Hypertension in the Oncology Setting

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Definition

By definition, BP is the product of cardiac output and peripheral vascular resistance (BP = cardiac output x peripheral resistance). HTN is caused by an increase in cardiac output, peripheral resistance, or both. Cardiac output may be increased by any condition that raises heart rate or stroke volume, whereas peripheral resistance is increased by any factor that raises blood viscosity or reduces vessel diameter (Brashers, Haak, & Richardson, 1998). Therefore, variation in extracellular fluid volume, the contractile state of the heart, and vascular tone determine the variation in BP level (Schwartz & Sheps, 2004).

Two types of HTN exist: primary and secondary. Primary HTN, also known as essential HTN, is of unknown cause. Secondary HTN, on the other hand, results from an underlying, identifiable, and often correctable cause. Some causes of secondary HTN include renovascular disease, polycystic renal disease, and pharmacologic or nonpharmacologic medication side effects (Onusko, 2003). Only 5%–10% of HTN cases are believed to result from secondary causes. A diagnosis of HTN is based on the average of two or more properly measured, elevated BP readings on each of two or more office visits (National Heart, Lung, and Blood Institute, 2003). See Table 1 for classification of adult BPs.

Oncologists use the Common Terminology Criteria for Adverse Events as developed by the National Cancer Institute to report and grade symptoms. This system classifies HTN somewhat differently than that outlined by HTN specialists and is explained in Table 2.

In incidence and Epidemiology

HTN has been found in more than half of people older than 65 years (Kaplan, 1998b). As many as 65 million individuals with HTN currently take antihypertensive medications or have received recommendations from a physician to initiate treatment (Centers for Disease Control and Prevention, 2004). This equates to about one in three U.S. adults with high BP.

The American Cancer Society (2005) estimated that one in three Americans can expect to be diagnosed with cancer in their lifetime. The overlap between these two serious and often chronic conditions is significant.

Pathophysiology

Several hypotheses for the pathogenesis of essential HTN exist. Some of these include high dietary sodium intake and defects in renal sodium excretion, increases in blood volume, inappropriate autoregulation, over-stimulation of sympathetic neural fibers in the heart and vessels, and hormonal inhibition of sodium-potassium transport across cell walls in the kidneys and blood vessels (Brashers et al., 1998).

Secondary HTN is caused by a systemic disease process that raises either peripheral vascular resistance or cardiac output. Renal, endocrine, vascular, and neurologic disorders; acute stresses (e.g., surgery, hyperventilation); and drugs may elevate BP. If the cause of the elevation is removed before permanent structural changes occur, BP should return to normal (Onusko, 2003).

Patients with cancer are at risk for HTN secondary to a number of causes, including...
use of corticosteroids (secondary to sodium and water retention), surgical resection of a tumor (acute stress precipitating the release of catecholamines and glucocorticoids), paraneoplastic syndromes (e.g., aldosterone secreting tumor), and, most recently, the use of biologic agents such as bevacizumab.

Signs and Symptoms

Early in the disease process, HTN has no clinical manifestations other than an elevation in BP. Some patients with HTN never have signs or symptoms, whereas others may become very ill. Symptoms and signs are related to the systems that have been affected by the process and may include renal insufficiency, central nervous system dysfunction, impaired vision, impaired mobility, vascular occlusion, and edema (Brashers et al., 1998).

Assessment

When treating patients with cancer and HTN (generally defined as greater than 140/90 mmHg), proper identification and management can be crucial to the continuation of patients’ cancer treatments. An adequate medical history, physical examination, update of medication list, and baseline laboratory data should be obtained.

Medical history: Some comorbidities, such as diabetes mellitus or renal disease, would dictate a lower targeted BP (< 130/80 mmHg). Other conditions are expected to contribute to increased risk of HTN, such as preexisting cardiovascular disease, hyperthyroidism, hypothyroidism, and obstructive sleep apnea.

Physical examination: Evaluation should include measurement of BP, with verification in the contralateral arm. A thorough physical examination should focus on potential causes or complications of elevated BP.

Medications Causing Hypertension

Many prescription and nonprescription drugs can cause or exacerbate HTN. Specific to the oncology setting are growth factors and some biologic agents such as bevacizumab.

Growth factors: Growth factors, such as erythropoietin and darbepoetin, are used commonly in the oncology setting for the treatment of chemotherapy-induced anemia. A high erythropoietin level can elevate BP secondary to polycythemia and hyperviscosity mechanisms or by direct pressor effects (Onusko, 2003). These medications are contraindicated in individuals with uncontrolled HTN.

Biologic agents: Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor and is used for the treatment of advanced colorectal cancer. The incidence of HTN is approximately 15% when bevacizumab is added to FOLFOX over FOLFOX alone (Hurwitz et al., 2005). HTN from bevacizumab most commonly is mild to moderate in severity and rarely requires discontinuation of the medication. The condition is reversible when the medication is discontinued. Bevacizumab should be discontinued permanently in patients with hypertensive crisis. Temporary suspension is recommended in patients with severe HTN that is not controlled with medication management (Genentech, Inc., 2004).

Miscellaneous agents: Some immunosuppressive agents such as cyclosporine (Sandimmune, Novartis Pharmaceuticals, East Hanover, NJ), tacrolimus (Prograf, Astellas Pharma US, Inc., Deerfield, IL), and corticosteroids have been correlated with elevated BP. Nonsteroidal anti-inflammatory drugs can aggravate underlying HTN by virtue of their antiplatelet effects on the kidneys. Herbal preparations and supplements that also have been found to increase BP or interfere with the effectiveness of BP medications are listed in Table 3.

Diagnostic Tests

Patients with newly diagnosed HTN may have a 12-lead electrocardiogram to rule out other cardiovascular complications as arrhythmias. Other testing may include an echocardiogram or a multiple gated acquisition scan. Laboratory data should include a complete blood count to observe hematocrit; a urinalysis to assess kidney function; a comprehensive metabolic panel to assess for hepatic, renal, and cardiovascular complications; and a lipid panel that measures total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides (National Heart, Lung, and Blood Institute, 2003).

Pharmacologic and Nonpharmacologic Interventions

The ultimate goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Established target BP goals are less than 140/90 mmHg for most patients; for patients with a history of renal disease and/or diabetes, the goal is less than 130/80 mmHg.

Several classes of antihypertensive medications are used to successfully treat high BP, including thiazide-type diuretics, beta blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). Most patients will require two or more antihypertensive medications to achieve their BP goals. Typically, treatment is initiated with a single drug. If mono-therapy is ineffective, the current recommendation is to add a second drug from a different class. If a drug is not tolerated or is contraindicated, another class of medication should be used. See Figure 1 for a treatment algorithm.

Diuretics: Diuretics are virtually unmatched in preventing the cardiovascular complications of HTN and should be used

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### Table 1. Classification of Blood Pressure for Adults 18 Years of Age or Older

<table>
<thead>
<tr>
<th>Category</th>
<th>Blood Pressure Level (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Systolic &lt; 120, diastolic &lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>Systolic 120–139, diastolic 80–89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Stage 1: Systolic 140–159, diastolic 90–99</td>
</tr>
<tr>
<td></td>
<td>Stage 2: Systolic ≥ 160, diastolic ≥ 100</td>
</tr>
</tbody>
</table>


### Table 2. Grading of Hypertension

<table>
<thead>
<tr>
<th>Grade</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic, transient (&lt; 24 hours) increase by &gt; 20 mmHg (diastolic) or to 150/100 mmHg if previously within normal limits (WNL); 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 WNL; monotherapy may be indicated</td>
</tr>
<tr>
<td>3</td>
<td>Requiring more than one drug or more intensive therapy than previously; &gt; 150/100 mmHg</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences (e.g., hypertensive crisis); &gt; 200/110 mmHg</td>
</tr>
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</table>

as initial therapy for most patients with HTN. They enhance the antihypertensive efficacy of multidrug regimens and are more affordable than other BP agents. Thiazide diuretics, such as hydrochlorothiazide or chlorothiazide, are best in patients with a serum creatinine level below 1.5 mg/dl (133 mmol/L), whereas torsemide and metolazone are preferred in patients with higher serum creatinine levels (Kaplan, 1998a). Loop diuretics such as furosemide work, but they are too short acting to provide the continual diuretic effects needed to keep serum creatinine levels (Kaplan, 1998a). Loop diuretics may decrease sympathetic outflow from the kidneys and may decrease salt and water excretion (Kaplan, 1998a).

Others

Herbal remedies: These are too short acting to provide the continual diuretic effects needed to keep serum creatinine levels (Kaplan, 1998a). Loop diuretics such as furosemide work, but they are too short acting to provide the continual diuretic effects needed to keep serum creatinine levels (Kaplan, 1998a). Loop diuretics may decrease sympathetic outflow from the kidneys and may decrease salt and water excretion (Kaplan, 1998a).

Angiotensin II receptor blockers: ARBs are medications that block the action of angiotensin II. Their pharmacologic effects are similar to ACEIs in that they produce vasodilation and block aldosterone secretion. Side effect profile is similar to ACEIs, with a reduced risk of cough. Examples of ARBs are candesartan, eprosartan, irbesartan, valsartan, and losartan.

Calcium channel blockers: Calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. CCBs block the inward movement of calcium by binding to calcium channels in the heart and smooth muscle of the coronary and peripheral vasculature. The end result is relaxation of vascular smooth muscle, dilating mainly arterioles. CCBs are useful in the treatment of hypertensive patients with asthma, diabetes, angina, and/or peripheral vascular disease. Examples include verapamil, amlodipine, and nifedipine (Mycek et al., 2000).

In choosing an antihypertensive medication, consideration should be taken for long-acting agents, which may improve compliance, reduce the cost of therapy, and reduce the risk of cardiovascular complications.

### Table 3. Miscellaneous Drugs That Can Raise Blood Pressure or Interfere With Antihypertensive Medication Efficacy

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>DRUG EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Moderate or heavy intake (may increase cortisol secretion)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Nicotine, cocaine, amphetamines</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants (phenelzine, bupropion, venlafaxine)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Weight-loss preparations with ephedra (ma huang)</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Over-the-counter decongestants (pseudoephedrine)</td>
</tr>
<tr>
<td>Herbal remedies</td>
<td>Yohimbine, ginkgo, ginseng, licorice, blue cohosh, foxglove</td>
</tr>
<tr>
<td>Others</td>
<td>Hormones (estrogen, testosterone), methylphenidate</td>
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</tbody>
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**Lifestyle modifications**

- Not at goal blood pressure (<140/90 mmHg)
- (<130/80 mmHg for those with diabetes and chronic kidney disease)

**Initial drug choices**

**Stage 1 Hypertension**

- (SBP 140–159 mmHg or DBP 90–99 mmHg)
- Thiazide-type diuretics for most. May consider ACEIs, ARBs, BBs, CCBs, or combination.

**Stage 2 Hypertension**

- (SBP ≥ 180 mmHg or DBP ≥ 100 mmHg)
- Two-drug combination for most (usually thiazide-type diuretic and ACEIs, ARBs, BBs, or CCBs).

**Not at global blood pressure**

- Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.

**Drug(s) for the compelling indications**

Other antihypertensive drugs (diuretics, ACEIs, ARBs, BBs, CCBs) as needed.

ACEI—angiotensin-converting enzyme inhibitor; ARB—angiotensin receptor blocker; BB—beta blocker; CCB—calcium channel blocker; DBP—diastolic blood pressure; SBP—systolic blood pressure

**Figure 1. Algorithm for Treatment of Hypertension**

Special Considerations: African Americans

Prevalence, severity, and impact of HTN are increased in African Americans. First choice of therapy should include a diuretic. BBs generally are less effective in African Americans. And although rare, ACEI-induced angioedema occurs two to four times more often in African Americans than in other groups (National Heart, Lung, and Blood Institute, 2003). Second-line therapy may include CCBs, BBs, ACEIs, and ARBs.

Nonpharmacologic Recommendations

Nonpharmacologic recommendations for management of HTN include maintenance of weight through regular exercise and diet. Sodium restriction to less than 2 g per day is recommended to maintain BP (National Heart, Lung, and Blood Institute, 2003).

Patient Education

Patient education should include an explanation of the possible causes of elevated BP and the importance of treating HTN during cancer treatment. Self-monitoring should include instruction on how and when to take BP at home, identification of worrisome symptoms, medication-related instructions, and when to call the clinic.

Recommendations for Follow-Up

Generally, patients with high BP currently undergoing treatment for cancer can be managed on an outpatient basis with one to two antihypertensive medications. Recommended follow-up is at monthly intervals until the BP goal is reached. If a patient’s BP is uncontrolled despite appropriate adjustments in medication doses and class, referral to the patient’s primary care provider or cardiologist is indicated.

Follow-Up of Case Presentation

On K.A.’s return to the clinic for her sixth cycle of chemotherapy, her average BP was 148/88 mmHg. Her lisinopril was increased to 20 mg daily; hydrochlorothiazide remained at 25 mg daily. After one week on this therapy, her BP measurements averaged 135/84 mmHg. In reviewing her past medical history and medication list, the HTN was attributed to bevacizumab.

Summary

In the oncology setting, HTN is a common comorbidity and complication of some treatments. A thorough assessment of each patient, including medical history and current medication list, is used to screen for HTN. The Joint National Committee guidelines (National Heart, Lung, and Blood Institute, 2003) have provided a resource for proper selection of medications for management of HTN, with considerations for special populations.

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References


