

On the occasion of World Cancer Day 2024; focus on hypertension and anti-cancer agents

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ABSTRACT

Oncohypertension is a relatively recent concept that refers to the development of elevated blood pressure in patients with cancer, which is driven by the tumor itself. This review article aims to provide an overview of oncohypertension, including its pathophysiology, clinical implications, diagnostic approaches, and management strategies. The study discusses the association between oncological disorders and hypertension, highlighting the underlying mechanisms responsible for the development of oncohypertension. Furthermore, various diagnostic methods, including imaging techniques and laboratory tests, are discussed in detail. Finally, treatment options for oncohypertension, including both pharmacological and non-pharmacological approaches, are thoroughly reviewed to optimize blood pressure control and improve patient outcomes.

Keywords: Oncohypertension, High blood pressure, Cancer, Blood pressure, Pathophysiology, Diagnosis

Implication for health policy/practice/research/medical education:

Oncohypertension refers to the development of high blood pressure in cancer patients. Oncohypertension is a complex condition that requires a comprehensive understanding of the relationship between hypertension and cancer, the effects of anti-cancer agents on blood pressure, and the management of hypertension in cancer patients.

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Introduction

Oncohypertension is a recently proposed concept that encompasses the complex interactions among hypertension, cancer, and cancer treatment. It is an emerging subspecialty, which requires a multidisciplinary approach between oncology, primary care physicians, nephrology, and cardiology (1). There are no set guidelines for managing hypertension in cancer patients, and the therapy should be individualized based on the treatment guidelines for the general population (2). In this review, we sought to explain the challenges of treating high blood pressure in individuals with cancer.

Search strategy

In conducting this review, an extensive search was carried out across multiple scholarly databases, including

PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase. A comprehensive set of keywords was employed to ensure thorough coverage of relevant literature, encompassing terms such as oncohypertension, high blood pressure, cancer, blood pressure, pathophysiology, diagnosis, treatment, renin-angiotensin-aldosterone system, hypertension, nephrology, cardiology, oncologists, endothelial dysfunction, endothelial growth factor, platelet-derived growth factor, and chemotherapy.

Definition of oncohypertension

Oncohypertension refers to a condition characterized by high blood pressure (hypertension) that is directly related to and caused by underlying cancer or cancer treatment (3). It is a well-recognized phenomenon in oncology, and

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it can occur as a side effect of certain types of cancers, such as renal cell carcinoma or pheochromocytoma, or as a result of certain cancer treatments, such as chemotherapy or targeted therapy (4). Oncohypertension can be challenging to manage, requiring a multidisciplinary approach involving oncologists, cardiologists, and other healthcare professionals. Treatment may involve a combination of antihypertensive medications and the management of the underlying cancer or cancer treatment (1).

Prevalence and significance

The prevalence of oncohypertension is not well-established, as it can vary depending on the specific type of cancer and the population being studied (5,6).

The significance of oncohypertension lies in its potential impact on the management and prognosis of cancer patients. Hypertension can result from the direct effects of the tumor itself or cancer treatments, such as certain chemotherapy drugs or targeted therapies. Additionally, metabolic and hormonal changes that occur in cancer can also contribute to the development of hypertension (7,8).

The significance of oncohypertension can be addressed by the following entities. Firstly, it can increase the risk of cardiovascular complications, such as heart attack or stroke, which may further complicate the management of cancer patients. Secondly, oncohypertension can affect the delivery of cancer therapies, as high blood pressure may limit the use of certain medications or require additional medications to control blood pressure levels (1,9). Lastly, the presence of hypertension may indicate the need for further investigation and monitoring of cardiovascular health in cancer patients.

Pathophysiology of oncohypertension

The pathophysiology of oncohypertension is complex and involves various mechanisms. Cancer cells release various substances or factors that can impair the normal functioning of the endothelium, which leads to endothelial dysfunction, as the inner lining of blood vessels. This can lead to reduced production of nitric oxide, a vasodilator, and increased production of vasoconstrictors, such as endothelin-1. The imbalance between vasodilation and vasoconstriction can increase vascular resistance and elevated blood pressure (3,10). Further, certain cancers, such as renal cell carcinoma, can directly stimulate renin secretion by the kidneys, leading to increased production of angiotensin II (activation of the renin-angiotensin-aldosterone system). Angiotensin II is a potent vasoconstrictor and can stimulate the release of aldosterone, which promotes sodium and water retention by the kidneys. These actions can increase volume and elevate blood pressure (11,12). Furthermore, cancer-related factors can activate the sympathetic nervous system, leading to increased release of catecholamines (such

as epinephrine and norepinephrine). Catecholamines can cause vasoconstriction and increase heart rate and cardiac output, thereby raising blood pressure (13,14). Moreover, some tumors produce hormones or substances that can directly affect blood pressure regulation. For example, pheochromocytomas are tumors of the adrenal glands that can produce excessive amounts of catecholamines, leading to episodic hypertension (15,16). Meanwhile, certain cancers, such as renal cell carcinoma or pheochromocytomas, can cause physical obstruction of blood flow, particularly in the renal arteries. This condition can lead to reduced blood flow to the kidneys and activation of mechanisms that regulate blood pressure, such as the renin-angiotensin-aldosterone system (17-22). Additionally, several tumor-induced factors contribute to the development of high blood pressure. Tumors can stimulate the production of vascular growth factors like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These growth factors promote the formation of new blood vessels (angiogenesis) to supply nutrients and oxygen to the tumor. However, excessive angiogenesis can lead to high blood pressure due to increased blood vessel density and resistance to blood flow (23,24). Some tumors, particularly those in the adrenal gland, can produce excess amounts of hormones like aldosterone or catecholamines. These hormones can cause the kidneys to retain sodium and water, increasing blood volume and, subsequently high blood pressure (25,26).

Paraneoplastic syndromes are a group of rare, non-metastatic disorders that can occur in individuals with cancer. They are caused by a reaction of the immune system to certain substances produced by the tumor. In the context of oncohypertension, paraneoplastic syndromes can also affect blood pressure regulation (27,28).

Paraneoplastic hypertensive disorders, also known as oncohypertension, can manifest as high blood pressure in individuals with cancer. These conditions result from the tumor's production of substances that can directly affect blood pressure control in the body. The exact mechanisms behind oncohypertension are still not fully understood (1).

The most commonly associated paraneoplastic syndrome with oncohypertension is called paraneoplastic renal hypertension. It occurs when a tumor secretes a substance that affects the function of the kidneys and leads to increased blood pressure. This syndrome can be challenging to diagnose, as it often presents with atypical symptoms (28,29).

Other paraneoplastic syndromes that can contribute to oncohypertension include paraneoplastic autonomic dysfunction and paraneoplastic cerebellar degeneration. While these syndromes primarily affect the autonomic nervous system and cerebellum, they can also disrupt normal blood pressure regulation (27-32).

Angiogenesis is the growth of new blood vessels from existing ones. It plays a crucial role in tumor growth and metastasis. In cancer, the process of angiogenesis is dysregulated, leading to the formation of abnormal blood vessels. These abnormal vessels can increase vascular resistance and hypertension (33,34).

Additionally, some cancer treatments, such as certain targeted therapies or chemotherapy drugs, can also cause hypertension as a side effect. These medications can directly affect blood vessel function or alter the balance of vasoactive substances in the body, leading to increased blood pressure (3,10).

Clinical implications of oncohypertension

Oncohypertension can increase the risk of various cardiovascular complications such as heart attack, stroke, heart failure, and arrhythmias. It can also accelerate the progression of existing cardiovascular conditions (1,4). Patients with oncohypertension may require close monitoring of their renal function and may need additional treatments to protect their kidneys (9,35,36). Accordingly, patients with oncohypertension may experience more severe side effects from chemotherapy, including cardiovascular toxicity. Careful monitoring and managing blood pressure becomes essential to minimize these risks (37-41). Likewise, antihypertensive medications used to manage oncohypertension may interact with cancer treatments, potentially affecting their efficacy or causing adverse effects (7,39). Some studies have suggested that uncontrolled hypertension in cancer patients may negatively impact response to therapy and overall survival rates. Optimizing blood pressure control in these patients may therefore be beneficial (3,9). Oncohypertension often coexists with other comorbidities commonly seen in cancer patients, such as diabetes and obesity. The presence of multiple medical conditions can complicate overall management strategies and require a holistic approach (4,42). Finally, like any medical condition, a personalized approach is required when treating oncohypertension. Factors such as the patient's overall health, cancer stage, and treatment plan need to be taken into account to develop an effective treatment strategy that manages both the cancer and the hypertension effectively (36).

Profiling patients at risk

Profiling patients at risk for oncohypertension involves identifying certain characteristics and factors that increase the likelihood of developing this condition in cancer patients. Here are some key points to consider when profiling patients at risk for oncohypertension. Certain types of cancer, such as renal cell carcinoma, pheochromocytoma, and adrenal cortical carcinoma, are commonly associated with oncohypertension. Patients diagnosed with these cancers have a higher risk of developing hypertension (43,44). Additionally, the size

and location of the tumor can affect the risk of developing oncohypertension. For example, large tumors or tumors in close proximity to blood vessels or hormone-producing glands are more likely to cause hypertension (45). Similarly, a family history of hypertension may increase the risk for developing the condition. Genetics can play a role in the susceptibility to high blood pressure (46). Although oncohypertension can occur at any age, it tends to be more common in older adults. Additionally, some studies suggest a higher prevalence of oncohypertension in males compared to females (47). Hence, individuals with pre-existing hypertension, vascular diseases, or kidney problems may be at increased risk for experiencing oncohypertension when diagnosed with cancer (48).

Previous studies showed that certain cancer treatments, such as targeted therapies or immunotherapies, could lead to hypertension as a side effect. Assessing the patient's treatment plan and understanding the potential effects of medications is crucial for identifying the risk of oncohypertension (2). Other factors, including lifestyle factors like smoking, alcohol consumption, poor diet, sedentary behavior, and stress, can contribute to hypertension development. Assessing these factors can help in profiling patients at risk for oncohypertension (49). In this regard, obesity is a known risk factor for hypertension and is common among cancer patients. Measuring body mass index can be useful for assessing the risk of hypertension development (50).

Diagnosis of oncohypertension

Diagnosing oncohypertension involves a thorough medical history and physical examination, including blood pressure measurement. First, check for abnormalities in the blood, such as electrolyte imbalances or kidney dysfunction (1). These tests may include a complete blood count (CBC), lipid profile, kidney function tests (such as serum creatinine and blood urea nitrogen), electrolyte levels (such as sodium and potassium), fasting glucose levels, and thyroid function tests. Urine tests may also be conducted to check for proteinuria or hematuria (1,51-55). Accordingly, checking for proteinuria or hematuria, as the signs of kidney damage, is necessary (51). Other tests, such as computed tomography (CT) scans, magnetic resonance imaging (MRI), or ultrasound, look for any tumors or other abnormalities in the body (52). Other investigations, such as an electrocardiogram or echocardiogram, evaluate the heart's function and rule out any underlying cardiac conditions (53). Finally, if a tumor is suspected, a biopsy may be done to confirm the diagnosis (3,54).

Renal and hormonal assessments

Since kidney problems can cause hypertension or can lead to kidney damage, evaluating renal function is crucial. This may involve measuring the glomerular filtration rate (GFR) using creatinine clearance or estimated

GFR equations (56,57). Certain hormonal imbalances can contribute to hypertension. Therefore, hormonal assessments may be performed to evaluate levels of hormones such as aldosterone, renin, cortisol, and thyroid hormones (58).

Imaging modalities

Imaging techniques are conducted to assess the structure and function of organs affected by hypertension. These may include echocardiography to evaluate heart function and detect any abnormalities such as left ventricular hypertrophy. Other imaging modalities like those that computed tomography scans or magnetic resonance imaging may be used to assess the brain, kidneys, or other organs for potential damage caused by hypertension (59). Renal ultrasound, CT angiography, MRA, or renal scintigraphy may be conducted for this purpose (60). In addition, tumor-imaging techniques like CT scans, MRI, or nuclear medicine scans can help identify the presence and location of these tumors (61).

Management of oncohypertension

The management of oncohypertension, contains a combination of lifestyle modifications and medication. The specific approach may vary depending on the underlying cause of the hypertension and the individual patient's medical history. Here are some general strategies for managing oncohypertension (61). For example, encourage a healthy, balanced diet that is low in sodium (salt) and rich in fruits, vegetables, whole grains, and lean proteins (62). Promote weight loss if overweight or obese, as excess weight can contribute to high blood pressure (63). Besides, encourage regular physical activity such as walking, swimming, or cycling to help lower blood pressure and recommend stress management techniques such as meditation, deep breathing exercises, or yoga to help lower blood pressure. Finally, prescribing medications to help lower blood pressure is necessary. Commonly administered classes include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, diuretics, and calcium channel blockers (64). However, if certain chemotherapy drugs cause the hypertension, adjusting the dosage or switching to alternative medications may be necessary (10). Along with hypertension treatment, monitoring of blood pressure regularly to assess its control and adjust the medications are also recommended. Patient education also should not be forgotten. Since providing enough information about oncohypertension causes, treatment options, lifestyle modifications, and potential complications could improve patient cooperation (65).

Conclusion

This review provides a comprehensive overview of oncohypertension, including its underlying pathophysiology,

clinical implications, diagnostic approaches, and management strategies. Oncohypertension is a complex condition that requires a comprehensive understanding of the relationship between hypertension and cancer, the effects of anti-cancer agents on blood pressure, and the management of hypertension in cancer patients.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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