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# Cancer Therapy-Related Hypertension:

## A Scientific Statement from the American Heart Association

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## Abstract

Contemporary anti-cancer drugs have significantly improved cancer survival, but this has been at the expense of cardiovascular toxicities, including heart disease, thromboembolic disease and hypertension. One of the most common side effects of these drugs is hypertension, especially in patients treated with vascular endothelial growth factor inhibitors, as well as tyrosine kinase inhibitors and proteasome inhibitors. Adjunctive therapy including corticosteroids, calcineurin inhibitors and non-steroidal anti-inflammatories, as well as anti-androgen hormone therapy for prostate cancer may further increase blood pressure in these patients. Cancer therapy-induced hypertension is often dose-limiting, increases cardiovascular mortality in cancer survivors, and is usually reversible after interruption or discontinuation of treatment. Exact molecular mechanisms

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CONFLICTS

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underlying hypertension are unclear, but recent discoveries indicate an important role for reduced nitric oxide generation, oxidative stress, endothelin-1, prostaglandins, endothelial dysfunction, increased sympathetic outflow, and microvascular rarefaction. In addition, genetic polymorphisms in vascular endothelial growth factor receptors are implicated in vascular endothelial growth factor inhibitor-induced hypertension. Diagnosis, management and follow up of cancer therapy-induced hypertension follow national hypertension guidelines, since evidence-based clinical trials specifically addressing patients who develop hypertension due to cancer therapy, are currently lacking. Rigorous baseline assessment of patients prior to commencing therapy requires particular emphasis on assessing and treating cardiovascular risk factors. Hypertension management follows guidelines for the general population, although special attention should be given to rebound hypotension following termination of cancer therapy. Management of these complex patients requires collaborative care involving oncologists, cardiologists, hypertension specialists, primary care providers and pharmacists to ensure optimal therapeutic effect from cancer treatment while minimizing competing cardiovascular toxicities.

### Keywords

cardio-oncology; cardiovascular toxicities; blood pressure; anti-angiogenesis; tyrosine kinase inhibitors

## INTRODUCTION

Hypertension is more common in patients on anti-cancer therapy than the general population due to multiple mechanisms, including direct vascular and renal effects of anti-cancer therapy. Hypertension and blood pressure (BP) lability begin at the time of initiation of anti-cancer therapy and continue lifelong, which can result in interruptions in treatment and place patients at increased risk of cardiovascular disease (CVD) and mortality.[1] Many contemporary cancer therapies are associated with cardiovascular-toxicity leading to heart disease, thromboembolic disease, and hypertension. Management of hypertension in patients on anti-cancer therapy is largely empiric, with no current trial data supporting specific agents or treatment goals in this distinctive population. This paper provides an overview of the mechanisms and clinical management of anti-cancer therapy-induced hypertension.

## EPIDEMIOLOGY

### Hypertension and cancer as major causes of global morbidity and mortality

Cancer and CVD are major causes of morbidity and mortality globally.[2] Hypertension is one of the main risk factors for the development of CVD, including ischemic heart disease, heart failure, stroke, and kidney disease. The prevalence of hypertension worldwide is increasing, reaching 1.3 billion in adults in 2019.[3] Despite availability of effective antihypertensive drugs, BP is inadequately controlled in almost 50% of those known to have hypertension. The current definitions of normal BP, elevated BP, and hypertension, based on the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines as well as other major guidelines are presented in Table 1.[4] The incidence of cancer is also

increasing. The Global Cancer Observatory estimates that the number of new cancer cases worldwide will increase from 19.3 million in 2020 to >28 million in 2040.[5]

### Common risk factors of hypertension and cancer

A bidirectional relationship between cancer and hypertension has been proposed. Hypertension is associated with an increased risk of cancer. This is most clearly displayed by the increased risk of renal cell carcinoma in patients with hypertension.[6] Additionally, the prevalence of hypertension is higher in patients with cancer and cancer survivors than in the general population.[1] A prospective cohort study of >17,000 patients with cancer found that hypertension was the most common comorbidity (38% prevalence).[7] The frequent concurrence of cancer and hypertension and the increased cardiovascular risk in patients with cancer are most likely explained by the presence of common risk factors and pathophysiological mechanisms, including smoking, diabetes, chronic kidney disease, physical inactivity, obesity, oxidative stress, and inflammation.[8–10] CVD morbidity and mortality are increased in patients with cancer and cancer survivors.[11] In addition, many anti-cancer drugs cause BP elevation through numerous mechanisms.

## ANTI-CANCER DRUGS THAT CAUSE HYPERTENSION AND POTENTIAL MECHANISMS

### Vascular endothelial growth factor (VEGF) signaling pathway inhibitors (VSPIs)

VSPIs exert their anti-cancer effects by inhibition of VEGF-mediated tumor angiogenesis, depriving tumor cells of oxygen and nutrient supply. These agents act via inhibition of VEGF directly or by inhibition of tyrosine kinase receptors (Table 2). As recently reviewed by Camarda et al.,[12] they have well-established treatment efficacy in numerous cancers, especially renal, hepatocellular, thyroid, gastrointestinal stromal and others.

VSPIs are associated with adverse cardiovascular effects, of which hypertension is the most frequent. They cause an acute increase in BP that is sustained during treatment in the majority of patients. The reported incidence of VSPI-induced hypertension ranges from 20%–90% and varies with VSPI potency and dosage as well as methods and definitions for reporting BP.[8] In a meta-analysis of 29,000 patients with cancer, there was a 3.8-fold higher relative risk for hypertension in those treated with a VEGF tyrosine kinase inhibitor (TKI) compared to controls (Table 2).[13] VSPI-associated hypertension is reversible and resolves upon discontinuation of the agent, indicating an ‘on-target’ effect. Accordingly, VSPI-induced hypertension has been suggested as a predictor or biomarker of therapeutic efficacy.[14]

VEGF is a potent vasodilator and its absence is associated with reduced bioavailability of the vasodilator nitric oxide (NO) and increased concentrations of the potent vasoconstrictor, endothelin-1, important in hypertension pathophysiology (Figure 1). VEGF signalling pathway inhibition is also associated with increased generation of reactive oxygen species (ROS), including reactive nitrogen species, $H_2O_2$, and $O_2^-$, causing vascular oxidative stress.[15] Rarefaction (reduced microvascular density) occurs (previously observed in the skin and oral mucosa), with a consequent increase in vascular resistance thought to lead

to elevated BP.[16] VSPIs are associated with nephrotoxicity, which may also contribute to their prohypertensive effects via impaired natriuresis.[8] Current evidence does not suggest a major role for the renin-angiotensin-aldosterone system in the pathophysiology of VSPI-associated hypertension. VSPIs also interfere with other growth factor pathways, including platelet-derived growth factor, fibroblast growth factor, fms-like tyrosine kinase 3 and c-Kit. Inhibition of these pathways evokes further potential prohypertensive mechanisms.[8]

## Rapidly accelerated fibrosarcoma B-type (BRAF) and mitogen-activated kinase kinase (MEK) inhibitors

BRAF/MEK inhibitors are used in the treatment of BRAF-mutant melanoma and BRAF mutant colorectal cancer.[17] These agents are frequently prescribed in combination. Approximately 60% of patients with melanoma harbor a BRAF gene mutation with subsequent dysregulation of the Raf-MEK-extracellular signal-regulated kinases signaling pathway (Table 2). These pathways are also necessary for normal vascular and cardiac physiology.

Hypertension is the most common adverse cardiovascular event reported with BRAF/MEK inhibitors.[17] A meta-analysis including 5 randomized clinical trials (RCTs) reported an increased risk of systemic hypertension, which occurred in 19.5% of patients treated with combined BRAF/MEK inhibitors and 14% of those treated with BRAF inhibitor monotherapy.[18] BRAF/MEK inhibitor-associated hypertension may be a consequence of reduced NO bioavailability. Inhibition of BRAF and MEK is associated with upregulation of expression of Cluster of Differentiation 47 in melanoma cells in vitro. Cluster of Differentiation 47 inhibits NO/cyclic guanosine monophosphate signaling via thrombospondin-1, leading to a reduction in NO bioavailability with consequent vasoconstriction and hypertension.[18]

## Bruton’s tyrosine kinase inhibitors

Bruton’s TKIs are used in the treatment of chronic lymphocytic leukemia and mantle cell lymphoma. Ibrutinib has variable prohypertensive effects. In a study of 562 patients, treatment with ibrutinib was associated with new-onset hypertension in 71% of patients with normal BP at baseline, and with worsening of preexisting hypertension in 83%.[19] A meta-analysis including 2,580 participants revealed a 2.8-fold increased risk for hypertension in patients treated with ibrutinib.[19] Given that both hypertension and Bruton’s TKIs increase the risk of atrial fibrillation, the prohypertensive effect of these drugs is of added significance.[19] Patients are frequently treated with Bruton’s TKIs for many years and therefore the life-time risk of exposure to the prohypertensive effects is especially relevant. Mechanisms underpinning Bruton’s TKI-associated hypertension are unclear, but a decrease in heat shock protein 70 signaling and inhibition of phosphatidylinositol 3-kinase-dependent NO production may be important.[8]

## Rearranged during transfection receptor (RET)-TKIs

RET-TKIs are indicated for the treatment of non-small cell lung cancer and thyroid cancer with an activating mutation in the RET proto-oncogene. In a study of 162 patients with thyroid cancer treated with selpercatinib, 43% developed hypertension and 21% had

BP >160/100 mmHg.[20] In the ARROW RCT examining pralsetinib in non-small cell lung cancer, 21% of those treated with pralsetinib developed hypertension.[21] Mechanisms underlying the prohypertensive effects of RET-TKIs are unknown.

### Poly adenosine diphosphate ribose polymerase inhibitors

Poly adenosine diphosphate ribose polymerase inhibitors are used in the treatment of breast and ovarian cancer with BReast CAncer (BRCA) mutation. In this drug class, only niraparib has been associated with prohypertensive effects. In the NOVA RCT of niraparib in recurrent ovarian cancer, 19% patients treated with niraparib developed hypertension, versus 5% of patients receiving placebo.[22] In the recent NORA RCT (niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose), hypertension occurred in 11% of patients treated with niraparib, compared with only 1% of patients receiving placebo.[23, 24] When niraparib was given in combination with the VSPI bevacizumab for ovarian cancer, hypertension occurred in 56% of patients.[23, 24] The mechanisms underlying niraparib-induced hypertension remain unclear.[8]

### Proteasome inhibitors

Proteasome inhibitors (bortezomib, carfilzomib and ixazomib) have become the cornerstone of therapy for multiple myeloma. Cardiovascular adverse events occur with all proteasome inhibitors, but are mostly associated with carfilzomib.[25] In the carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR) trial, hypertension developed in 32% of patients receiving carfilzomib compared to 10% receiving bortezomib.[26] In a prospective study of 70 patients with multiple myeloma treated with carfilzomib, 33% developed adverse cardiovascular events, 91% of whom had uncontrolled hypertension.[27] Hypertension often reverses after discontinuation of these agents.

Proteasome inhibitors mediate oxidative stress by increasing ROS production and suppressing antioxidant pathways. By binding to the 20S proteolytic core of the proteasome and thereby inhibiting its catalytic activity, proteasome inhibitors lead to an intracellular accumulation of aggregated proteins that can be toxic to malignant cells.[28] This also has adverse cardiovascular effects, including endothelial dysfunction and reduced NO bioavailability.[28] Pre-existing vascular risk factors and anti-cancer therapies associated with oxidative stress make the vasculature more vulnerable to these adverse effects.[29]

### Platinum-based compounds

Platinum-based compounds (cisplatin, carboplatin, oxaliplatin) are used to treat testicular, bladder, gynecological, breast, colorectal and lung cancers, as well as mesothelioma. Their anti-cancer effects result from platinum uptake to DNA with consequent apoptotic cell death. Hypertension is associated with exposure to platinum-based compounds but tends to be a late effect, which can occur many years after treatment of the index cancer. Platinum-based chemotherapy is associated with excellent long-term survival for patients with testicular cancer, the most common cancer in young men. In a study of testicular cancer survivors with a median follow-up of 11 years, hypertension was observed in 53% of those treated with cisplatin and was 2.3 times more frequent than in healthy controls.[30]

Cisplatin is detected in the circulation even after 13 years post-drug exposure and this may be responsible for chronic endothelial injury and dysfunction. Increased circulating platinum concentrations are associated with an increased risk of hypertension.[31] Proximal tubular renal cells are the major site for cisplatin-induced renal injury, and accumulation of cisplatin in the kidney can reach levels five times higher than the serum concentration.[32] Cisplatin nephrotoxicity is dose-dependent and has been attributed to cellular mitochondrial damage, oxidative stress, apoptosis, and decreased NO bioavailability.[33]

### Alkylating agents

Alkylating antineoplastic agents such as busulfan, ifosfamide and cyclophosphamide are used in the treatment of hematologic malignancies and solid organ malignancies. These are classical chemotherapeutic agents that have been previously linked to hypertension; however, concomitant use of glucocorticoids may be a confounding factor in these observations.

Busulfan is mainly used as part of a pre-transplant conditioning regimen for both pediatric and adult patients with hematological malignancies. Hypertension has been noted in up to 36% of adults treated with busulfan and in up to 58% of children.[10] The prevalence of hypertension after ifosfamide was reported to be 15% at 5 years of follow-up in a childhood cancer survivorship study.[34]

In cyclophosphamide-treated patients with breast cancer, reduced VEGF concentrations have been demonstrated with associated endothelial dysfunction. These processes can explain, in part, the development of hypertension in patients on cyclophosphamide.[35] In addition, direct vascular toxicity and nephrotoxicity may contribute to the prohypertensive effects of these agents.[36]

### Calcineurin inhibitors (CNIs)

CNIs such as tacrolimus and cyclosporin are often administered concurrently with other cancer agents, mainly after hematopoietic stem cell transplantation to prevent or treat graft versus host disease.[37] CNIs contribute to the development of hypertension or worsening BP control in patients with a history of hypertension.[38] In patients undergoing bone marrow transplantation, there was a 30–60% increase in the rate of hypertension diagnoses after cyclosporin became the mainstay of treatment.[39] CNIs cause widespread vasoconstriction, with activation of the renin-angiotensin-aldosterone system, oxidative stress, an increase in endothelin-1 generation and sympathetic nervous system activity.[40] In addition, they inhibit NO synthesis and NO-mediated vasodilation.[41]

### Mammalian target of rapamycin (mTOR) inhibitors

Inhibitors of mTOR, including everolimus and sirolimus, are third-line treatment options for renal cell carcinoma. In a RCT including patients with metastatic renal cell carcinoma, everolimus was associated with a 10% incidence of hypertension.[8] *In vitro* studies in predominantly tumor cell lines show decreased VEGF secretion upon mTOR inhibition. Thus, inhibition of mTOR may have prohypertensive effects similar to VSPIs.[41] The

combination of everolimus with the VSPI lenvatinib was associated with hypertension in 41% of patients and high-grade hypertension in 14%, higher than either medication alone.[41]

### Endocrine therapy (anti-androgens/aromatase inhibitors)

Survival for patients with metastatic prostate cancer is improved by androgen deprivation therapy. These agents block the trophic effects of androgens on prostate cancer cells. Gonadotropin-releasing hormone agonists directly inhibit androgen production and signaling and are associated with potentially adverse cardiovascular effects including elevation of serum lipid levels, decreased insulin sensitivity and obesity. Abiraterone, an inhibitor of androgen synthesis and enzalutamide, an androgen receptor antagonist, are both associated with hypertension.[8, 42] Abiraterone inhibits testosterone production via inhibition of the cytochrome P450 enzyme with consequent accumulation of mineralocorticoid precursors. This effect contributes to its prohypertensive effects.[42] Mechanisms underlying enzalutamide-induced hypertension are unclear.

The cardiovascular toxic effects of abiraterone and enzalutamide were evaluated in a meta-analysis of 8660 patients with prostate cancer. All-grade and high-grade hypertension were observed more frequently in the abiraterone group (26% and 7%, respectively) compared with placebo (15% and 4%, respectively). Similar results were reported with enzalutamide (11% and 5%, respectively) compared with placebo (4% and 2%, respectively).[42] These rates of hypertension occurred irrespective of corticosteroid use, which is often administered concomitantly.[8, 42]

Aromatase inhibitors including nonsteroidal (anastrazole and letrozole) and steroidal (exemestane) formulations, reduce breast cancer-related mortality in post-menopausal women with estrogen positive breast cancer.[43, 44] The association between aromatase inhibitors and cardiovascular risk is controversial with some studies identifying increased risk of hypertension and cardiovascular-related mortality.[8, 43]

### Adjunctive Therapies Used in Cancer Management

In addition to the BP effects associated with the specific anti-cancer drugs outlined above, many other agents prescribed for patients with cancer can contribute to unwanted BP effects. Corticosteroids are a frequent component of contemporary cancer treatment regimens and often used in supportive care management. Corticosteroids can provoke a substantial rise in BP, in isolation, and in the context of other prohypertensive therapies. Similarly, exogenous erythropoietin and non-steroidal anti-inflammatory drugs frequently cause BP elevation.[8]

## DIAGNOSIS AND MANAGEMENT OF ANTI-CANCER THERAPY-INDUCED HYPERTENSION

### Diagnosis of hypertension in anti-cancer therapy-induced hypertension.

Accurate measurement of BP is crucial for hypertension diagnosis and management and special attention should be given to optimal control of anxiety and pain in patients with cancer. In general, patients should be seated quietly for 3–5 minutes before any measurement is taken, the patient’s bladder should be empty, and they should have abstained

from exercise and consumption of caffeine or smoking for 30 minutes.[4] The legs should touch the floor and not be crossed and the back should be well supported. The arm used for BP measurement should be in a resting position at the level of the heart. A calibrated and validated automated office BP device and a proper cuff size should be used.[10] At least 2–3 BP readings should be obtained and averaged. Elevated BP readings should be verified on at least 1 more occasion prior to a diagnosis of hypertension.[4, 45] 24-hour ambulatory BP monitoring is recommended for confirmation after initial readings of an elevated BP but is not always feasible. Home BP monitoring (self-monitoring of BP) with a validated device should be used in situations where frequent BP measurements over longer time periods are required, e.g. during treatment initiation or dose changes in patients receiving VSPIs wherein worsening hypertension often occurs in days and can progress to hypertensive emergency.[46, 47] Baseline measurement before the initiation of prohypertensive anti-cancer therapies is mandatory, as some patients may present with a notable rise in BP while on these agents requiring prompt initiation or escalation of antihypertensive therapy.

## Blood Pressure targets

Patients with cancer are frequently underrepresented or excluded from major cardiovascular or hypertension RCTs. RCTs are needed to define BP targets either in the context of specific anti-cancer therapies, or in patients with cancer in general. Defining BP goals for treatment and diagnosis in patients with cancer therefore is an important unmet need. The definition of hypertension varies between guidelines (Table 1). Based on the AHA/ACC guidelines, BP is categorized as normal, elevated, stage 1, or stage 2 hypertension. Normal BP is defined as <120/<80 mm Hg; elevated BP as 120–129/<80 mm Hg; hypertension stage 1 as systolic BP 130–139 or diastolic BP 80–89 mm Hg, and hypertension stage 2 as ≥140 or ≥90 mm Hg.[4] For patients with atherosclerotic CVD 10-year risk ≥10%, or comorbidities such as chronic kidney disease and diabetes mellitus, treatment should be initiated in stage 1 hypertension. For others, treatment should be initiated in stage 2. The goal BP is <130/80 mmHg for all indivduals. To date there are no specific hypertension guidelines for patients with cancer, although the International Cardio-Oncology Society recently published a consensus statement on the definition of hypertension in cancer, representing a multidisciplinary effort.[47] The treatment threshold is defined as in the AHA/ACC recommendations, and treatment goals match the treatment threshold. The threshold for recommending withholding anti-cancer therapy is systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg, which is similar to the hypertensive crisis definition in the AHA/ACC guidelines (≥180 mmHg systolic and ≥120 mmHg diastolic).

## Management of hypertension in anti-cancer therapy-induced hypertension

**Antihypertensive Medications—**Among patients with hypertension, antihypertensive therapy should be optimized prior to initiation of anti-cancer therapy, preferably with multi-disciplinary input from the cardio-oncology care team (Figure 2). Patients should be counseled on the potential need to escalate antihypertensive treatment quickly if potentially pro-hypertensive anti-cancer therapy is scheduled. Insufficient evidence exists supporting a specific antihypertensive medication strategy specific to patients with anti-cancer therapy-induced hypertension. Therefore, antihypertensive management should reflect current guidelines for the general population.[4, 48] First-line therapy should include an angiotensin

receptor blocker or angiotensin-converting enzyme inhibitor, dihydropyridine calcium channel blocker, or thiazide or thiazide-like diuretic.[48] Selection of antihypertensive therapy should otherwise be informed by individual patient risk factors. For example, patients with proteinuria should be treated with an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor[45, 48]; those at high risk of volume depletion should avoid use of diuretics.[10] As with the general population, mineralocorticoid receptor antagonists should be the initial agent of choice for the treatment of resistant hypertension, unless there is a contraindication such as hyperkalemia.[4, 49] Beta-blockers should not be used as first-line antihypertensive therapy, and should be reserved for individuals with a specific indication for their use (e.g., atrial fibrillation, recent myocardial infarction, heart failure with reduced ejection fraction), who are already optimized on maximum tolerated doses of first-line antihypertensive agents, or with contraindications to first-line antihypertensive agents.[4, 45] Non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) should be used with caution in this patient population, as these antihypertensive agents are susceptible to interactions with several anti-cancer therapies that are metabolized by P-glycoprotein and cytochrome P450 3A4.[50]

**Lifestyle Modifications—**Patients should be counseled on important lifestyle modifications that can help to improve BP control, including limiting sodium intake (with consideration for risk of hypovolemia), non-steroidal anti-inflammatory drug use, caffeine use, and alcohol use and increasing physical activity and potassium intake.[4, 45, 49] When evaluating patients for rising BP during anti-cancer therapy, providers should address the potential role of inadequate pain control and concomitant therapies that may exacerbate hypertension, such as erythropoietin stimulating agents and corticosteroids. Evaluation of co-morbidities that may increase BP (e.g., obstructive sleep apnea) is also important.

### Long-term management of cancer drug-induced hypertension in cancer survivors

After completing anti-cancer therapy with agents known to increase BP, patients may need to reduce antihypertensive treatment to avoid rebound hypotension and ischemic events. In patients treated with anti-cancer therapy requiring significant escalation of antihypertensive therapy at the onset, reduction in antihypertensive therapy may need to occur within days of cessation of treatment, and daily home BP monitoring may be necessary. Over the long-term, the prevalence of hypertension in cancer survivors is higher than in the general population.[1] Therefore, cancer survivors are likely to benefit from closer monitoring for the development of hypertension than the general population, including a combination of in-office and home BP monitoring. Similar to patients undergoing active anti-cancer therapy, there is insufficient evidence to support a specific or targeted approach to managing hypertension in cancer survivors. Therefore, these patients should be treated based on current best evidence for the general population.[4, 45, 49]

## KEY GAPS AND UNMET NEEDS

Gaps in knowledge remain in our understanding of the epidemiology of concomitant hypertension and cancer, especially regarding common risk factors. While these conditions are both more prevalent with aging, age alone does not seem to be the link between

hypertension and cancer. Contributing to the clinical burden of co-morbidity, many anti-cancer drugs themselves cause hypertension especially VSPIs, BRAF/MEK inhibitors, BTK inhibitors, RET-TKIs, some poly adenosine diphosphate ribose polymerase inhibitors, and mTOR inhibitors. Pro-hypertensive effects may be direct or indirect but underlying mechanisms are elusive. There are major gaps in the understanding of how these anti-cancer drugs cause hypertension. In addition, the relative contributions of direct vascular and renal toxicity to hypertension induced by alkylating agents, the role of decreased VEGF secretion as a potential mediator of hypertension induced by the Inhibition of mTOR, and the association between aromatase inhibitors and increased cardiovascular risk including hypertension, need to be elucidated. Whether anti-cancer therapy-induced hypertension is truly a predictor of drug efficacy awaits further clarification in large prospective cancer trials. Key gaps also include the timing and frequency of BP monitoring and cardiovascular risk assessment in patients with cancer during, and after therapy, and the relationship of concurrent cardiovascular risk factors with anti-cancer therapy-induced hypertension and outcomes. Evidence-based trials to treat anti-cancer drug-induced hypertension are lacking and accordingly it remains unclear as to which antihypertensive drugs should be used.

## FUTURE DIRECTIONS

Future directions for research on hypertension in cancer include epidemiological topics on common risk factors and mechanisms of hypertension and cancer, optimal strategies for BP monitoring during and after anti-cancer therapy, and the diagnosis and management of anti-cancer drug-induced hypertension. Future research will need to address molecular mechanisms underlying anti-cancer therapy-induced hypertension to better understand measures needed to minimize cardiovascular toxicity and hypertension, while at the same time optimizing cancer survival. The bidirectional relationship between cancer and hypertension, pathophysiology of heart failure with preserved ejection fraction resulting from anti-cancer therapy, risk of lifetime exposure to Bruton's TKIs for prolonged periods, extent of lifetime risk from cisplatin exposure, potential cardiovascular protective effect of Janise kinase inhibitors possibly through their ant-inflammatory effects are all topics for further exploration. The optimal timing and frequency of BP monitoring in patients with cancer and cancer survivors on drugs that induce hypertension, particularly at initiation of and changes in cancer medication regimen, must be evaluated. The optimal BP targets in individuals with cancer will also need to be determined, especially since it is unclear whether the final BP is more important for end organ effects than the magnitude of initial BP increase from baseline. Use of algorithms for monitoring vital signs, laboratory values, and ECG's with certain frequency for particular drugs should be incorporated into treatment plans for patients on anti-cancer therapy. BP management when cancer medication therapies are stopped (completed or discontinued) will need to be streamlined, especially since there may be rebound hypotension. RCTs are needed to investigate the "best antihypertensives" for individuals with cancer treated with various cancer medications to optimize BP and limit end organ damage. Of major importance sex and racial/ethnic differences, differential therapeutic responses, as well as disparities regarding management, outcomes, and adherence in patients with hypertension and cancer, will need to be carefully evaluated.

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## CLINICAL PEARLS

- Many anti-cancer drugs have cardiovascular toxicities including hypertension.
- Cancer therapy-induced hypertension, especially by VSPIs and proteasome inhibitors, is often reversible after discontinuation of these agents.
- Many anti-cancer drugs may worsen BP control in patients with existing hypertension.
- Hypertension control is important prior to, during, and following completion of cancer treatment.
- At least weekly BP monitoring is suggested for the first 4–8 weeks on cancer drugs that increase BP and upon discontinuing these drugs, given distinct risk of BP lability; holding parameters and atypical dosing of antihypertensive medications may be necessary.
- Home BP monitoring should be encouraged.
- Cancer survivors are at increased risk of hypertension-associated complications such as atrial fibrillation, heart failure, and chronic kidney disease, necessitating a multidisciplinary approach for optimal management.

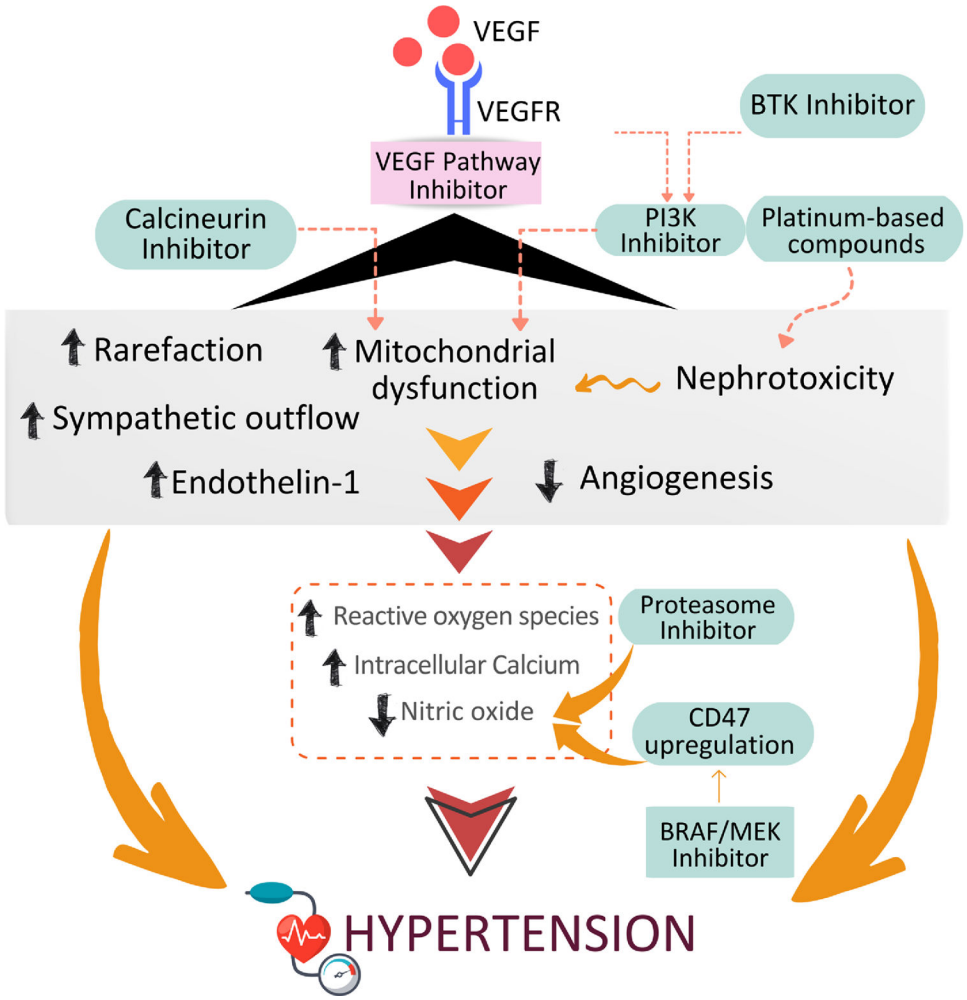


**Figure 1.**

Putative mechanisms whereby major classes of anti-cancer therapies cause hypertension. VEGF, Vascular epidemanl growth factor; VEGFR, VEGF receptor; BTK, Brutons tyrosine kinase; PI3K, Phosphoinositide 3-kinases; CD47, Cluster of Differentiation 47; MEK, mitogen-actvated protein kinase kinase.

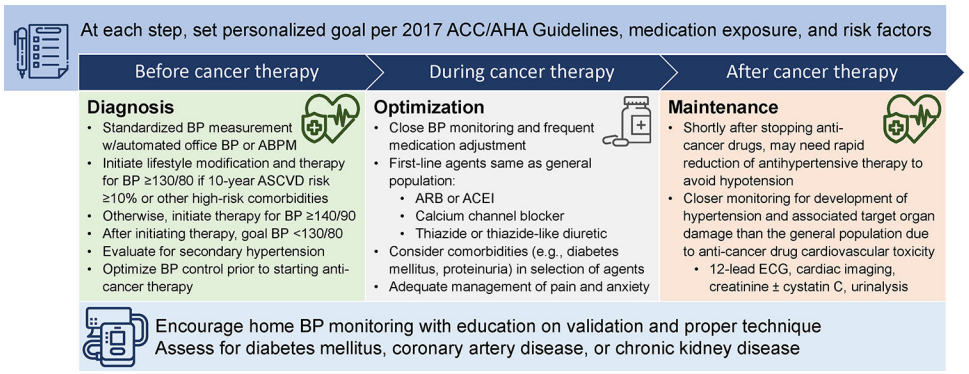


**Figure 2.**

Practical suggestions for the diagnosis and management of hypertension before, during and after commencing anti-cancer therapy.

**Table 1:**

Definition of hypertension in patients with cancer and the general adult population according to major guidelines

| | | | | | | |
|---|---|---|---|---|---|---|
| **IC-OS*** | **Normal**<br><br>**SBP ≤130 mmHg**<br>**DBP ≤80 mmHg** | | **Treatment threshold**<br><br>**CVD or ASCVD risk ≥ 10%:**<br>**SBP ≥130 mmHg and/or**<br>**DBP ≥80 mmHg**<br><br>**Otherwise:**<br>**SBP ≥140 mmHg and/or**<br>**DBP ≥90 mmHg** | **Cancer therapy holding threshold**<br><br>**SBP ≥180 mmHg and/or**<br>**DBP ≥110 mmHg** | **Exaggerated hypertensive response**<br>**SBP increase >20 mmHg or mean arterial BP increase >15 mmHg** | **Hypertensive emergency response**<br><br>**Very high BP elevations associated with acute hypertension-mediated organ damage (heart, brain, kidneys), requiring immediate BP reduction to limit target organ damage** |
| NCI CTCAE V5 | **Grade 1**<br>SBP 120–139 mmHg or DBP 80–89 mmHg | | **Grade 2**<br>SBP 140–159 mmHg or DBP 90–99 mmHg<br>if previously WNL.<br><br>Change in baseline medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg; monotherapy indicated or initiate | **Grade 3**<br>SBP ≥160 mmHg or DBP ≥100 mmHg<br><br>Medical intervention indicated; > 1 drug or more intensive therapy than previously used indicated | **Grade 4**<br>Life-threatening complications (i.e., transient, or permanent neurologic deficit, hypertensive crisis).<br><br>Urgent intervention indicated | |
| ACC/AHA 2017 | **Normal**<br>SBP <120 mmHg<br>DBP <80 mmHg | | **Elevated**<br>SBP120–129 mmHg<br>DBP<80 mmHg | **Stage 1**<br>SBP 130–139 mmHg<br>DBP 80–90 mmHg<br><br>Drug therapy indicated if ASCVD risk>10% | **Stage 2**<br>SBP >140 mmHg<br>DBP >90 mmHg<br><br>Drug therapy goal BP<130/80 mmHg | **Hypertensive Crisis**<br>SBP >180 mmHg<br>DBP >120 mmHg<br><br>Urgent BP drug therapy initiation |
| ESC 2018 | **Optimal**<br>SBP<120 mmHg<br>DBP <80 mmHg | **Normal**<br>SBP 120–129 mmHg<br>DBP 80–84 mmHg | **High Normal**<br>SBP 130–139 mmHg<br>DBP 85–89 mmHg<br><br>Drug therapy considered if ASCVD risk>10% or established CVD, CKD, or DM | **Grade 1**<br>SBP 140–159 mmHg<br>DBP 90–99 mmHg<br><br>First drug therapy target <140/90 mmHg, consider <130/80 mmHg if tolerated, but not SBP <120 mmHg.<br><br>In older >65 years, target SBP 130–140 mmHg, and DBP <80 mmHg, initiate with two-drug combination | **Grade 2**<br>SBP 160–179 mmHg<br>DBP 100–109 mmHg<br><br>Drug therapy goal as for Grade 1 | **Grade 3**<br>SBP ≥ 180 mmHg<br>DBP ≥110 mmHg<br><br>Urgent drug therapy goal as for Grade 1 |
| ISH | **Normal**<br>SBP <130 mmHg<br>DBP <85 mmHg | | **High normal**<br>SBP 130–139 mmHg<br>DBP 85–89 mmHg | **Grade 1**<br>SBP 140–159 mmHg<br>DBP 90–99 mmHg<br><br>Drug therapy indicated if ASCVD risk>10% or established CVD, CKD, DM<br>Target BP reduction by 20/10 mmHg, ideally to <140/90 mmHg.<br>Optimal targets:<br><65 years: 120–130/70–79mmHg | **Grade 2**<br>SBP ≥160 mmHg<br>DBP ≥100 mmHg<br><br>Immediate drug treatment in all patients | |

| IC-OS* | Normal | Treatment threshold | Cancer therapy holding threshold | Exaggerated hypertensive response | Hypertensive emergency response |
|---|---|---|---|---|---|
| | **SBP ≤130 mmHg<br>DBP ≤80 mmHg** | **CVD or ASCVD risk ≥ 10%:<br>SBP ≥130 mmHg and/or<br>DBP ≥80 mmHg<br><br>Otherwise:<br>SBP ≥140 mmHg and/or<br>DBP ≥90 mmHg** | **SBP ≥180 mmHg and/or<br>DBP ≥110 mmHg** | **SBP increase >20 mmHg or mean arterial BP increase >15 mmHg** | **Very high BP elevations associated with acute hypertension-mediated organ damage (heart, brain, kidneys), requiring immediate BP reduction to limit target organ damage** |
| | | | ≥65 years: <140/90 mmHg | | |

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CTCAE, Common Terminology Criteria for Adverse Events; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic BP; DM, diabetes mellitus; ESC, European Society of Cardiology; HTN, hypertension; IC-OS, International Cardio-Oncology Society; ISH, International Society of Hypertension; NCI, National Cancer Institute; SBP systolic BP. BP values are based on office BP measurement.

*Definition of hypertension aspect in the cancer patient

**Table 2.**

Incidence of hypertension induced by different classes of anti-cancer drugs

| Drug Class | Select example drugs | Select malignancies treated | Incidence of hypertension |
|---|---|---|---|
| Vascular endothelial growth factor (VEGF) signaling pathway inhibitors (VSPIs) | Bevacizumab, Sorafenib<br>Sunitinib<br>Nilotinib<br>Pazopanib<br>Dasatinib<br>Regorafenib<br>Cabozantinib<br>Lenvatinib<br>Ponatinib<br>Axitinib<br>Tivozanib<br>Vandetanib<br>Ramucirumab | Renal, hepatocellular, thyroid, gastrointestinal stromal (GIST) | 20%-90%[8] |
| Bruton's tyrosine kinase inhibitors (TKIs) | Ibrutinib<br>Acalabrutinib | Chronic lymphocytic leukaemia (CLL), Mantle cell lymphoma | 71%[19] |
| Proteasome inhibitors | Carfilzomib<br>Bortezomib | Multiple myeloma | 32%[26]<br>10%[26] |
| Platinum-based compounds | Cisplatin<br>Carboplatin<br>Oxaliplatin | Mesothelioma†, testicular, bladder, gynecological, colorectal, and lung cancers† | 53%[30] |
| Alkylating agents | Cyclophosphamide<br>Busulfan<br>Ifosfamide | Hematologic and solid organ malignancies | 36% in adults[10]<br>58% in children[10]<br>15% in children[34] |
| Calcineurin inhibitors (CNIs) | Tacrolimus<br>Cyclosporin | After stem cell transplantation | 30%-60%[39] |
| Serine/threonine-protein kinase B-Raf/ mitogen-activated extracellular signal-regulated kinase (BRAF/MEK) inhibitors | Vemurafenib<br>Dabrafenib<br>Encorafenib<br>Trametinib<br>Binimetinib<br>Cobimetinib | Melanoma, colorectal | 19.5% *[18] |
| Rearranged during transfection (RET) kinase inhibitors | Selpercatinib<br>Pralsetinib | Thyroid, Non-small cell lung cancer | 43%[20]<br>21%[20] |
| Poly ADP ribose polymerase (PARP) inhibitors | Niraparib | Breast, Ovarian | 19%[22] |
| Androgen receptor blockers | Enzalutamide | Metastatic prostate cancer | 11 (5%)[42] |
| Androgen synthesis inhibitors | Abiraterone<br>Leuprolide | Metastatic prostate cancer<br>Prostate cancer | 26 (7%)[42]<br>15%[8] |
| Aromatase inhibitors | Anastrazole | Breast | 13 %[43] |
| | Letrozole | Breast | 8 %[43] |
| | Exemestane | Breast | 10 %[43] |
| Mammalian target of rapamycin mTOR inhibitors | Everolimus<br>Sirolimus | Renal cell cancer, breast, pancreatic neuroendocrine tumor (PNET) | 13 % (PNET)[8] |

*From systematic review including all drugs

†Denotes malignancies for which treatment is not approved by the Food and Drug Administration (i.e., currently given off-label)