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

Paula J. Franson, RN, MS, AOCN®, and Denise V. Lapka, RN, MS, AOCN®, CCNS

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 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) 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.

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, 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 (Volker, 2001).
Angiogenesis occurs when proangiogenic and antiangiogenic factors are imbalanced. Several proangiogenic factors are hepatocyte growth factor, placental growth factor, tumor necrosis factor-α, and VEGF. Endostatin, angiostatin, platelet factor-4, thrombospondin-1, and interferon alfa, beta, and gamma are all antiangiogenic factors (Ferrara, 2004; Hanahan & Folkman, 1996) (see Table 1).

Although VEGF-A is the most studied, at least four other subclasses of VEGF exist: B, C, D, and E (Ellis, 2002). Placental growth factor is a member of the VEGF family. These molecules have four receptors: neuropilin-1, VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3. VEGFR-3 binds with VEGF-C and VEGF-D, but little is known about neuropilin. The main receptors for VEGF-A are VEGFR-1 and VEGFR-2, which are found on vascular endothelial cells. The binding stimulates endothelial cell survival, proliferation, migration, and inhibition of endothelial cell apoptosis (Ferrara, 2002), which initiates angiogenesis. Activated endothelial cells secrete a plasminogen activator, causing the breakdown of the basement membrane. Endothelial cells then migrate into the surrounding tissue and secrete substances such as type IV collagen, which cause the formation of new blood vessels (Gaiso, 1999). These newly formed blood vessels increase the opportunity for tumor cells to access the circulation and form metastases.

**Table 1. Angiogenesis Activators and Growth Factors**

<table>
<thead>
<tr>
<th>Activity or Activators</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiates angiogenesis</td>
<td>Hypoxia, cyclooxygenase-2, and nitric oxide</td>
</tr>
<tr>
<td>Proangiogenic factors</td>
<td>Vascular endothelial growth factor, basic fibroblast growth factor, interleukin-8, hepatocyte growth factor, and placental growth factor</td>
</tr>
<tr>
<td>Direct</td>
<td></td>
</tr>
<tr>
<td>Indirect</td>
<td>Interleukin-6, tumor necrosis factor-α, platelet-derived growth factor, transforming growth factor-β, and epidermal growth factor</td>
</tr>
<tr>
<td>Antiangiogenic factors</td>
<td>Thrombospondin-1, angiostatin, endostatin, platelet factor-4, and interferon α, β, and γ</td>
</tr>
</tbody>
</table>

Note. Based on information from Ferrara, 2004; Hanahan & Folkman, 1996.

**Figure 1. Bevacizumab Neutralizes Vascular Endothelial Growth Factor**

Table 1 displays the angiogenesis activators and growth factors. Bevacizumab attaches to VEGF; therefore, the receptors on endothelial cells cannot attach to VEGF. Without this attachment, the receptors cannot stimulate the growth and survival of endothelial cells, which inhibit the angiogenesis-signaling cascade (Ferrara, 2002) (see Figure 1).

In colorectal cancer, increased VEGF expression has been correlated with vascularity, invasiveness, metastasis, and poor prognosis (Choi, Hyun, Jung, Kim, & Hong, 1999; Tokunaga et al., 1998). Up-regulation of the VEGFRs, VEGFR-1 and VEGFR-2, also has been observed in colon liver metastases tissue compared with adjacent nontumorous liver tissue (Warren, Yuan, Matli, Gillett, & Ferrara, 1995). In addition, various preclinical studies have suggested that bevacizumab enhances the effectiveness of chemotherapy (Soffer et al., 2001). Based on these observations, several studies have examined bevacizumab in combination with cytotoxic agents in previously untreated patients with metastatic colorectal cancer.

**Bevacizumab in Advanced Colorectal Cancer**

Bevacizumab is a humanized, anti-VEGF monoclonal antibody. Approximately 93% of the antibody’s amino acid sequence is derived from human immunoglobulin G, whereas 7% is from the murine antibody (Presta et al., 1997). Bevacizumab has been combined with 5-FU and leucovorin (LV) in three randomized, phase II studies. Mass et al. (2004) recently presented the results of a large combined analysis from these studies. They showed that adding bevacizumab to 5-FU and LV significantly increased survival (17.9 versus 14.6 months, p = 0.0081) and progression-free survival (8.8 versus 5.6 months, p = 0.0001) compared with the combined control. Bevacizumab was generally well tolerated. Possible bevacizumab-related toxicities included bleeding, thrombosis, hypertension, diarrhea, and proteinuria (Hurwitz, Fehrenbacher, Novotny, et al., 2004; Kabbinavar et al., 2003, 2004). The events typically were mild to moderate or manageable (proteinuria or hypertension). These data suggest that bevacizumab plus 5-FU and LV should be considered a standard option for the initial treatment of metastatic colorectal cancer.

**Bevacizumab Plus 5-Fluorouracil and Leucovorin**

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**Bevacizumab Plus Irinotecan, 5-Fluorouracil, and Leucovorin**

In a phase III trial, adding bevacizumab to IFL in first-line treatment for metastatic colorectal cancer demonstrated increased response rates and survival (Hurwitz, Fehrenbacher, Novotny, et al., 2004). More than 900 patients with previously untreated metastatic colorectal cancer were enrolled and received IFL plus placebo, IFL plus bevacizumab (5 mg/kg every two weeks), or 5-FU and LV plus bevacizumab. Treatment continued until disease progression, unacceptable toxicity, or 96 weeks passed. Patients receiving bevacizumab could continue with the drug during second-line therapy. The results showed that those receiving bevacizumab with IFL survived for an additional five months compared with patients who received IFL plus placebo (20.3 versus 15.6 months, p < 0.001). The survival advantage was statistically significant (Hurwitz, Fehrenbacher, Novotny, et al.). Overall response rates increased from 35% in the IFL plus placebo arm to 45% in the IFL plus bevacizumab arm. A delayed time to cancer progression also was noted (10.6 versus 6.2 months, p < 0.001). The third arm of the study, bevacizumab plus 5-FU and LV, was discontinued after the safety of the bevacizumab plus IFL regimen was established (Hurwitz, Fehrenbacher, Hainsworth, et al., 2004).
A recent study assessed the impact of additional cancer treatment after disease progression (postprogression therapy [PPT]) on survival (Hedrick et al., 2004). A total of 231 (56.2%) and 222 (55.2%) patients received PPT in two randomized treatment arms: IFL and placebo, and IFL and bevacizumab, respectively. Among the patients who received second-line therapy with oxaliplatin, overall survival was 25.1 months for the IFL plus bevacizumab arm and 22.2 months for the placebo arm versus 19.6 months and 15.8 months, respectively, for those receiving nonoxaliplatin-based regimens (Hedrick et al.). These results suggest that first-line therapy with bevacizumab plus two active chemotherapies, followed by PPT with a third active chemotherapy over the course of disease, optimizes overall survival. These findings are consistent with those from previous studies (Grothey, Sargent, Goldberg, & Schmoll, 2004).

In general, bevacizumab therapy was well tolerated (Hurwitz, Fehrenbacher, Novotny, et al., 2004); most side effects were mild to moderate (see Table 2). Grade 3 and 4 side effects increased, mainly as a result of grade 3 hypertension (2.3% in the placebo arm and 11.0% in the bevacizumab arm), but this was controlled easily with oral medication (Hurwitz, Fehrenbacher, Novotny, et al.). The incidence of diarrhea and leukopenia escalated slightly, but increases in thrombosis, major bleeding, and grade 3 proteinuria, which were identified in previous phase II studies, were not observed; however, six cases of gastrointestinal perforations occurred in the bevacizumab arm. One patient died, and two discontinued treatment. Three patients stopped treatment but were able to resume with bevacizumab (Hurwitz, Fehrenbacher, Novotny, et al.).

A potential difficulty with antiangiogenic agents such as bevacizumab is the risk of delayed wound healing. Scappaticci et al. (2004) recently analyzed wound healing and bleeding complications among patients who underwent major surgery prior to receiving therapy in their phase III trial. The results suggest that initiating bevacizumab in patients within 28–60 days after surgery does not lead to a significant increase in wound healing or bleeding complications. These data are encouraging for planned trials of bevacizumab in adjuvant colorectal cancer.

An ongoing phase II trial is studying the effects of adding bevacizumab to IFL in untreated patients with measurable advanced colorectal cancer. Ninety-two patients were treated with a modified IFL and bevacizumab regimen. Interim safety data for 83 patients showed no statistically significant differences in overall grade 3 or 4 toxicity, and most of the reported side effects were attributed to IFL (Giantonio, Levy, et al., 2004).

### Table 2. Selected Adverse Events: Phase III Trial of Bevacizumab Plus IFL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>IFL + Placebo (n = 397)</th>
<th>IFL + Bevacizumab (n = 393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 adverse event</td>
<td>74.0</td>
<td>84.9*</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>7.1</td>
<td>8.4</td>
</tr>
<tr>
<td>Adverse event leading to death</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Grade 3/4 leukopenia</td>
<td>31.1</td>
<td>37.0</td>
</tr>
<tr>
<td>Grade 3/4 diarrhea</td>
<td>24.7</td>
<td>32.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>8.3</td>
<td>22.4*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2.3</td>
<td>11.0*</td>
</tr>
<tr>
<td>Any thrombotic event</td>
<td>16.2</td>
<td>19.4</td>
</tr>
<tr>
<td>Deep thrombophlebitis</td>
<td>6.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>5.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Grade 3/4 bleeding</td>
<td>2.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>21.7</td>
<td>26.5</td>
</tr>
<tr>
<td>Grade 2</td>
<td>5.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>0.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* p < 0.01

IFL—irinotecan, bolus fluorouracil, and leucovorin


Future Development of Bevacizumab

Phase II and III trials currently are examining bevacizumab in combination with various chemotherapeutic regimens. An ongoing phase III trial (i.e., Eastern Cooperative Oncology Group [ECOG] 3200) is studying bevacizumab plus FOLFOX4 (i.e., oxaliplatin 85 mg/m², LV 200 mg/m², 5-FU bolus 400 mg/m² plus infusional 600 mg/m²) as second-line treatment for patients with metastatic colorectal cancer. Analysis of these data is ongoing, but preliminary findings showed that median survival for patients receiving bevacizumab plus FOLFOX4 was 12.4 months compared with 10.7 months for those receiving FOLFOX4 alone. An interim safety analysis showed that the toxicity profile of this regimen is acceptable (Giantonio, Catalano, Meropol, O’Dwyer, & Benson, 2004). According to ECOG, preliminary study results were presented at the American Society of Clinical Oncology’s Gastrointestinal Cancers Symposium in January 2005 (Genentech, Inc., 2004b). In a recent study, Chen et al. (2004) reported preliminary data for a single arm, multicenter trial conducted through the National Cancer Institute Treatment Referral Center. The trial evaluated bevacizumab with 5-FU and LV for patients who had exhausted standard therapy. Preliminary data suggest that this regimen produced low response rates in patients who previously failed irinotecan- and oxaliplatin-based therapy. This study is expected to provide important safety and efficacy data about bevacizumab plus 5-FU and LV in the third-line setting. In addition, multiple studies with bevacizumab are ongoing for many tumor types, including lung, head and neck, metastatic breast, and renal cell cancers, as well as hematologic malignancies. For a complete list of trials with bevacizumab, visit www.clinicaltrials.gov. This Web site provides regular updates on federally and privately supported clinical research with human volunteers. In addition, the site lists the purpose of each trial, who may participate, locations, and contact information for more details.

### Nursing Implications

In planning care for patients with metastatic colorectal cancer, oncology nurses should anticipate some of the multiple problems that can develop and strive to prevent them. Patient education should include the...
mechanism of action of the therapies being administered, symptom prevention and management, and self-care strategies. Cultural diversity implications, psychosocial needs, and patient wishes also must be considered (Berg, 2003; King, 2001).

Reported side effects of bevacizumab are hypertension, hemorrhage, thromboembolism, proteinuria, and gastrointestinal perforation (Hurwitz, Fehrenbacher, Novotny, et al., 2004; Kabbinavar et al., 2003). For patients receiving bevacizumab, nurses should include questions about hypertension in their assessments. Patients’ blood pressure should be monitored before treatment and every two to three weeks during treatment (Middleton & Lapka, 2004). If hypertension occurs with bevacizumab, angiotensin-converting enzyme inhibitors, beta blockers, diuretics, or calcium channel blockers may be prescribed (Genentech, Inc., 2004a). Antihypertensive medications may need to be adjusted to maintain normal blood pressure in patients already taking antihypertensives. Patients with uncontrolled hypertension or in hypertensive crisis should discontinue bevacizumab. Individuals who develop hypertension should continue to have their blood pressure monitored after treatment is stopped.

Traditional approaches to hypertension management should be incorporated into the treatment plan, including stress management, diet, and physical activity. Although rarely successful in controlling blood pressure individually, they are important factors, especially when combined (Logan & Moore, 2004). A diet low in sodium and high in fruits, vegetables, and calcium is helpful when treating hypertension. A reduction in alcohol intake is one of the quickest ways to lower blood pressure. Studies show that more than 1 oz of alcohol a day in men and 0.5 oz a day in women will raise blood pressure (Gregoire, 2004).

Signs and symptoms of altered hemostasis include thrombosis, embolism, central nervous system bleed, epistaxis, hematemesis, hemoptysis, and bleeding at tumor sites. In the Hurwitz, Fehrenbacher, Novotny, et al. (2004) trial, epistaxis was the most commonly reported bleeding event with bevacizumab. It lasted less than five minutes, and no treatment was needed. Aspirin and nonsteroidal anti-inflammatory medications may be given. Concomitant full-dose anticoagulation therapy with bevacizumab plus chemotherapy does not appear to increase the risk of hemorrhagic complications in patients with metastatic colorectal cancer (Hambleton et al., 2004).

VEGF plays a role in wound healing, but bevacizumab may delay this process; therefore, treatment should not begin until 28 days after major surgery (Genentech, Inc., 2004a). This interval includes the half-life of bevacizumab (i.e., approximately 20 days). Patients requiring elective surgery should discontinue therapy before surgery. Any patient on bevacizumab experiencing wound dehiscence that requires medical intervention should discontinue therapy permanently. Monitoring for signs and symptoms of gastrointestinal perforations such as abdominal pain, constipation, and vomiting is essential. Differential diagnosis is key because similar symptoms can occur from the malignancy, medications, or dietary changes. If a patient develops a perforation, therapy should be suspended permanently.

An increase in the incidence and severity of proteinuria has been observed in patients receiving bevacizumab (Genentech, Inc., 2004a). In the majority of the clinical trials, baseline urine dipstick for proteinuria was assessed prior to bevacizumab therapy. Baseline urine dipstick or urinalysis should be monitored monthly (Muehlbauer, 2003). Management of abnormalities should be discussed with the physician, and 24-hour urine collections should be considered in patients who develop moderate proteinuria. In the majority of studies, bevacizumab was discontinued temporarily when proteinuria was 2 g or more in a 24-hour collection period. Once the level of proteinuria decreases to less than 2 g over 24 hours, treatment can be resumed (Genentech, Inc., 2004a). Hydration and nutrition have a role in urine concentration; therefore, patients’ dietary habits should be assessed regularly. Other comorbid conditions such as hypertension, diabetes, and cachexia can contribute to proteinuria. Bevacizumab should be discontinued permanently if a nephrotic syndrome develops. This syndrome typically is characterized by significant proteinuria, hyperaluminemia, periorbital edema, peripheral edema, and hyperlipidemia.

Patients with cancer are at increased risk for developing deep vein thrombosis. In fact, 50% of patients with cancer reportedly have had venous thrombosis at the time of autopsy, and 15% of patients with cancer develop significant thromboembolic events (Viale & Schwartz, 2004). Many factors contribute to the increased risk of thromboembolic events, and certain tumors are more likely to cause thrombosis (e.g., pancreatic, brain, prostate, gastric, lung). Cancer disrupts the normal coagulation by producing procoagulant factors. History of abnormal clotting, a sedentary lifestyle, chemotherapy, and cigarette smoking increase the risk for thrombosis. Patients should be assessed for symptoms, including chest pain or shortness of breath; pain in the abdomen, thighs, or legs; edema; skin discoloration or warmth; dizziness; light-headedness; and increased headaches or visual disturbances. Patients should be encouraged to exercise regularly to prevent stasis.

Infusion reactions with bevacizumab are rare (< 3%) (Genentech, Inc., 2004a); therefore, premedications are not required, but patients should be observed for hypersensitivity reactions, including fever, chills, rigors, and myalgias, during infusion of bevacizumab. If infusion reactions develop, symptoms should be treated as other biologic agents: Stop the infusion, assess the patient, and notify the physician. Standard treatment for anaphylactic reactions includes epinephrine 1:1000, hydrocortisone, and diphenhydramine; oxygen and IV fluids also may be required. Fever should be treated symptomatically, and meperidine may be given for rigors. For mild reactions, administer prophylactic diphenhydramine 25 mg IV and rantidine 50 mg IV; prolonged infusion time may allow therapy to be continued (CancerSourceRN.com, 2004).

Conclusion

Antiangiogenics, unlike other cancer treatments, are designed to limit the blood supply to tumors, causing a reduction in tumor burden. One advantage of using agents that target processes involving normally dividing endothelial cells, as opposed to tumor cells, is the possibility of circumventing drug resistance. Endothelial cells generally do not mutate as tumor cells do and do not generate the genetic diversity needed to produce drug-resistant cells. Antiangiogenic agents given with standard chemotherapy could reduce initial tumor burden and be used as adjuvant treatment to prolong disease-free survival in patients with cancer. Bevacizumab is an exciting addition to the repertoire of available agents in the treatment of colon cancer. Data continue to emerge, and additional clinical trials are needed to fully assess this agent. Oncology professionals must continually update their scientific knowledge regarding how these newer agents function and differ from traditional chemotherapy to provide effective patient education.

Author Contact: Denise V. Lapka, RN, MS, AOCN®, CCNS, can be reached at lapka .denise@gene.com, with copy to editor at CJONeditor@jsobel.com.


Rapid Recap

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

- Tumor growth is dependent on the development of new blood vessels (angiogenesis). One of the most potent regulators of angiogenesis is vascular endothelial growth factor.
- Bevacizumab recently was approved by the U.S. Food and Drug Administration in combination with IV 5-fluorouracil–based chemotherapy as a first-line treatment for patients with metastatic colorectal cancer.
- The main side effect with bevacizumab is hypertension, which is manageable with standard medication.