Hypertension Management in the Era of Targeted Therapies for Cancer

April 08, 2009
By Sandra E. Kurtin, RN, MS [1]

Hypertension (HTN) is prevalent in the general population, particularly in individuals over the age of 60 years. More than 50% of individuals aged 60 to 69 years and more than 75% of individuals age 70 or older are affected.[1]

Hypertension (HTN) is prevalent in the general population, particularly in individuals over the age of 60 years. More than 50% of individuals aged 60 to 69 years and more than 75% of individuals age 70 or older are affected.[1]

These populations also are more likely to have a diagnosis of cancer. Risk factors for HTN are well established and include modifiable risk factors (obesity, tobacco and alcohol abuse, and physical inactivity), disease-related factors (diabetes mellitus, renal insufficiency or failure, thyroid or parathyroid disease, hyperlipidemia), increasing age, family history, and drug-induced or drug-related causes.[2] Many of these same factors are associated with an increased risk of malignancy.

As the population ages, both HTN and cancer will become more common. Therefore, patients with cancer who have existing HTN and those who are at an increased risk because of age or other risk factors will be common in the oncology setting. There are numerous considerations in the patient with both cancer and HTN, either as a primary problem or secondary to other comorbid conditions such as diabetes. Many newer therapeutic agents, specifically antiangiogenesis agents, are associated with HTN. Understanding the risk factors, pathophysiology, and clinical measures of HTN in the general population and the unique needs of the cancer patient with HTN will improve the individualized management of these patients.

BASICS OF HYPERTENSION MANAGEMENT

Hypertension is considered a common but manageable problem. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) defines HTN as a systolic blood pressure (SBP) of 140–159 mmHg or a diastolic blood pressure (DBP) of 90–99 mmHg. The generally accepted target blood pressure is 120/80 mmHg. A pressure of 140/90 mmHg indicates the need for antihypertensive treatment in otherwise healthy individuals. This target is 130/80 mmHg for patients with additional risk factors, specifically cardiovascular disease (CVD), chronic renal disease, or diabetes.

The JNC guidelines further define levels of HTN and are widely used to determine management. It is important to note that these parameters are based on the average of two or more properly measured readings (sitting for at least 5 minutes at rest with feet on floor and arms supported at heart level) at each of two or more visits after an initial screening visit, and are applied to adults who are not acutely ill and are not taking antihypertensive medications.[1]

Newly diagnosed cancer, recurrence or progression of cancer, and certainly the administration of treatment require clinicians to further characterize HTN in the oncology population. Furthermore, clinical measures of blood pressure (BP) are often taken after walking a patient back to an examination room or intake area. Additional factors that may affect BP measures include smoking within 15 minutes of a BP check, time of day (ie, circadian rhythm, as BP values are higher in the early morning, lower during sleep or rest), the presence of pain, and “white coat” syndrome.
Boggia et al found average ambulatory readings from patients, taken over a 24-hour period, were lower than clinic readings by between 10/5 and 20/10 mmHg.[3] Thus multiple measures representing variable times of day and settings are most helpful in determining a 24-hour average BP. Several studies support a 24-hour average BP > 135/85 mmHg as being linked to adverse cardiovascular events.[4]

More recently, several epidemiological studies have suggested microalbuminuria (30–300 mg/d) as a strong predictor of cardiovascular events and death in hypertensive patients. Institution of antihypertensive therapy is an effective tool for reduction of albuminuria and secondary adverse events.[5] The National Institutes of Health and National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) are the most commonly used criteria for classification of adverse events in oncology clinical trials. The criteria specific to grading of HTN in the oncology population focus on changes in blood pressure measures from baseline.

Data from observational trials of more than 1 million individuals support the relationship between blood pressure and risk of cardiovascular disease and stroke as a continuous process independent of any other risk factor.[6] Specifically, for each incremental increase in SBP of 20 mmHg or DBP of 10 mmHg from baseline there is a doubling of mortality associated with CVD or ischemic heart disease. Sustained episodes of HTN increase this risk. Thus the NCI CTCAE grading scale focuses on duration of HTN and incremental change in BP from baseline, the presence of symptoms attributable to the change in BP, and the need to institute therapy. It is implied that these changes are attributable to the cancer therapy. Severe HTN (SBP > 180 mmHg or DBP > 120 mmHg) and sustained BP > 150/100 despite modification of the antihypertension regimen require immediate intervention and modification or discontinuation of the cancer therapy. Although the NCI CTCAE criteria and the JNC guidelines provide basic parameters for HTN grading and management, each patient must be evaluated according to his baseline blood pressure (preferably prior to the cancer diagnosis), the presence of additional risk factors for CVD, age, ethnicity, and response to treatment for HTN. Identification of the underlying cause of the HTN is critical to guide treatment and avoid unnecessary

<table>
<thead>
<tr>
<th>Agent and Dosing</th>
<th>FDA-Approved Indication(s)</th>
<th>Class</th>
<th>Therapeutic Targets</th>
<th>Incidence of HTN (grade 3/4)</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab 5–15 mg/kg given every 2 to 3 weeks IV</td>
<td>Colorectal Cancer (m) Lung Cancer (m) Breast Cancer(m)</td>
<td>MoAb</td>
<td>VEGF ligand</td>
<td>22% (11%)</td>
<td>• Median time to onset of HTN: 131 days (7–16) • No drug-drug interactions</td>
</tr>
<tr>
<td>Sorafenib 400 mg PO bid</td>
<td>RCC HCC</td>
<td>MoAb</td>
<td>c-KIT PDGFR VEGFR1-3 Raf B-Raf ERK</td>
<td>17% (4%)</td>
<td>• Most common in the first 4 weeks of treatment. • Undergoes partial metabolism by CYP3A4—monitor closely if administering ritampin, irinotecan, docetaxel, doxorubicin, or fluorouracil • Co-administration of inhibitors may require dose adjustment</td>
</tr>
</tbody>
</table>

GIST = gastrointestinal stromal tumors, HCC = hepatocellular cancer, m = metastatic, MoAb = monoclonal antibody, RCC = renal cell cancer, iHTN = treatment-related hypertension

Information from References 15,17–19.
changes to the cancer therapy. Familiarity with cancer therapies associated with HTN is essential. All clinical trials exclude patients thought to have uncontrolled CVD or HTN, thus limiting knowledge specific to use of these agents in the general population, which tends to be older and to have more comorbid conditions.[7] Postmarketing use of agents associated with HTN requires integration of an individualized approach to treatment incorporating these general guidelines. Ongoing evaluation of the cancer patient is necessary to identify factors that may alter blood pressure, including weight loss, exacerbation of diabetes by steroid administration, chronic inflammatory states common to disseminated disease, thyroid imbalances, and renal effects of treatment or disease.

HYPERTENSION AND ANTIANGIOGENIC AGENTS

Both angiogenesis and endothelial function are thought to play a role in treatment-related HTN (tHTN).[8] Antiangiogenic therapies in particular are known to cause hypertension (see Table 1). The exact mechanisms are not known; however, several contributing factors are suspected. Antiangiogenic properties thought to play a role in hypertension include a reduction in the number of arterioles and capillaries, which contributes to vascular stiffness and increased peripheral vascular resistance (rarefaction); decreased nitric oxide bioavailability, resulting in vasoconstriction; and decreased sodium ion renal excretion and thus increased cardiac afterload.[9,10] Interestingly, rarefaction is common with aging and is also reported in younger patients who have a genetic predisposition for HTN, placing these patients at increased risk when treated with angiogenesis inhibiting agents.[10] The hypertensive effects of the antiangiogenic agents vary in onset and duration.

MANAGEMENT OF t-HTN IN THE ONCOLOGY SETTING

Continued collaboration with referring providers is advised for optimal management of HTN in the cancer patient. Effective evaluation of patients with complex cardiovascular histories or long-standing diabetes by primary care providers or specialists who are familiar with the patient’s history will provide useful information when considering cancer therapies associated with HTN. These providers are generally more familiar with the most current antihypertensive strategies and those that may be potentially detrimental to the individual patient.

However, the oncology clinician must be familiar with drugs commonly used in the oncology setting that are known to be associated with HTN, as well as the basic principles of HTN management and guidelines for dose modification or cessation of therapy. Aggressive management of hypertension in these patients will promote safe continuation of cancer therapies.

Baseline evaluation of hypertensive risk is necessary prior to initiating therapies associated with HTN. This should include a review of the patient’s medical history, social history including lifestyle (tobacco, caffeine, alcohol), family history of CVD/HTN, and medication profile. The medication review should include any over-the-counter (OTC) herbal medications as many of these may contribute to hypertension. (Prescription and OTC medications to check for include MAO [monoamine oxidase] inhibitors, SSRI [selective serotonin reuptake inhibitor] agents, tricyclic antidepressants, ephedra, pseudophedrine, hormones, cohosh, foxglove, and selected other agents).[11] Complete physical examination with particular attention to cardiopulmonary evaluation should be completed at baseline and with each return visit. Laboratory analysis should include hepatic, renal, and hematological parameters at baseline and at regular intervals during treatment. Additional parameters that should be considered in patients receiving antiangiogenic drugs include a baseline lipid profile, thyroid function tests, urinalysis including urine protein and albumin, and if urinalysis results are abnormal, a 24-hour urine test for complete evaluation. Patients presenting with HTN or a high-risk profile may benefit from a baseline EKG and echocardiogram or multiple gated acquisition (MUGA) scan to evaluate underlying cardiovascular disease. Consultation with the primary care physician or cardiologist often will provide results of cardiovascular testing, avoiding duplication of testing.

Angiogenesis inhibitors can be associated with tHTN. Three such FDA-approved agents are bevacizumab (Avastin), sorafenib (Nexavar), and sunitinib (Sutent). Additional ones that are in clinical trials appear to pose a similar risk of tHTN. The frequency and onset of HTN vary with each drug and are estimated based on clinical trial data. The actual incidence in postmarketing use of the drugs is not known, as these patients likely include more individuals who are older, who have pre-existing HTN and/or a higher risk profile, and more ethnic minorities, often underrepresented in
Yang et al reported median time to onset of hypertension after the initial dose of bevacizumab was 131 days (range, 7–316 days).[12] Veronese et al reported an increase in systolic BP of 20 mmHg within 3 weeks of initiating treatment with sorafenib at a dosage of 400 mg twice daily, which is the currently approved dosage for renal cell and hepatocellular carcinoma.[10] Sustained hypertension following discontinuation of these drugs has also been reported and is important to consider in effective management of tHTN, as the antihypertensive medications may need to be gradually titrated. In the event of a drug holiday for adverse events, it is likely that the patient will need to continue the antihypertensive regimen. Increased frequency of monitoring may be indicated in these instances. In addition, sustained moderate to severe hypertension is thought to contribute to a rare but potentially fatal complication of reversible posterior leukoencephalopathy.

All guidelines for management of HTN include recommendations for lifestyle management including diet (low salt, low fat), exercise, avoidance of substances known to exacerbate HTN (tobacco, alcohol, stimulants), stress management, and aggressive management of comorbid conditions. Frequency of dosing, the number of drugs required, cost to the patient, and potential toxicities of the antihypertensive agents also must be considered. Patient education outlining the importance of effective HTN management to allow continuation of therapy, discussing reportable signs and symptoms, and demonstrating home BP checks, as well as periodic calibration of the home BP cuff, will encourage adherence to the regimen.

There is no consensus on recommendations of specific antihypertensive regimens used to manage tHTN specifically related to angiogenesis antagonists. Most clinical trials using oral antiangiogenic agents excluded the use of antihypertensive agents known to require CYP450 metabolism, and specific antihypertensive protocols were not included in the registration trials for these agents. Postmarketing use of these agents is common. Consideration of the underlying mechanism of tHTN specific to antiangiogenesis suggests use of ACE (angiotensin-converting enzyme) inhibitors may be beneficial as they affect nitric oxide.[13] The American Diabetes Association recommends use of angiotensin-receptor blockers as the treatment of choice in hypertensive patients with diabetes, frank proteinuria, and/or microalbuminuria.[14] Sunitinib undergoes partial metabolism via cytochrome P450, which is inhibited by verapamil and diltiazem, creating a potential for increased toxicity. It also may be affected by high-fat meals, which delay absorption and increase the risk of toxicity.[15] Diuretics remain the first-line choice for
treatment of HTN in all patient populations, except those with chronic kidney disease (CRD), which is an important consideration for patients with metastatic renal cell carcinoma or a history of CRD.[1] Rare cases of cardiac ischemia have been reported for both sorafenib and sunitinib, requiring careful monitoring and aggressive control of hypertension. Early signs of congestive heart failure should be investigated further as potential indication of cardiac damage.[16] Application of the general guidelines provided by consensus groups and knowledge of the principles of HTN provide an initial platform for management of tHTN in the oncology setting. However, several other factors need to be considered for these patients to allow continuation of their antiangiogenic therapies. Drug-specific criteria for discontinuing therapy based on the specific disease entity, pathophysiology, and risk of secondary effects may need to be developed, as the consensus guidelines for secondary HTN in the general population may not adequately characterize these patients. These guidelines may include a threshold for initiating antihypertensive therapy that is lower than those thresholds cited in the consensus statements when the expected risk of tHTN is high. Starting antihypertensive therapies in patients with existing HTN or those at high risk prior to starting their treatment may be an effective way to prevent dose reductions, dose delays, or adverse events. Initiating both antihypertensive agents and antiangiogenic agents simultaneously may make it difficult to appropriately attribute adverse events such as nausea, dizziness, diarrhea, palpitations, or cough to the appropriate agent. HTN can vary over the course of treatment and the antihypertensive regimen may require intermittent modification for optimal control. It will be necessary to continue to refine tHTN guidelines specific to these agents and include HTN management as a part of ongoing clinical trials to identify the most effective strategies.


Source URL:

Links: