Hypertension Associated With Bevacizumab

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As an advanced practice nurse, you care for patients who have a variety of chronic conditions, and you are expected to handle them all. How do you keep up with all of the advances in cardiology, endocrinology, gastroenterology, and infectious disease? You read this column, dedicated to managing a variety of primary care disorders in conjunction with cancer treatment. If you have developed expertise in management of one or more chronic diseases, consider writing for this column. Contact Associate Editor Joyce Marrs, MS, APRN-BC, OCN®, AOCNP, via e-mail at joycemrn@sbcglobal.net.

Case Study

Mr. B is a 49-year-old man who was diagnosed with stage III colon cancer in 2001. He initially underwent a right hemicolectomy followed by adjuvant 5-fluorouracil (5-FU) and leucovorin (LV). He did well until fall 2003, at which time progressive disease was noted in his lungs on a computed tomography (CT) scan, although he was asymptomatic. The decision was made to watch for disease progression or development of symptoms before initiation of first-line treatment for metastatic disease.

Mr. B did well until May 2004, when a CT scan showed that his lung metastases slowly had increased in size. The decision was made to begin chemotherapy along with a newly approved monoclonal antibody.

Treatment of Metastatic Colon Cancer

In February 2004, bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA) was approved by the U.S. Food and Drug Administration for use in first-line treatment, in combination with IV 5-FU-based regimens, for metastatic colorectal cancer based on the results of a phase III study by Hurwitz et al. (2004). Bevacizumab is a recombinant humanized monoclonal antibody that targets and inhibits vascular endothelial growth factor (VEGF) responsible for stimulating angiogenesis. Angiogenesis is the formation of new blood vessels (Franson & Lapka, 2005). Without the formation of new vascular growth, tumors are unable to increase in size by more than 1–2 mm from their blood supply (Berlin, 2002; Fernando & Hurwitz, 2004). Bevacizumab is theorized to prevent cancer from spreading by blocking the attachment of VEGF to endothelial cells, thereby stopping the signal to stimulate growth of new vessels necessary for cell proliferation and spread of the tumor (Fernando & Hurwitz; Wilkes, 2005). Rather than directly destroying cells to reduce tumor burden as conventional chemotherapy does, this drug prevents the growth and spread of cancer cells (Fernando & Hurwitz; Hurwitz et al.). In addition, bevacizumab may have an effect on remodeling existing tumor vasculature to improve drug penetration, thereby enhancing antitumor efficacy of chemotherapeutic agents (Hicklin & Ellis, 2005).

Adverse effects associated with bevacizumab therapy are increased incidences of hypertension, thrombosis, bleeding, proteinuria, and diarrhea. Although rare, a “black box warning” for gastrointestinal perforation has been indicated on bevacizumab’s package insert (Hurwitz et al., 2004). Kabbinavar et al. (2003) also reported fever, headache, rash, epistaxis, and chills in association with bevacizumab.

In June 2004, Mr. B’s medical oncologist started him on a combination treatment of LV 500 mg/m² by two-hour weekly IV infusion at six times per eight-week cycle, 5-FU 500 mg/m² by IV bolus one hour after initiation of each LV infusion, and bevacizumab 5 mg/kg over 90 minutes IV infusion every two weeks (Kabbinavar et al., 2003). Prior to the start of treatment, Mr. B’s Eastern Cooperative Oncology Group performance status was 0, and he had no significant comorbidities. He was 6’ 1”, weighed 205 lbs, and had a body mass index (BMI) of 27.1. Baseline blood pressure (BP) was elevated at 142/86 mmHg. Complete blood count and renal and liver function tests were within normal ranges. Dipstick urinalysis was negative for protein. He was on no medications other than a daily multivitamin.

Hypertension Associated With Bevacizumab

Hypertension is defined as consistent elevation of systemic arterial BP (McCance & Huether, 2002). In 2003, the seventh report of the Joint National Committee (JNC 7)
on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure issued new guidelines for the definition and management of hypertension (Chobanian et al., 2003). Blood pressure less than 120/80 mmHg is considered normal. Hypertension is defined as BP greater than 140/90 mmHg. The Cancer Therapy Evaluation Program (2003), in association with the National Cancer Institute and National Institutes of Health, described the Common Terminology Criteria for Adverse Events (CTCAE) that define grades of hypertension toxicity. These are explained in terms of greater than 20 mmHg increases in BP from baseline, or greater than 150/100 mmHg if previously normal. Table 1 shows a comparison of these stages, grades, and definitions.

In a phase III study by Hurwitz et al. (2004), the incidence of grade 3 hypertension in patients receiving bevacizumab plus chemotherapy was 11%, compared to 2.3% in those receiving the same regimen without this targeted therapy. The incidence of hypertension of any grade was 22.4%. No episodes of hypertensive crisis or deaths related to hypertension occurred.

Kabbinavar et al. (2003) reported that 19 of 104 (18%) patients experienced hypertension, with 47% of those having a preexisting history of elevated blood pressure. With higher doses of bevacizumab (10 mg/kg), the incidence of any grade of hypertension increased to 28%. Grade 3 hypertension occurred in 25% of participants in the higher-dose group. At lower doses (5 mg/kg), the incidence of hypertension was 11%, with 9% being grade 3.

According to the Avastin (bevacizumab) package insert (Genentech, Inc., 2004), the incidence of hypertension in individuals receiving bevacizumab with 5-FU-based regimens ranges from 60%–67%, compared to 43% in controls not receiving bevacizumab. Severe hypertension occurred in 7%–10%, compared to 2% in those not treated with bevacizumab.

The mechanism of hypertension is poorly understood. BP is controlled by factors affecting cardiac output and/or total peripheral resistance (McCance & Huether, 2002). A possible explanation for the occurrence of hypertension associated with bevacizumab may be related to the inhibition of VEGF. VEGF is a stimulator of nitrous oxide, a vasodilator (Sane, Anton, & Brosnihan, 2004). Normally, small amounts of nitrous oxide are released continually, which overcomes the vessels’ natural tendency to constrict. By inhibiting VEGF, less nitrous oxide is available for vasodilatation and vasoconstriction may occur. The vasoconstriction can cause a significant increase in blood pressure resulting from changes in peripheral vascular resistance (Hicklin & Ellis, 2005; Sane et al.).

Sane et al. (2004) also hypothesized that VEGF may have effects on the renin-angiotensin system, particularly on receptors associated with angiotensin I and angiotensin II. Components of this system may function as growth factors as well as in regulation of homeostasis and blood pressure. The vasomotor effect of angiotensin in stimulating vasopressin and aldosterone to increase water and sodium reabsorption is well known. However, the relationship of VEGF as an inhibitor or stimulator of various receptor types, including angiotensin, is unclear as yet. Further study of this area is necessary to understand these interactions and effects.

On Mr. B’s return to the clinic for his second treatment cycle, his blood pressure was 180/104 mmHg. The clinic nurse brought this to the attention of the nurse practitioner, who then evaluated Mr. B.

### Assessment of Hypertension

According to the JNC 7 report, “the relationship between BP and risk of cardiovascular disease events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance of myocardial infarction, heart failure, stroke and kidney disease” (Chobanian et al., 2003, p. 2562).

The three objectives of evaluation for hypertension are to assess lifestyle and identify other cardiovascular risk factors or concomitant conditions, determine identifiable causes of hypertension, and assess for presence or absence of target organ disease or cardiovascular disease (Chobanian et al., 2003) (see Figure 1). Many patients with cancer present with some or all of these risk factors and/or comorbidities and need to be evaluated and treated accordingly. Practitioners must be alert for these comorbidities as they provide supportive care for other effects of the illness and treatment.

Mr. B., upon starting his current treatment, had untreated stage 1 hypertension when classified using the JNC 7 system. As treatment progressed and he received cumulative bevacizumab doses, he developed CTCAE grade 3, or JNC 7 stage 2, hypertension. The nurse practitioner reviewed Mr. B’s current medication list, other comorbidities, the number of bevacizumab treatments thus far, blood values such as complete blood count, kidney and liver function tests, and urine dipstick for protein levels. When assessing for major cardiac risk factors, the nurse noted that he was not obese (BMI < 30) (National Institutes of Health [NIH] & National Heart, Lung,

### Table 1. Comparison of JNC 7 Blood Pressure Classification and Common Terminology Criteria for Adverse Events Grading of Hypertension

<table>
<thead>
<tr>
<th>Blood Pressure Classification</th>
<th>Systolic Blood Pressure (mmHg)</th>
<th>Diastolic Blood Pressure (mmHg)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–99</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>&gt; 160</td>
<td>&gt; 100</td>
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</tbody>
</table>

### Common Terminology Criteria for Adverse Events (v 3.0) Grading of Hypertension

<table>
<thead>
<tr>
<th>Grade</th>
<th>Adverse Event</th>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic, transient (&lt; 24 hours) increase by &gt; 20 mmHg (diastolic) or to &gt; 150/100 mmHg if previously within normal limits; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Recurrent or persistent (&gt; 24 hours) or symptomatic increase by &gt; 20 mmHg (diastolic) or to &gt; 150/100 mmHg if previously within normal limits; monotherapy may be indicated</td>
</tr>
<tr>
<td>3</td>
<td>Requiring more than one drug or more intensive therapy than previously</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences (e.g., hypertensive crisis)</td>
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<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

JNC 7—Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Major Cardiovascular Risk Factors

Hypertension

Cigarette smoking

Obesity (body mass index ≥ 30)

Physical inactivity

Dyslipidemia

Diabetes mellitus

Microalbuminuria or estimated glomerular filtration rate < 60 ml per minute

Age (> 55 years for men, > 65 years for women)

Family history of premature cardiovascular disease (men < 55 years or women < 65 years)

Identifiable Causes of Hypertension

Sleep apnea

Drug induced or drug related

Chronic kidney disease

Primary aldosteronism

Renovascular disease

Chronic steroid therapy and Cushing syndrome

Pheochromocytoma

Coarctation of the aorta

Thyroid or parathyroid disease

Indications of Target Organ Damage

Heart

• Left ventricular hypertrophy

• Angina or prior myocardial infarction

• Prior coronary revascularization

• Heart failure

Brain

• Stroke or transient ischemic attack

Chronic kidney disease

Peripheral vascular disease

Retinopathy

Figure 1. Assessment Objectives of Hypertension Evaluation


and Blood Institute, 1998), although he was considered overweight by the NIH standard because his BMI was higher than 25.0. He did not have a previous diagnosis of dyslipidemia, diabetes mellitus, or microalbuminuria, and he was younger than 55 years. Mr. B also was a nonsmoker and did not live a sedentary lifestyle. Other than his metastatic colon cancer and his treatment with bevacizumab, he did not have any notable drug-induced or disease-related identifiable causes for his hypertension. He showed no indications of target organ damage on examination.

Treatment of Hypertension

Therapeutic lifestyle changes are the mainstay of treatment for hypertension and are indicated for those with normal BP levels as well as those with any level of hypertension (Chobanian et al., 2003). Reducing weight to a BMI of 18.5–24.9, adopting an eating plan rich in fruits and vegetables and reduced content of saturated and total fat, exercising regularly for 30 minutes per day most days of the week, and limiting alcohol consumption to one ounce of ethanol per day are recommended for all individuals. Some of these recommendations may be difficult for individuals with cancer to follow. Fatigue caused by chemotherapy may make the ability to engage in aerobic activity for a 30-minute period difficult if not impossible. Anorexia, cachexia, nausea, and/or vomiting may limit intake or guide dietary preferences to items not recommended by these limitations.

For hypertension inadequately responsive to lifestyle modifications, JNC 7 (Chobanian et al., 2003) recommended that a thiazide-type diuretic should be used in most individuals with uncomplicated hypertension. Most individuals require treatment with two or more medications. Figure 2 shows the algorithm for treatment of hypertension proposed by JNC 7 (Chobanian et al.). JNC 7 also recommended the use of agents other than thiazide-type diuretics as initial treatment in cases with compelling indications for certain high-risk conditions (see Table 2).

Eighty-four percent of those experiencing hypertension in the Kabbinavar et al. (2003) study required oral antihypertensive therapy. Hurwitz et al. (2004) reported that all episodes of hypertension occurring in relation to bevacizumab were manageable with standard oral antihypertensive agents (i.e., calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics).

The nurse practitioner discussed the situation with Mr. B, who denied headaches,
Dizziness, tinnitus, vision changes, or other signs of a hypertensive crisis. He verbalized that he never had been prescribed an antihypertensive and, after being instructed about the rationale behind hypertension management, he agreed to begin treatment. He was started on lisinopril 20 mg daily in light of the risk of proteinuria associated with bevacizumab (Kabbinavar et al., 2003). He received written and verbal information about potential side effects and was instructed to contact his healthcare providers should the side effects occur.

Monitoring Recommendations

Hypertension may develop at any point during treatment with bevacizumab. Blood pressure should be monitored every two to three weeks and more frequently if hypertension develops (Knop, 2005). Wilkes (2005) recommended that BP should be assessed prior to each chemotherapy treatment, between physician visits, and for as long as three months following completion of bevacizumab therapy. One advantage of the oncology setting as opposed to the primary care setting is that patients visit clinics more frequently, which enables monitoring of responses to interventions much more closely.

Mr. B returned on a weekly basis for his treatment and had his BP checked at each visit. The nurse practitioner was able to meet with him to assess for compliance, side effects, and understanding of the treatment plan. As noted previously, the JCN 7 guidelines stated that most patients with hypertension require two or more antihypertensive medications to achieve a goal BP of less than 140/90 mmHg. At his last treatment, Mr. B’s BP was 132/80 mmHg, he was tolerating therapy well, and he required only one antihypertensive medication.

Table 2. Compelling Indications for Use of Individual Drug Classes in the Treatment of Hypertension

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Diuretic</th>
<th>BB</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>ALDO ANT</th>
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<tbody>
<tr>
<td>Heart failure</td>
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<td>Postmyocardial infarction</td>
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<td>High coronary disease risk</td>
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<td>Diabetes</td>
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<td>Chronic kidney disease</td>
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<td>Recurrent stroke prevention</td>
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</tbody>
</table>

ACEI—angiotensin-converting enzyme inhibitor; Aldo ANT—aldosterone antagonist; ARB—angiotensin receptor blocker; BB—beta blocker; CCB—calcium channel blocker.

References


Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., et al. (2004). Bevacizumab plus irinotecan,


