ORIGINAL RESEARCH PAPER

Clinical Science

KEY WORDS: BLOOD, PRESSURE, CHEMOTERAPY

ETIOLOGY OF HIGH BLOOD PRESSURE AND CHEMOTERAPY

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ABSTRACT

High blood pressure, is a condition that can damage the arteries, heart and other organs. It is common for cancer patients to have high blood pressure because some cancer treatments including chemotherapy, hormone therapy and targeted therapy, may have side effects on the cardiovascular system. If left untreated, high blood pressure may lead to a heart attack, heart disease, heart failure, stroke, kidney damage and peripheral arterial disease, among other health problems. High blood pressure affects the heart by injuring the walls of the arteries. The force on the arteries is so great, it creates small tears in the artery walls. Through natural aging, your arteries harden and become much less elastic. Uncontrolled high blood pressure speeds up this progression, accelerating hardening of the arteries. Damaged arteries cannot deliver adequate blood flow to the body's organs. As a result, these "damaged" organs suffer because they do not receive proper blood supply. This may lead to a heart attack, stroke or other life-threatening illnesses.

INTRODUCTION

Some medications used to treat cancer can cause a rapid onset of elevated blood pressure, also called hypertension. The class of cancer treatment medications that are most associated with a rise in blood pressure are anti-VEGF medications. Vascular endothelial growth factor (VEGF) is a protein that stimulates the formation of small blood vessels. Medications that block VEGF help block the blood flow supply to tumors, helping shrink or eradicate the cancer. However, the medications frequently affect other blood vessels in the body which can lead to high blood pressure. Regardless of which cancer treatment you are receiving, your cardio-oncology team will help control your blood pressure so that you can receive the anti-cancer treatment that you need.

Hypertension has been reported to be the most common comorbidity encountered in patients with malignancy (37%).

The much higher rate is observed after the initiation of certain chemotherapeutic agents (angiogenesis inhibitors, 17%–80%; alkylating agents, 36%–39%; and immuno suppressants after stem-cell transplantation, 30%–80%).

The most common chemotherapeutic agents known to cause hypertension include several of the angiogenesis inhibitors commonly known as vascular signaling pathway (VSP) inhibitors.

These drugs include the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab and certain tyrosine kinase inhibitors (sunitinib, sorafenib, and pazopanib).

The incidence of de novo or worsening hypertension in association with these drugs varies between 17% and 80%. Several theories have been suggested, including endothelial dysfunction associated with reduced nitric oxide bioavailability and with increased vascular and renal endothelin production; increase in vascular tone; vascular rarefaction (decrease in density of microvessels); and renal thrombotic microangiopathy with secondary glomerular structural and functional changes that lead to proteinuria and hypertension.

Other classes of chemotherapeutic agents are known to induce hypertension by several mechanisms: alkylating agents and calcineurin can cause endothelial dysfunction and arterial vasoconstriction, calcineurin can activate the renin-angiotensin system, and steroids can increase patients' sensitivity to vasoactive substances and contribute to salt and fluid retention. Moreover, surgery or radiation therapy that involves the head or neck can lead to baroreflex failure and to associated difficult-to-treat labile hypertension and hypertensive crisis.

Anthracycline-based chemotherapy is well known to potentially cause irreversible damage to the heart in a dose-dependent manner. Recent data suggest that the presence of hypertension, particularly poorly-controlled hypertension, significantly increases the risk for chemotherapy-induced cardiomyopathy and heart failure. One of the earliest studies indicating this association was a retrospective analysis of 4018 patients published in 1979, which found that patients with underlying heart disease, hypertension, or both were at a higher risk for developing doxorubicin-induced heart failure. In a retrospective study by Hershman et al., patients with diffuse large B-cell lymphoma (DLBCL) receiving doxorubicin-based chemotherapy versus other chemotherapy were analyzed. After adjusting for cardiac risk factors, doxorubicin was associated with a higher risk of heart failure.

The mechanism of anthracycline-induced cardiotoxicity is postulated to be multifactorial involving the generation of reactive oxygen species, mitochondrial dysfunction, cardiomyocyte injury, and impaired repair mechanism.

Similarly, trastuzumab-associated cardiotoxicity has been demonstrated to be exacerbated by the presence of underlying hypertension. In patients with breast cancer receiving trastuzumab with or without anthracycline, the risk factors for the development of congestive heart failure are age > 65 years, diabetes, hypertension, obesity, and smoking history. One of the key mechanisms for myocardial injury in these patients is the alteration in nitric oxide (NO) synthesis and release from vascular endothelial cells. Among patients receiving trastuzumab therapy, inhibition of human epidermal growth factor receptor (HER2) activity in cardiomyocytes interrupts the HER2/neuregulin pathway, which is central to NO synthesis and sarcomere preservation. Disruption of this pathway reduces NO bioavailability with a concomitant increase in angiotensin-II and reactive oxygen species (ROS). These processes, in addition to the preexisting myocardial stress from underlying hypertension, culminate in endothelial dysfunction, which is a well-established contributor to the development of congestive heart failure.

Small molecule tyrosine kinase inhibitors (TKI), such as sorafenib, sunitinib, lenvatinib, and axitinib, are used for the treatment of a variety of solid tumors, including kidney cancer, hepatocellular carcinoma, metastatic melanoma, gastrointestinal stromal tumors (GIST), and neuroendocrine pancreatic neoplasms. Other drugs in this class include pazopanib, cabozantinib, nintedanib among others. The drugs in this class of multikinase inhibitors act by interrupting downstream intracellular VEGF signaling pathways and inhibit angiogenesis.

Cyclophosphamide, ifosfamide, busulfan, and cisplatin are commonly used in the treatment of hematologic malignancies (lymphoma, leukemia) and solid organ malignancies (head and neck cancers and genitourinary cancers). The predominant mechanism for arterial hypertension is suspected to be oxidative damage to endothelial cells, increased intimal thickness, and abnormal vascular remodeling.

Glucocorticoids are commonly used in anticancer regimens, especially for hematologic malignancies, such as lymphoma and MM. Steroids cause new-onset or worsening hypertension by promoting sodium and water retention, exerting its intrinsic vasoconstricting properties, and increasing sensitivity to endogenous vasopressors. Glucocorticoid-induced hypertension has been reported in up to 13% of patients.

Given the rapid development of new treatment regimens that counter the growth and spread of cancer and increase the longevity of patients, there is an urgent need to tackle non-cancer-related comorbid medical conditions, such as hypertension, that may interfere with successful cancer treatment. Management of underlying cancer and non-cancer comorbidities must go hand in hand, and the joint efforts of the oncologist, cardio-oncologist, and primary care provider are critical to provide optimal care in these patients. The composite goal is to reduce cardiovascular events while achieving maximum benefits from cancer therapy. Timely screening for hypertension, early diagnosis and prompt initiation of intervention, regular home BP monitoring, and close follow-up can reduce the burden of cardiovascular complications, leading to an improvement in the quality of life and overall survival in patients with cancer.

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