Targeting Vascular Endothelial Growth Factor in Colorectal Cancer

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By Jordan D. Berlin, MD [2]

Recent trials have established the IFL combination (fluorouracil [5-FU], leucovorin, and irinotecan [CPT-11, Camptosar]) as a new standard first-line therapy for patients with metastatic colorectal cancer. Median survival for such patients treated with IFL still ranges from approximately 14 to 18 months, however, underscoring the need for new agents with novel mechanisms of action.

Colorectal cancer is the second leading cause of cancer death in the United States, with approximately 45,000 deaths and 130,000 newly diagnosed patients per year.[1] Recently, two trials randomized patients to fluorouracil (5-FU)/leucovorin or IFL (5-FU/leucovorin plus irinotecan [CPT-11, Camptosar]) as first-line therapy for metastatic colorectal cancer. The primary end point of both trials was time to tumor progression. One of the trials, conducted in the United States, used IFL at a weekly × 4 schedule for each 6-week treatment cycle, and also had an irinotecan-alone arm.[2] This trial resulted in a higher response rate and longer time to tumor progression for IFL compared with 5-FU/leucovorin, and also a statistically significant survival benefit (14.8 vs 12.6 months, \( P = .04 \)).

The other trial, conducted in Europe, allowed sites to choose one of two infusion schedules (once weekly or every 2 weeks) for the 5-FU/leucovorin regimen.[3] Patients were then randomly assigned to the 5-FU/leucovorin regimen alone or in conjunction with irinotecan. Results of this trial also showed a higher response rate and longer time to tumor progression for IFL compared with 5-FU/leucovorin. A survival benefit was demonstrated for IFL compared with 5-FU/leucovorin as first-line therapy (17.4 vs 14.1 months, respectively; \( P = .031 \)). However, median survival (14.8 to 17.4 months) obtained with IFL is still limited. New active agents, ideally ones that target intracellular mechanisms or pathways, are still needed.

VEGF and Angiogenesis

The process of angiogenesis, or new blood vessel formation, has emerged as a novel target for development of anticancer agents. Preclinical data demonstrate that new blood vessel formation is required for tumors to grow beyond 1 to 2 mm³. Laboratory analyses also demonstrate that, in addition to being critical for tumor growth, angiogenesis is important for invasion and metastasis. Angiogenesis is a complex, multistep process involving breakdown of the extracellular matrix, invasion of tumor cells, signaling to stimulate endothelial cell growth, and blood vessel formation. One of the most potent stimulants of angiogenesis is vascular endothelial growth factor (VEGF).

VEGF was reported to be overexpressed in 48% to 53% of colorectal cancers.[4] The same study suggested that VEGF expression correlated with progression of disease and appeared to be an independent prognostic factor in colorectal cancer. Another study suggested that high preoperative serum VEGF levels were associated with increased likelihood of recurrence in patients with resected colorectal malignancies.[5] Other study results have also shown correlation of VEGF overexpression with advanced disease stage, likelihood of developing metastases after surgery, and overall prognosis.[6-8]

The cellular receptors for VEGF are tyrosine kinases (eg, KDR or flk-1 and FLT-1) that initiate the angiogenesis process through phosphorylation cascades. When VEGF binds to its endothelial cell receptor, the intracellular tyrosine kinase portion is activated, resulting in a phosphorylation cascade that stimulates endothelial cell proliferation and new blood vessel growth. Inhibiting VEGF effects appears to reduce angiogenesis (reduced vessel density) in vitro, and limits tumor growth in vivo.[9-11] Two agents developed to inhibit VEGF action have entered clinical trials, namely, bevacizumab (Avastin) and SU5416.

Bevacizumab
Murine monoclonal antibodies have been developed to inhibit VEGF in a variety of tumor models. However, murine antibodies can readily induce human antimurine antibody (HAMA) responses. Bevacizumab, a recombinant humanized monoclonal antibody to VEGF, was designed with a human IgG1 framework and a murine VEGF-binding portion. In the first phase I trial of single-agent bevacizumab, 25 patients were treated on five dose levels ranging from 0.1 to 10 mg/kg.[12] While no grade 3 or 4 toxicities were clearly related to therapy, there were two episodes of serious bleeding from tumor that were not clearly related to therapy. No partial or complete responses occurred, but one patient had a minor response and 12 experienced stable disease during the 70-day study period. No patient developed antibodies to bevacizumab.

Subsequently, in a phase Ib trial, 12 patients were assigned to one of three treatment arms (four patients per arm). Treatments included bevacizumab combined with either doxorubicin, carboplatin (Paraplatin)/paclitaxel, or 5-FU/leucovorin.[13] Results showed that bevacizumab could be safely combined with three chemotherapy regimens. One patient with colorectal cancer responded to 5-FU/leucovorin plus bevacizumab treatment.

A subsequent randomized phase II trial evaluated the efficacy and tolerability of two different doses of bevacizumab in conjunction with 5-FU and leucovorin. A total of 104 patients were randomly assigned to receive 5-FU and leucovorin, or 5-FU and leucovorin with either 5 or 10 mg/kg of bevacizumab.[14] Randomized phase II trials are designed to evaluate each arm individually and comparisons between treatment arms have to be viewed cautiously. Nonetheless, time to disease progression was longer than expected in patients receiving 5 mg/kg bevacizumab than in those receiving 5-FU and leucovorin alone (9.2 vs 5.2 months, respectively, when independent review facility results were included; time to disease progression was 7.2 months in patients receiving 10 mg/kg bevacizumab). These data led to a randomized trial that is currently testing IFL plus placebo vs IFL plus bevacizumab in patients with metastatic colorectal cancer.

**Inhibition of the Flk-1 (KDR) Receptor With SU5416**

The tyrosine kinase inhibitor SU5416 blocks the kinase activity of the Flk-1 receptor for VEGF. This small molecule appears to inhibit tyrosine kinase at levels of 40 nM.[15] In animal models of liver metastasis, SU5416 decreased the number of liver metastases by 48% and microvessel formation by 42%. SU5416 administration increased the rate of apoptosis 3-fold in tumor cells and 19-fold in endothelial cells.[16] Two phase I trials of twice-weekly SU5416 were performed. One study established a recommended phase II dose of 145 mg/m² twice weekly, with dose-limiting toxicities of headache and emesis.[17] Pharmacokinetic analysis demonstrated that at the 145 mg/m² dose level, an area under the concentration-time curve of 0 to 24 for SU5416 was similar to that producing "effective tumor growth inhibition" in animal studies.[18]

Another phase I trial using the twice-weekly dosing schedule showed that emesis and headache were dose-related, but a maximum tolerated dose had not been reached at the time of report.[19] This trial also assessed vascular permeability by using dynamic contrast magnetic resonance imaging. Preliminary analysis suggested that vascular permeability increased in patients with stable disease. Results from both of these phase I trials suggested that SU5416 can induce its own clearance and that the half-life is short.

SU5416 was then assessed in a phase II trial of patients who had received no more than two previous therapies for advanced colorectal cancer.[20] Preliminary findings for the first 15 enrolled patients suggested that 7 patients had stable disease. A phase I/II trial evaluated SU5416 combined with 5-FU and leucovorin,[21] using the two most common 5-FU plus leucovorin schedules: daily × 5 every 4 to 5 weeks (Mayo Clinic regimen) and weekly × 6 every 8 weeks (Roswell Park regimen). The regimens were well tolerated overall; fewer side effects were seen in patients receiving the Roswell Park regimen. Responses were seen and the long survival time in this study was promising.

Vanderbilt University initiated a phase I/II trial of SU5416 plus IFL.[22] SU5416 was given as a 3-hour infusion twice weekly throughout the cycle. Irinotecan, 5-FU, and leucovorin were administered weekly for 4 weeks followed by a 2-week rest (6-week cycles). Eligible patients had not received previous treatment for colorectal cancer (previous adjuvant therapy was allowed providing at least 1 year had lapsed since the last dose). However, further development of this agent has been halted since the early results of a trial in patients with colorectal carcinoma were not promising.

**Conclusions**

Two new VEGF inhibitors, SU5416 and bevacizumab, have shown intriguing signs of antitumor activity in vitro and in the clinic. SU5416 and bevacizumab may potentially enhance the effects of...
current standard chemotherapy regimens for colorectal cancer (eg, IFL), possibly prolonging time to
tumor progression and survival; however, results of several ongoing and planned trials are needed to
determine the roles of these agents in this disease. Bevacizumab is currently being investigated in a
randomized trial comparing IFL to IFL plus bevacizumab. Several other trials are assessing
bevacizumab, including an Eastern Cooperative Oncology Group study of second-line therapy that
includes a single-agent bevacizumab arm. These trials will help define the role of bevacizumab in
first- and/or second-line treatment of colorectal cancer. Further development of SU5416 has been
halted, but other tyrosine kinase inhibitors of VEGF-mediated angiogenesis are under development.

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