinotecan chemotherapy. BV was approved for front-line mCRC therapy based on results from a double-blind study of FOLFOX4 vs. XELOX (CAPOX) = capecitabine/oxaliplatin; OS was improved 2.6 months (P = 0.026). While the addition of BV to oxaliplatin-based chemotherapy did not significantly increase PFS or OS, the combination was associated with greater toxicity. BOND-2 was one of the first studies to combine VEGF- and PDGF-targeting therapies. BOND-2 used panitumumab and BV as salvage therapy for mCRC patients refractory to BV. In contrast, the BOND-1 study, which showed that the addition of BV to either single-agent cetuximab or cetuximab/irinotecan improved PFS by 4.1 and 3.9 months, respectively, vs. historical control. BOND-3 will compare cetuximab, BV/irinotecan vs. cetuximab/BV in mCRC patients refractory to BV. In contrast, the BOND-2 study, which showed that the addition of BV to either single-agent cetuximab or cetuximab/irinotecan improved PFS by 4.1 and 3.9 months, respectively, vs. historical control. BOND-3 will compare cetuximab, BV/irinotecan vs. cetuximab/BV in mCRC patients refractory to BV.

Side Effects of Antiangiogenic Therapy

Unlike cytotoxic chemotherapy, which often becomes discontinued due to side effects, antiangiogenic therapy may be continued for a long period of time with minimal toxicity. However, some agents may be discontinued due to side effects. Some of the most common side effects associated with VEGF inhibitors include hypertension occurs in approximately 10-18% of patients treated with BV and can usually be effectively managed with routine antihypertensive therapy. Other side effects observed with BV include bone-marrow effects (<5%), gastrointestinal perforations ( concave increases) in the tumor microenvironment, which can be achieved via various mechanisms including: (1) increased production of VEGF by the tumor in response to treatment; (2) Upregulation of other angiogenic cytokines and growth factors (such as thrombospondin); 3) Cooption of existing blood vessels that are less susceptible to regression. Hence, the BV/irinotecan combination may be beneficial for refractory mCRC patients who received BV in combination with various chemotherapy regimens. BV/irinotecan vs. BV/5-FU/leucovorin (5-FU/leucovorin) as salvage therapy for mCRC until improved survival is demonstrated in the front-line setting.