Hypertension in cancer patients

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Hypertension is the force of blood pushing against the walls of the arteries. It is measured as systolic pressure when the heart beats and pumps blood and as diastolic pressure in the arteries when the heart rests between beats.[1] There are 4 stages in blood pressure classification—normal, prehypertension, stage 1, and stage 2. Hypertension affects approximately 50 million people in the United States and 1 billion people worldwide. People who are normotensive at age 55 years have a 90% chance of developing hypertension in their lifetime. Starting with a blood pressure of 115/75 mmHg, the risk of cardiovascular death doubles with each 20/10 mmHg increment.[2]

Currently, there are many different drug classes that can increase blood pressure. These include acetaminophen and NSAIDs, antidepressants, birth control, decongestants, steroids, and chemotherapy agents. In the oncology setting, steroids and chemotherapy agents are encountered most often. Drugs such as bevacizumab, tamoxifen, and sorafenib have been shown to cause an increase in blood pressure.[3] Aromatase inhibitors such as tamoxifen have been associated with an increase in thromboembolic events, including an increase in blood pressure. Studies have shown a significant increase in the risk of ischemic heart disease and cerebrovascular accidents in women who were put on tamoxifen and had pre-existing hypertension.[4]

The blood pressure goal for most patients is less than 140/90 mmHg; for patients with diabetes mellitus it is less than 130/80 mmHg, and for patients with diabetes mellitus and chronic kidney disease, a good goal would be 125/75 mmHg. In patients who have prehypertension, or a blood pressure of 120-139/80-89 mmHg, lifestyle modifications should be implemented before drug regimens are initiated (Table 1). Weight reduction to maintain a body mass index < 24.9 kg/m^2 offers the largest decrease in systolic pressure ranging from 5-20 mmHg with a 10-kg weight loss. Exercise and diet also play an important role in reducing blood pressure and should be incorporated into each patient's care plan. The dietary approach to stop hypertension (DASH) diet consists of eating more fruits and vegetables and less saturated fat and sodium. Exercise should be moderate aerobic activity for 30 minutes a day most days of the week. Alcohol consumption should also be limited to help reduce overall blood pressure. For patients who are not able to control blood pressure with diet and exercise alone, there are many drug therapy options available.[2]

When lifestyle modifications are not enough to contain hypertension, there are many pharmacologic agents that may be given (Table 2). Diuretics increase the frequency of urination fluid loss leading to a decrease in blood pressure. Each class of diuretic inhibits sodium reabsorption in different areas of the kidney nephron and cause varying side effects. Osmotic agents such as mannitol increase the osmolarity of tubular fluid and work throughout the nephron but they are rarely used at this time. Carbonic anhydrase inhibitors such as acetazolamide exhibit their action in the proximal convoluted tubule leading to decreased bicarbonate and sodium reabsorption. The loop of Henle is separated into descending and ascending segments. Loop diuretics exhibit their action in the thick ascending loop of Henle and include agents such as furosemide and bumetanide and have a short but powerful diuretic effect. In the distal convoluted tubule, thiazides, a derivative of benzothiadiazines such as hydrochlorothiazide and indapamide, exert moderate diuretic effects over a long period of time. The distal convoluted tubule gives rise to the collecting duct, where potassium sparing diuretics such as triamterene and amiloride exert a weak diuresis but prevent potas-

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Therapy options for cancer patients with hypertension: Case 1

Description. JG is a 52-year-old African American man who returns to the oncology clinic for the second cycle of chemotherapy for his metastatic colorectal cancer. He continues to have stomach pain, nausea, and vomiting throughout the day and night but denies fever, chills, or bloody stool. His blood pressure at his last visit was 168/94 mmHg.

PMH renal insufficiency, gastroesophageal reflux disease; **SH** (+) Tobacco × 20 years, (+) EtOH socially, married with 3 children; **FH** father diagnosed with colon cancer 2003; mother alive, has hypertension; **VS** HR, 75 beats per minute; BP, 170/92 mmHg; RR, 17 breaths per minute; O_2 saturation, 98%; temperature, 98.2°F; height, 67 inches, weight, 93 kg.

Laboratory findings. Sodium, 139 mEq/L; potassium, 3.6 mEq/L; chloride, 105 mEq/L; bicarbonate, 26 mEq/L; BUN, 15 mg/dL; SCr, 1.9 mg/L; glucose, 97 mg/dL. Miscellaneous: CEA, 73.3 ng/mL; Hb, 10.5 g/dL; Hct, 37%; PLT, 250 × 10^3/mm^3; WBC, 9 × 10^3/mm^3; AST, 39 IU/L; ALT, 32 IU/L; TBILI, 0.6 mg/dL; AKP, 45 IU/L; LDH, 105 IU/L.

Current medications.[a] Leucovorin, 400 mg/m^2; fluorouracil 2,400 mg/m^2; oxaliplatin, 130 mg/m^2; bevacizumab, 5 mg/kg; ranitidine, 150 mg (all by mouth, all twice a day).

Questions/responses

It is decided to put him on a medication for his hypertension. What drug classes would be appropriate to choose from?

Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists would be appropriate because of his renal dysfunction. Appropriate starting regimens can include: lisinopril, 10 mg; ramipril, 5 mg; benazepril, 10 mg; valsartan, 80 mg; candesartan, 16 mg, or losartan 50 mg, all by mouth and all daily.

It is decided to put him on lisinopril 10 mg once daily. Three weeks later he returns to the office complaining of a cough. What should the medication be switched to?

He can be switched to an angiotensin II receptor antagonists. According to the ONTARGET trial, telmisartan was shown to have similar effects to ramipril with lower incidence of cough and angioedema. With both ACE inhibitors and ARBs, he will need a repeat basic metabolic panel check in about 1-2 weeks to make sure his potassium is not getting too high.

What would be appropriate he did not have renal insufficiency?

If he did not have renal insufficiency, he could be started on a thiazide diuretic such as hydrochlorothiazide 25 mg once daily or a calcium channel blocker such as amlodipine 5 mg once daily. As his potassium is borderline low, he will need a repeat basic metabolic panel after starting hydrochlorothiazide to evaluate for hypokalemia.

Abbreviation: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; FH, family history; Hct, hematocrit; Hgb, hemoglobin; HR, heart rate; HTN, hypertension; LDH, lactate dehydrogenase; MI, myocardial infarction; PLT, platelet count; PMH, past medical history; POHA, Progressive Osseous Heteroplasia Association; RR, respiration rate; SCr, serum creatine; SH, social history; TBILI, total bilirubin; VS vital signs; WBC, white blood cell count.
[a]Can be changed as needed based on POHA regimens.

sium wasting. Side effects of diuretics are mostly associated with electrolyte abnormalities and should be monitored regularly. Patients who are allergic to sulfonamides should not take carbonic anhydrase inhibitors, many loop diuretics, or thiazides because they have a sulfur component.[5,6] However, we can still use ethacrynic acid in such patients.

There are many agents aside from diuretics that can be used to treat hypertension. Aldosterone is a mineralocorticoid produced by the adrenal gland that can cause fluid retention and increased blood pressure due to altering sodium and potassium metabolism.[7] Agents such as spironolactone are mineralocorticoid receptor blockers that compete with aldosterone in the distal renal tubule to lower pressure through natriuresis.[8] The renin-angiotensin system is also important for blood pressure control and is inhibited by angiotensin-converting enzyme (ACE) inhibitors such as benazepril and lisinopril. ACE inhibitors also break down bradykinin, which activates L-arginine nitric oxide. They are also thought to have vascular protective effects due to increasing responses to endothelium-dependent agonists with chronic use.[9] ACE inhibitors also exhibit vasodilatory effects in the small arteries and large vessels via the bradykinin-nitric oxide-cGMP path-

TABLE 1 Lifestyle modifications for the reduction of blood pressure in patients with prehypertension or a blood pressure of 120-139/80-89 mmHg

Lifestyle modification	Approximate reduction in systolic blood pressure (mmHg)
Weight reduction	5-20
Dietary approaches to stop hypertension (DASH) diet	8-14
Sodium restriction	2-8
Exercise	4-9
Moderation of alcohol intake	2-4

way. This leads to increased bradykinin concentrations that can subsequently lead to cough in 10%-20% of patients. Similar agents, including angiotensin II receptor antagonists (ARBs), also help to decrease aldosterone secretion by inhibiting the angiotensin type 1 (AT1) receptor. However, these agents do not directly inhibit the breakdown of bradykinin.[10]

Inside the heart, there are multiple agents that work to slow the pumping force to reduce overall cardiac output and decrease blood pressure. Beta blockers are defined by blocking beta-1, beta-2, and alpha-1 adrenergic receptors. Beta blockers such as atenolol and metoprolol inhibit beta-1 adrenergic receptors leading to negative chronotropic and inotropic effects and are considered to be cardioselective. Nadolol and sotalol are examples of nonselective agents that block beta-1 and beta-2 receptors that play a role in cardiac function, metabolism, and vascular tone. Carvedilol and labetalol also block alpha-1 receptors which cause vasodilation and are considered nonselective.[11,12] Contraindications to beta-blockers include patient with bronchospasm and advanced heart block owing to exacerbation of these conditions. They should also not be used in patients that require beta-agonists such as those with decompensated heart failure.[12]

Calcium channel blockers inhibit the influx of calcium into the slow calcium channels in the myocardium during depolarization, which produces relaxation of smooth muscle and vasodilation. There are 2 classes of calcium channel blockers including the nondihydropyridines and the dihydropyridines. Nondihydropyridines such as verapamil and dilatizem also slow automaticity and prolong conduction of the atrioventricular (AV) node and refractoriness. They are also metabolized through the cytochrome P450 pathways and can have numerous drug interactions. Dihydropyridine calcium channel blockers such as amlodipine, nifedipine, and nicardipine do not have the additional heart effects or the drug interactions.[13]

Alpha receptors are also important in blood pressure control. Alpha-1 blockers such as doxazosin and terazosin inhibit postsynaptic alpha-adrenergic receptors resulting in vasodilation and decreased peripheral resistance where alpha-2 agonists such as clonidine target the brainstem and decrease sympathetic outflow and heart rate.[14] Guanosine monophosphate (GMP) is a nucleotide that causes vasodilation of the smooth muscle and is generated by nitric oxide and atrial natriuretic factor.[15] Hydralazine is a vasodilator that has multiple proposed mechanisms of action, including increasing GMP and calcium blockade that results in lowering of blood pressure. Its use is often combined with isosorbide dinitrate for patients with congestive heart failure who cannot tolerate or who have contraindications to ACE inhibitors or ARBs to improve exercise capacity.[15]

In the current JNC 7 guidelines,[2] treatment is based on blood pressure levels and compelling indications. Patients who have stage 1 hypertension and who do not have compelling indications can be started on a thiazide-type diuretic initially and then have other agents added as needed. Patients with stage 2 hypertension that does not have compelling indications may be started on multiple agents, 1 of which may include a thiazide-type diuretic to achieve the blood pressure goals. Patients who have compelling indications (Table 3) should be started on the medication that would be most appropriate for the management of their hypertension.[2]

Compelling indications are high-risk situations such as heart failure, postmyocardial infarction, coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention. In those patients, only certain drug classes should be used. For example, in patients who have heart failure, each class of antihypertensive medication can be used except for nondihydropyridine calcium channel blockers. This is because calcium channel blockers can cause worsening systolic function and can exacerbate heart failure. For this reason, calcium channel blockers should also be avoided in patients who have had a myocardial infarction. ACE inhibitors can be used in all compelling indications and are useful for patients with chronic kidney disease because of their renal protective effects.[2]

However, the JNC 7 guidelines have not been updated since 2004. JNC 8 is expected out in 2012 and there are several major trials that have come out that may change the way the new guidelines are written. These trials include ACCOMPLISH, ONTARGET, and ACCORD.

Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients or the ACCOMPLISH

TABLE 2 Pharmacologic agents that help contain hypertension if lifestyle modifications are not effective

Class	Examples	Mechanism of action	Side effects
Thiazide diuretics	Hydrochlorothiazide Indapamide	Inhibits Na reabsorption in the distal convoluted tubules causing increased excretion of Na + H_2O as well as K+ and H+.	Hypokalemia Hypomagnesemia Hypercalcemia Hyperuricemia Hyperglycemia Impotence
Loop diuretics	Furosemide Bumetanide	Inhibits reabsorption of Na in the ascending loop of Henle and distal renal tubule.	Hypokalemia Hypomagnesemia Hypocalcemia Hyperuricemia Hyperglycemia
Potassium-sparing diuretics	Triamterene	Blocks sodium channels in the distal convoluted tubule and collecting duct. Decreases the function of Na+/K+ ATPase leading to K retention.	Hyperkalemia Dyspnea
Aldosterone receptor Blockers	Spironolactone	Competes with aldosterone in the distal renal tubules.	Hyperkalemia Agranulocytosis Rash Gynecomastia
Beta-blockers	Atenolol Metoprolol Propranolol	Inhibit beta-1 adrenergic receptors leading to negative chronotropic and inotropic effects.	Bradycardia First degree heart block Dizziness Depression
Angiotensin-converting enzyme inhibitors	Benazepril Captopril Lisinopril Ramipril	Inhibits the enzyme that converts angiotensin I to angiotensin II (a potent vasoconstrictor). Results in an increase in renin and reduction of aldosterone secretion.	Hyperkalemia, renal insufficiency Angioedema Cough Congenital malformations
Angiotensin II antagonists	Candesartan Losartan Valsartan	Inhibits the AT1 angiotensin II receptor causing vasodilation and a decrease in aldosterone secretion.	Hyperkalemia Renal insufficiency Angioedema
Nondihydropyridine calcium channel blockers	Diltiazem Verapamil	Inhibits slow calcium channels in the vascular smooth muscle and myocardium during depolarization producing relaxation of smooth muscle and vasodilation. Slows automaticity and conduction of AV node	Bradycardia AV block Headache Gingival hyperplasia
Dihydropyridine calcium channel clockers	Amlodipine Nicardipine Nifedipine	Inhibits slow calcium channels in the vascular smooth muscle and myocardium during depolarization producing relaxation of smooth muscle and vasodilation.	Dizziness Flushing Headache Gingival Hyperplasia Edema
Alpha-1 Blockers	Doxazosin Terazosin	Inhibits postsynaptic alpha adrenergic receptors resulting in vasodilation and deceased peripheral resistance	Dizziness Faintness Syncope (first dose effects) Priapism
Alpha-2 agonist	Clonidine	Stimulates alpha2 in the brainstem resulting in reducing sympathetic outflow; decreased peripheral and renal resistance, and heart rate.	Depression Dizziness Anticholinergic effects Rebound hypertension
Vasodilator	Hydralazine	Inhibits cellular calcium metabolism via increased guanosine monophosphate in the vascular smooth muscle resulting in vasodilatory effects.	Angina Lupus-like-syndrome Fever Neuropathies Headache Hepatitis

Therapy options for cancer patients with hypertension: Case 2

Description. TM is a 63-year-old white man who presents to the oncology clinic for his Kaposi's sarcoma.

PMH AIDS, hypertension, diabetes mellitus, MI; **SH** (+) Tobacco × 35 years, (+) illicit drug use, never married, no children; **FH** father died of a heart attack in 2005; mother alive, has diabetes mellitus; **VS** HR, 83 beats per minute; BP, 152/93 mmHg; RR, 18 breathes per minute; O_2 saturation, 100%; temperature, 98.5°F; height; 69 inches; weight, 89 kg

Laboratory findings. Sodium, 142 mEq/L; potassium, 3.7 mEq/L; chloride, 107 mEq/L; bicarbonate, 24 mEq/L; BUN, 16 mg/dL; SCr, 1.0 mg/L; glucose, 180 mg/dL; Hb, 12.0 g/dL; Hct, 38%; PLT, 300 × 10^3/mm^3; WBC, 9.4 × 10^3/mm^3; AST, 40 IU/L; ALT, 33 IU/L; TBILI, 0.7 mg/dL; AKP, 44 IU/L; LDH, 104 IU/L

Current medications.[a] Lisinopril, 20 mg by mouth daily; metoprolol, 50 mg by mouth twice daily; atripla daily; lantus, 15 units subcutaneously daily; aspirin, 325 mg by mouth daily; atorvastatin, 20 mg by mouth daily; doxil 20 mg/m^2 every three weeks

Questions/responses

What blood pressure lowering agent could be recommended for TM?

He has a PMH of MI and diabetes mellitus, and he is already on the only 2 agents recommended for his compelling indications (a beta-blocker and an ACE inhibitor). Because he is not on the maximum dose of either of his medications, it would be beneficial to increase lisinopril to 40 mg by mouth daily and metoprolol to 100 mg by mouth twice daily.

Other than compelling indications, why would a calcium channel blocker such as verapamil not be recommended?

There is a drug interaction between efavirenz and verapamil due to CYP metabolism. Efavirenz is a strong CYP3A4 inducer and verapamil is a CYP3A4 substrate. Verapamil may also increase the concentration of atorvastatin leading to side effects such as myopathy and GI discomfort.

What if he had not had a previous MI?

If he had not had a previous MI, then TM could be started on a calcium channel blocker such as amlodipine, or a diuretic such as hydrochlorothiazide.

Abbreviation: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; FH, family history; Hct, hematocrit; Hgb, hemoglobin; HR, heart rate; HTN, hypertension; LDH, lactate dehydrogenase; MI, myocardial infarction; PLT, platelet count; PMH, past medical history; POHA, Progressive Osseous Heteroplasia Association; RR, respiration rate; SCr, serum creatine; SH, social history; TBILI, total bilirubin; VS vital signs; WBC, white blood cell count.
[a]Can be changed as needed based on POHA regimens.

trial looked at a thiazide in comparison to a calcium channel blocker as first line treatment for hypertension and the time to a cardiovascular event. In this multicenter, double-blind study, patients either received benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The rates of morbidity and mortality from cardiovascular events were then compared. Results showed the mean blood pressures were similar among both groups but primary outcomes were different. In the amlodipine arm, 552 (9.6%) patients and 679 (11.8%) patients in the hydrochlorothiazide arm died due to cardiovascular events. Due to these results, it was concluded that treatment with amlodipine was superior to hydrochlorothiazide in reducing cardiovascular events and death among patients with hypertension.[16]

In the ONTARGET study, investigators looked at the benefits of ACE inhibitors compared with angiotensin II receptor blockers. Both agents have been shown to reduce cardiovascular effects, but ACE inhibitors are associated with higher rates of adverse effects. The trial was therefore designed to determine if ARBs were inferior to ACE inhibitors and if the combination would further reduce vascular events. Patients received telmisartan or ramipril or both drugs, and the rates of death from cardiovascular events, MI, or stroke were the outcomes of interest. Mean blood pressures were similar in the 2 single-agent arms, whereas the combination arm had a slightly decreased mean blood pressure. The rate of primary outcome was also similar in all treatment arms. However, the rates of adverse effects including renal impairment and cough were higher in the ramipril arm and greatest in the combination arm. It was concluded that telmisartan was equivalent to ramipril in the treatment of blood pressure and was associated with less angioedema and the combi-

TABLE 3 Compelling indications and appropriate medications[2]

Indication	Medication					
	Diuretic	B-blocker	ACE inhibitor	ARB	CCB	Aldosterone antagonist
Diabetes	✓	✓	✓	✓	✓	
Chronic Kidney Disease			✓	✓		
Heart Failure	✓	✓	✓	✓		✓
Post Myocardial Infarction		✓	✓			✓
High Coronary Disease Risk	✓	✓	✓		✓	
Recurrent Stroke Prevention	✓		✓			

nation of the two results in more serious adverse events without an increase in benefit.[17]

The final trial investigated the effects of intensive blood pressure control in type II diabetes mellitus or the ACCORD study group.[18] This trial was completed in order to determine if the current blood pressure goals are appropriate. JNC 7 states a blood pressure goal of less than 140/90 mmHg is appropriate for all patients except for those with diabetes mellitus in which case less than 130/80 mmHg is suitable. However, there is not sufficient evidence that supports this claim of a lower goal in these patients. In this non-blinded trial, patients either received standard therapy with a blood pressure goal of less than 140/90 mmHg, or intensive therapy with a goal of less than 120/80 mmHg. Primary outcomes included the first occurrence of major cardiovascular event. Patients in the intensive group were given more drugs in their regimens to achieve the goal and also reported significantly higher rates of serious adverse effects. The rate of stroke was significantly lower in the intensive therapy group compared to the standard therapy group but the rate of overall death between the two arms was similar. Therefore, it was concluded that because the rate of overall death did not differ but the adverse effects did, it may not be more beneficial to have a lower blood pressure goal in patients with diabetes mellitus. With the results of these trials, the expected JNC 8 guidelines may differ in the choices of first-line agents and blood pressure goals, possibly allowing higher blood pressure goals.

Looking more specifically at agents that will be seen in the oncology setting, there are many drug interactions with the nondihydropyridine calcium channel blockers,[13] antiretrovirals,[19] and chemotherapy agents that health care providers must be aware of. This is because many of these drugs use the cytochrome P450 pathway for metabolism. Protease inhibitors including atazanavir, darunavir, and nelfinavir are potent CYP3A4 inhibitors that may interact with verapamil or diltiazem if used to treat hypertension.[20] Delavirdine, a non-nucleoside reverse transcriptase inhibitor, is also a potent CYP3A4 inhibitor while efavirenz is an inducer of the enzyme.[20]

There are many chemotherapy agents that also use the cytochrome P450 pathways for metabolism. Tamoxifen, a selective estrogen receptor modulator, is a potent CYP450 inhibitor that should also be monitored with certain hypertensive medications.[21] Tyrosine kinases catalyze the phosphorylation of adenosine triphosphate to tyrosine in proteins and play a role in proliferation, angiogenesis, carcinogenesis, and cell differentiation. Tyrosine kinase inhibitors including imatinib, dasatinib, and lapatinib have changed the way in which many cancers have been treated. These agents are also potent CYP450 inhibitors and can interact with nondihydropyridines as well as corticosteroids which are potent CYP3A4 inducers.

Therefore, it is crucial for health care providers to be aware of what medications patients are on to allow for proper hypertension management.[22]

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