CHAPTER 3

Managing Side Effects of Anti-VEGF Treatment

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Managing Side Effects of Anti-VEGF Treatment (Bevacizumab)

*Bevacizumab* is a recombinant humanized IgG1 monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). VEGF is a natural protein that stimulates new blood vessel formation (angiogenesis). Its overexpression is common in tumor tissues, and it is associated with poorer prognosis in a variety of cancers. By binding to VEGF, bevacizumab chokes off tumor blood supply, thereby reducing tumor size and inhibiting metastasis.¹⁴

**Current and Future Uses**

*Bevacizumab* is the first antiangiogenic agent to receive approval from the FDA.³ It is indicated for

- First- or second-line treatment of metastatic colorectal cancer (mCRC) in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy
  - With IV 5-FU-based chemotherapy, recommended dosage is 5 mg/kg or 10 mg/kg every 2 weeks, administered as IV infusion
  - When used in combination with bolus-IFL (irinotecan, 5-FU, leucovorin), recommended dosage is 5 mg/kg every 2 weeks
  - When used in combination with FOLFOX4 (oxaliplatin, leucovorin, 5-FU), recommended dosage is 10 mg/kg every 2 weeks
- First-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous, non–small-cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel⁴
  - Recommended dosage is a 15 mg/kg IV infusion every 3 weeks⁴
- Treatment of metastatic human epidermal growth factor receptor 2 (HER2) negative breast cancer, in combination with paclitaxel for patients who have not received prior chemotherapy⁴
  - Recommended dosage is a 10 mg/kg IV infusion every 2 weeks⁴

More than 300 clinical trials are in progress investigating the efficacy of bevacizumab in the treatment of a variety of other cancers, including tumors of the head and neck, kidney, liver, esophagus, cervix, ovary, and pancreas. Trials are also investigating the use of bevacizumab in the treatment of other conditions, including macular degeneration and diabetic retinopathy.²⁵

**Side Effects**

Because bevacizumab is administered in combination with various chemotherapy regimens (eg, IFL, FOLFOX), the agent responsible for common side effects cannot always be identified with certainty. However, among the common side effects associated with treatment regimens that included bevacizumab in combination with chemotherapy in clinical trials are⁴

- Hypertension
- Minor bleeding
- Proteinuria
- Diarrhea
Fatigue
- Headache
- Vomiting
- Neutropenia and infection (depending on chemotherapy combination used)

Nasal septal perforation has been seen in postmarketing experience with bevacizumab.

Potentially serious side effects associated with bevacizumab include:
- Hypertension/hypertensive crisis
- Hemorrhage/bleeding events
- Proteinuria/nephrotic syndrome
- Arterial and venous thromboembolic events (ATEs and VTEs)
- Gastrointestinal (GI) perforations and fistulas
- Wound-healing complications
- Reversible posterior leukoencephalopathy syndrome (RPLS)

Side effects are graded on a scale of 1 to 4 according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events.

Managing Selected Side Effects
The prescribing information for bevacizumab does not recommend dose modifications. If intolerable adverse events occur, bevacizumab should be discontinued or suspended.

**Hypertension/ Hypertensive Crisis**
Hypertension is among the most common side effects of bevacizumab, but in most cases is manageable with standard oral antihypertensive medications. The incidence of grade 3 or 4 hypertension in clinical trials ranged from 8% to 18%. Complications of bevacizumab-induced hypertension can include potentially fatal hypertensive encephalopathy and central nervous system (CNS) hemorrhage. Hypertension can persist after bevacizumab is discontinued. Infusion reactions with the first dose of bevacizumab are rare (<3%) but have included hypertension and hypertensive crisis. Patients with uncontrolled hypertension should not be treated with bevacizumab.

To manage hypertension in patients treated with bevacizumab:
- Monitor blood pressure every 2 to 3 weeks during treatment with bevacizumab. Those who develop hypertension should have their pressure checked more frequently. Continue regular blood-pressure monitoring for patients who discontinue bevacizumab because of hypertension
- Incorporate lifestyle changes whenever possible: physical activity, diet, stress management, smoking cessation, limited alcohol consumption
- Apply standard guidelines for the use of antihypertensive medication, with the choice of specific agent to be determined by the treating physician
Medications used to control hypertension among patients being treated with bevacizumab have included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium-channel blockers. Suspend or discontinue bevacizumab when hypertension cannot be controlled with standard oral antihypertensive agents. Interrupt infusion of bevacizumab if severe infusion reaction occurs.

**Hemorrhage/Bleeding Events**

Bleeding events associated with bevacizumab range from mild nosebleeds, which are common, to serious—sometimes fatal—pulmonary hemorrhage. In clinical trials, serious or fatal hemorrhages occurred up to five times more often in patients treated with bevacizumab than in control groups. In addition to epistaxis and pulmonary hemorrhage, patients treated with bevacizumab have experienced hemoptysis, subarachnoid hemorrhage, GI hemorrhage, hematemesis, CNS hemorrhage, and vaginal bleeding.

Careful consideration should be given to risk of bleeding in determining candidacy for bevacizumab.

- Avoid bevacizumab for patients with lung metastases with central cavitation.
- Avoid bevacizumab for patients with CNS metastases because of the risk of CNS hemorrhage.
- Use particular caution when administering bevacizumab to patients with congenital or acquired bleeding or coagulation conditions.
- Exercise caution when administering bevacizumab to patients receiving full-dose anticoagulation therapy for the treatment of ATEs or VTEs. (See ATE/VTEs, page 5.)

During therapy with bevacizumab

- Discontinue treatment for any patient with hemorrhage that requires medical intervention. Serious hemorrhage should be treated with aggressive medical management.
- Discontinue treatment for any patient who has experienced recent hemoptysis involving ≥ ½ tsp of red blood. The drug’s prescribing information notes, however, that serious hemorrhagic events associated with bevacizumab generally occur without prior history of minor hemoptysis during its administration.
- Educate the patient about management of minor bleeding and the importance of reporting any bleeding events
  - If epistaxis (nosebleed) occurs, instruct the patient to lean forward and pinch the bridge of the nose between the thumb and forefinger
  - If epistaxis lasts for >10 to 15 minutes, or is accompanied by faintness or dizziness, instruct the patient to call his or her healthcare provider

**Proteinuria**

Severe proteinuria (>3.5 g/24 h) occurred in up to 3% of patients treated with bevacizumab in clinical trials. Patients who develop proteinuria are often asymptomatic. Factors that can impact proteinuria...
include hydration, nutrition, hypertension, and diabetes.\textsuperscript{11}

- Patients should undergo serial monitoring for protein levels prior to and during therapy.
  - Urinary dipstick or measurement of urine protein:creatinine ratio every two to three cycles\textsuperscript{11}
- If protein \( \geq 2 \) g/24 hours: Suspend bevacizumab, and restart when protein <2 g/24 hours\textsuperscript{4}
- Nephrotic syndrome: if protein >3.5 g protein/24 hours, hypoalbuminemia, edema, hyperlipidemia, and hypocoagulability, discontinue bevacizumab\textsuperscript{4,11}

**ATES and VTEs**

Bevacizumab has been associated with increased risk of serious, sometimes fatal, ATEs and VTEs. ATEs included cerebral infarction, myocardial infarction, transient ischemic attack, and angina. VTEs included deep venous thrombosis and intra-abdominal venous thrombosis.

The increased risk of ATEs applies to patients of all ages. However, patients who are \( \geq 65 \) years old are at additional risk, as are those with a prior history of ATEs\textsuperscript{4,12}

Patients were excluded from clinical trials if they had experienced clinically significant cardiovascular disease in the previous year.\textsuperscript{4} A pooled analysis of clinical trials found that the incidence of ATEs among patients treated with bevacizumab in combination with chemotherapy was 4.4\% compared with 1.9\% in patients treated with chemotherapy alone.\textsuperscript{4}

Hurwitz and Sain\textsuperscript{6} suggest that the risk of cancer mortality may outweigh the risk of ATEs, even in patients at higher risk for ATEs. However, this decision should be made between the treating physician and the patient after weighing all risks and benefits. Pooled analysis of bevacizumab trials has shown that the increased risk of ATE-related mortality is small compared with the increased risk of mortality related to cancer in the groups studied (ie, mCRC, relapsed metastatic breast cancer, and advanced or recurrent NSCLC).\textsuperscript{6}

To manage thrombosis in patients treated with bevacizumab

- Perform a complete history/physical assessment of a patient prior to that patient starting therapy with bevacizumab
  - Take note of the patient's age, as well as any prior history of ATEs/VTEs
- Assess for and advise patients to report any signs/symptoms of thrombosis (eg, new swelling, skin warmth or discoloration in legs or thighs, abdominal pain, rapid heartbeat, shortness of breath, chest pain or pressure, increased headaches or visual disturbances, lightheadedness or dizziness)
- Prescribers may consider anticoagulants for patients with ATEs/VTEs. Nurses should closely monitor patients who are on anticoagulant medications
  - If a patient is on an anticoagulant medication, caution should be exercised, since bleeding is a significant side effect of bevacizumab
However, a preliminary analysis of CRC patients being treated with bevacizumab found that those who began taking anticoagulants (primarily warfarin) after being diagnosed with ATEs or VTEs did not have increased risk of hemorrhagic complications. A second preliminary analysis found that low-dose aspirin therapy, when used to prevent primary or secondary ATEs, also did not appear to increase the risk of serious bleeding among patients being treated with bevacizumab. Further research is required before these results can be confidently applied in clinical practice.

- Permanently discontinue bevacizumab treatment in patients who experience a severe ATE.

**GI Perforation and Fistula Formation**

GI perforation associated with bevacizumab can include complication by fistula formation and intra-abdominal abscess. Reports have noted enterocutaneous, esophageal, duodenal, and rectal perforation, or fistula formation. Risk factors among mCRC patients who developed GI perforations included acute diverticulitis, obstruction, tumor at the site of perforation, abdominal carcinomatosis, and a history of abdominal radiation. The incidence of these events in clinical studies overall was 1%, but has been higher in some patient groups. Approximately 30% of reported cases have been fatal. In addition, non-GI fistulas, sometimes fatal, have been observed in <0.3% of patients.

- Monitor patients carefully for signs of GI perforation or fistula. Early detection is important.
- Instruct patient to immediately report any abdominal pain associated with nausea/vomiting or constipation.
  - Additional signs and symptoms of GI perforation include abdominal rigidity, rebound tenderness, fever or low temperature, tachycardia, and cool extremities.
  - Events usually appear within the first 50 days of treatment, although some have occurred after more than 1 year.
- Exercise special caution when treating patients at higher risk.
- Discontinue administration of bevacizumab in patients who develop GI perforation, fistula formation, and/or intra-abdominal abscess.

**Wound-Healing Complications**

Bevacizumab treatment may complicate wound healing, resulting in bleeding and dehiscence. Because evidence of wound-healing impairment emerged in animal studies, clinical trials excluded patients who had undergone surgery within <28 days.

In one trial of CRC patients, 15% of those who had surgery following treatment with chemotherapy plus bevacizumab developed wound-healing or bleeding complications, compared with 4% of control-group patients who had surgery. The longest interval between last dose of bevacizumab treatment and the development of a surgical complication observed in that study was 56 days. A phase III trial of CRC patients found no increase in complications involving insertion of venous access devices (eg, indwelling catheters) among patients receiving bevacizumab.
• Do not initiate bevacizumab therapy for at least 28 days following major surgery, and not before the surgical incision is fully healed\(^4\)

• Instruct the patient to discuss any plans for elective surgery with their oncologist/oncology healthcare provider

• Suspend bevacizumab therapy before elective surgery.\(^4\) The safe interval between termination of bevacizumab therapy and surgery is not precisely known, but the prescribing information notes that the drug has a half-life of approximately 20 days.\(^4\) Gordon and Cunningham\(^7\) recommend an interval of at least 30 days between discontinuation of bevacizumab therapy and surgery

• Conduct a careful risk:benefit analysis before performing emergency surgery on any patient undergoing bevacizumab treatment\(^7\)

• Implantation of a venous access device need not delay initiation of bevacizumab therapy\(^15\)

• Patients who develop wound-healing complications requiring medical intervention should discontinue bevacizumab therapy\(^4\)

**RPLS**

RPLS is a rare brain-capillary leak syndrome associated with hypertension, fluid retention, and cytotoxic effects of immunosuppressive drugs on the vascular endothelium.\(^16\) Reported incidence in clinical studies of bevacizumab and postmarketing experience is <0.1%.\(^16\)

- Diagnose RPLS with a magnetic resonance imaging scan
- Prompt recognition of RPLS is essential. Patient should be educated regarding the presenting symptoms and instructed to report immediately
  - Presenting symptoms may include headache, seizure, lethargy, confusion, visual abnormalities, and altered mental function

If RPLS occurs in patients treated with bevacizumab

- Discontinue bevacizumab. If or when it is safe to resume bevacizumab has not been determined
  - Symptoms usually resolve or improve within days\(^4,16\)
- Initiate treatment for hypertension when present\(^4,16\)

**Drug Interactions**

As noted above, caution should be exercised when combining bevacizumab with anticoagulant medications, including aspirin, due to the risk of bleeding. Otherwise few data are available on potential drug interactions with bevacizumab.\(^1,17\)

In a clinical trial in which CRC patients were randomized to receive bevacizumab in combination with bolus IFL chemotherapy or bolus IFL alone, patients in the bevacizumab arm had concentrations of SN38, the active metabolite of irinotecan, that were 33% higher, on average, than patients in the bolus IFL-alone arm. Patients in the bevacizumab plus bolus IFL arm also had higher incidence of grade 3 or 4 diarrhea and neutropenia.
In a small trial with NSCLC patients, three of eight patients treated with paclitaxel/carboplatin plus bevacizumab had a substantially lower paclitaxel exposure after four cycles of treatment than patients taking paclitaxel/carboplatin alone.4

**Special Populations**
Because bevacizumab inhibits angiogenesis, it is likely to have adverse effects on fetal development. Therefore, bevacizumab should not be used by pregnant women.4 Nursing mothers are advised to suspend nursing while undergoing treatment with bevacizumab and not to resume nursing until between 11 and 50 days after treatment has been discontinued.4

No dosage adjustments of bevacizumab are recommended based on age or gender. Although the risk of some side effects was found in various studies to be more pronounced in patients ≥65 years of age (eg, ATEs, hypertension, edema, proteinuria), bevacizumab appears to be, in general, safe for use in elderly patients.4,8,17 Studies have not been conducted to determine the safety of bevacizumab treatment in patients with renal or hepatic impairment,4 and the drug’s safety profile in treatment of children is unknown.4,17
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