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CKJ Review

CKJ REVIEW

Management of hypertension in patients with cancer: challenges and considerations

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ABSTRACT

The survival rates of many cancers have significantly improved due to recent advancements in cancer screening and therapeutics. Although better cancer outcomes are encouraging, additional health challenges have surfaced, the utmost of which is the burden imposed by various cardiovascular and renal toxicities of anticancer therapies. To improve the overall outcome of patients with cancer, it is essential to understand and manage these treatment-related adverse effects. The cardiovascular side effects of antineoplastic therapies are well-known and include left ventricular dysfunction, heart failure, myocardial ischaemia, QT prolongation, arrhythmia and hypertension. Among these, hypertension is the most common complication, prevalent in about 40% of all cancer patients, yet frequently overlooked and undertreated. This review explores the intricate connection between cancer and hypertension and provides distinct approaches to diagnosing, monitoring and managing hypertension in patients with cancer. We also outline the challenges and considerations that are relevant to the care of patients receiving anticancer drugs with prohypertensive potential.

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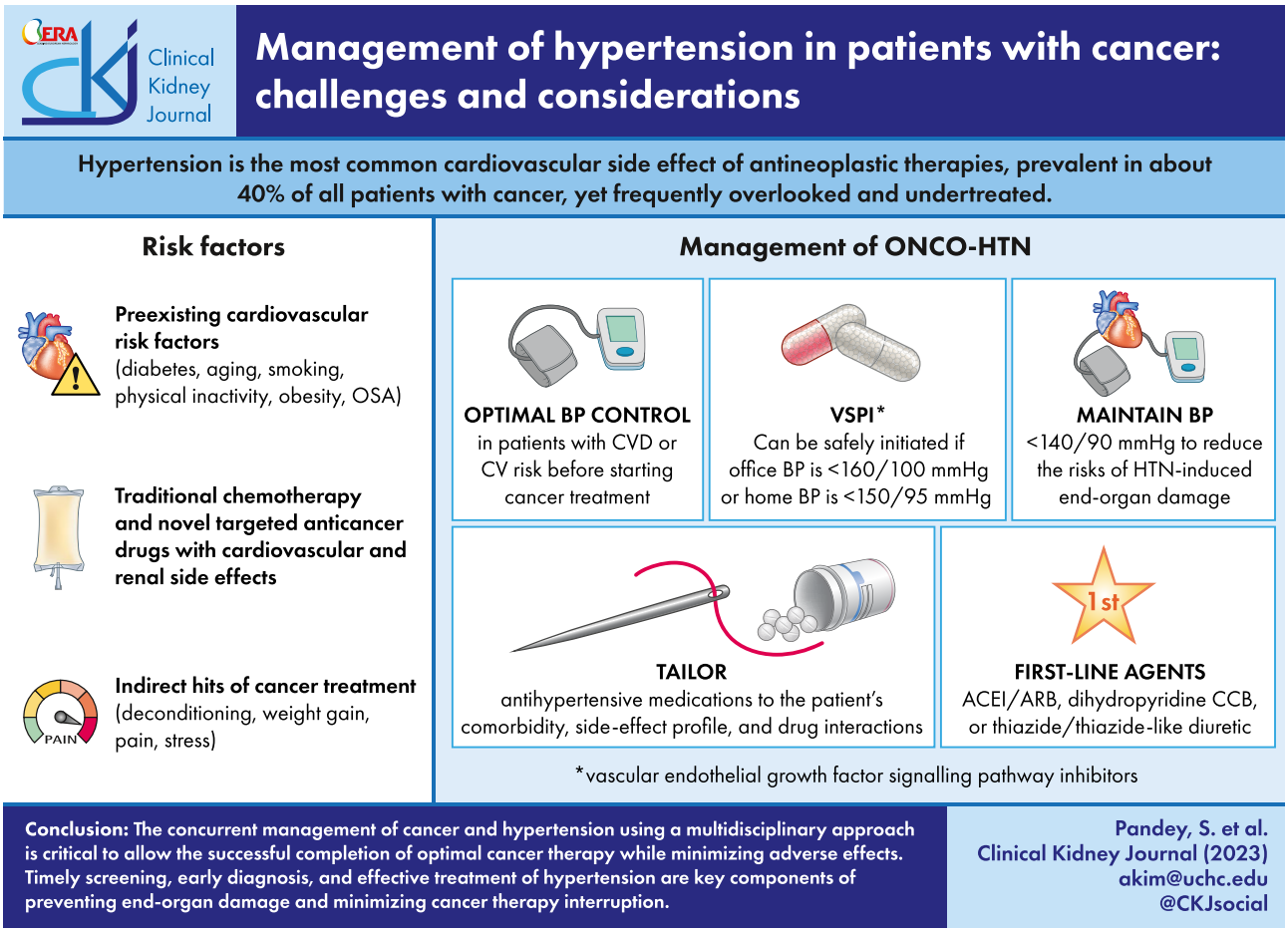
GRAPHICAL ABSTRACT



Keywords: blood pressure management, cancer, cardio-oncology, onco-hypertension, onco-nephrology, VEGF signalling pathway inhibitors

THE RELATIONSHIP BETWEEN CANCER AND HYPERTENSION

Cancer and hypertension are intricately linked, so much so that their association has inspired its own field of onco-hypertension [1, 2]. They share overlapping pathophysiological mechanisms, including inflammation and oxidative stress, which are associated with common risk factors: diabetes, smoking, obesity, physical inactivity and obstructive sleep apnoea [3]. Additional sequelae of cancer, including deconditioning, pain, anxiety and sleep disorders, may also indirectly promote hypertension. Various anticancer therapies and adjunctive therapies exert prohypertensive effects [4]. Both hypertension and certain anticancer drugs can increase the risk of direct toxicities on the heart, vasculature and kidney, which in turn, exacerbate hypertension in a vicious cycle (Fig. 1).

Furthermore, hypertension may be a risk factor for some cancers. An association between hypertension and the development of renal cell cancer has been demonstrated by several observational studies [5, 6]. The Metabolic Syndrome and Cancer Project, which prospectively followed a cohort of nearly 580 000 participants for 12 years, indicated that elevated blood pressure (BP) was independently associated with a slightly higher risk of cancer incidence in men and cancer-associated mortality in both men and women [7]. However, a clear causal relationship between hypertension and cancer has not been established.

Several observational studies have tried to determine whether there is an association between antihypertensive medications and an increased risk of cancer. Interestingly, three of the drug classes [calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARBs) and thiazide diuretics] that were investigated for carcinogenic potential are frequently used for the treatment of hypertension in cancer patients. Notably, there was a large-scale recall of several ARBs in 2018 due to concerns of potentially carcinogenic nitrosamine impurities [8]. However, various studies showed contradictory results and were fraught with confounders [1]. At present, there is no conclusive evidence to suggest a significantly elevated cancer risk, and the long-proven

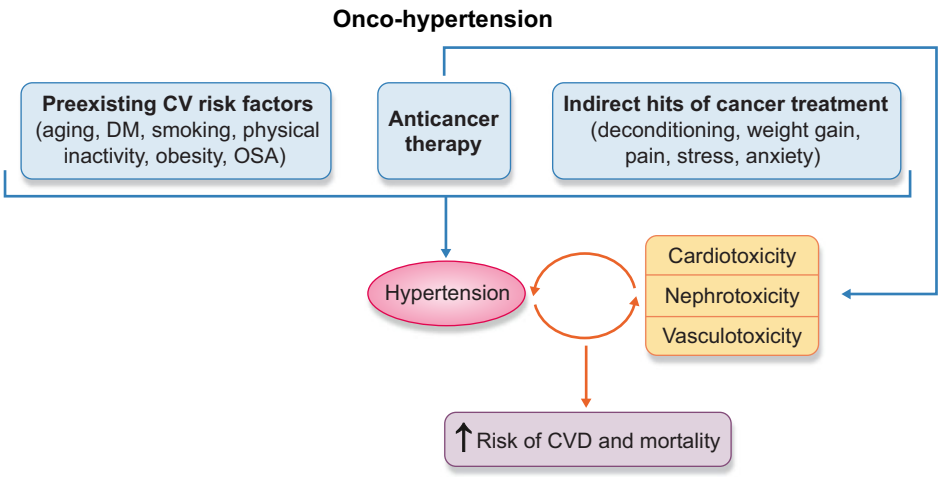


Figure 1: Onco-hypertension: the complex interplay between cancer and hypertension. Hypertension in cancer patients can occur due to overlapping risk factors and the direct or indirect effects of cancer therapy. The end-organ toxicity caused by either hypertension or chemotherapy further amplifies the hypertensive response in a vicious cycle.

cardiovascular (CV) benefits of these drugs outweigh the minuscule potential risk of cancer.

CAUSES OF HYPERTENSION IN PATIENTS WITH CANCER

Cancer therapy–related hypertension (CTRH) is the most extensively studied aspect of onco-hypertension. Several classes of cancer therapeutics have been associated with the development of hypertension (Fig. 2), of which vascular endothelial growth factor (VEGF) inhibitors, also known as VEGF signalling pathway inhibitors (VSPIs), are the most common. In fact, an increase in BP from baseline is seen in almost all patients on VSPIs, with new or worsening hypertension in up to 80% of the patients [9, 10]. A meta-analysis by Abdel-Qadir *et al*. reported a number needed to harm of 6 for the development of hypertension and 17 for severe hypertension [11]. The incidence of life-threatening hypertensive crises with bevacizumab has been estimated to be around 1% [10]. VEGF binding to its receptor (VEGFR) activates downstream intracellular signalling pathways critical for vasodilation and maintenance of vascular integrity via endothelial cell survival, proliferation and permeability. VEGF plays an important role in angiogenesis, the lymphatic system, and the glomerular filtration barrier [12] but also promotes tumour growth and metastasis. VSPIs exert anticancer effects by impairing tumour angiogenesis. Figure 3 illustrates the targets of various VSPIs along the VEGF pathway. The hypertensive effect of VSPIs is believed to be due to a combination of impaired nitric oxide (NO) production and vasodilation, abnormal endothelin-1 and prostacyclin signalling, microvessel rarefaction, increased vascular stiffness, and renal effects that include impaired renovascular homeostasis, decreased natriuresis, increased podocyte permeability (and proteinuria) and eventually glomerular endotheliosis and renal damage [9]. Anti-VEGF ligands such as bevacizumab and aflibercept can cause thrombotic microangiopathy (TMA), while VEGF-tyrosine kinase inhibitors (TKIs) have been associated with minimal change nephropathy and focal segmental glomerulosclerosis [13]. The early hypertensive response likely occurs due to dysfunction of vascular tone and natriuresis rather than glomerular damage, although observational studies suggest a possible association between impaired glomerular filtration rate and increased risk of VSPI-mediated rise in BP [14].

Apart from VSPIs, there are additional classes of cancer therapeutics that promote hypertension, ranging from traditional chemotherapeutic agents (platinum-based therapy, nucleoside analogues and alkylating agents [15, 16]) to targeted therapies. These include proteasome inhibitors for multiple myeloma [17, 18], Bruton's tyrosine kinase (BTK) inhibitors for chronic lymphocytic lymphoma (CLL) [19], rapidly accelerated fibrosarcoma B-type/mitogen-activated kinase kinase (BRAF/MEK) inhibitors for melanoma and colorectal cancer [20], rearranged during transfection (RET) kinase inhibitors for thyroid and non-small-cell lung cancer [21, 22], poly-ADP ribose polymerase (PARP) inhibitors for ovarian cancer [23, 24], and phosphatidylinositol-3-kinase (PI3K) inhibitors for CLL and breast cancer [25, 26], among others. While the prohypertensive mechanisms of these various medications are still being elucidated, most inhibit common intracellular signalling pathways that result in endothelial dysfunction and NO dysregulation (Table 1). Traditional chemotherapy also causes direct renal toxicity which can eventually contribute to hypertension, although certain agents like cisplatin can conversely lead to orthostatic hypotension and hyponatremia in the acute setting due to renal salt wasting and poor oral intake, especially in head and neck cancer patients [27]. Multivariate logistic regression analysis showed that low BP and the use of renin–angiotensin–aldosterone system (RAAS) inhibitors were associated with a higher incidence of cisplatin nephrotoxicity [28]. Proteasome inhibitors (e.g. carfilzomib, ixazomib or bortezomib) [29] and gemcitabine, a nucleoside analogue, can also cause TMA [30]. Many of these agents are used concurrently and compound the hypertensive effect.

Endocrine therapies can also cause hypertension, most notably androgen synthesis inhibitors (leuprolide, abiraterone) and androgen receptor blockers (enzalutamide), used in the treatment of metastatic prostate cancer [31, 32]. There are conflicting data regarding the association of hypertension with aromatase inhibitors. While prior studies suggested an increased risk of arterial hypertension [33] and CV events [34] compared with tamoxifen, a recent meta-analysis did not identify a statistically significant association [35]. Instead, this perceived difference between the two drug classes may be due to the cardioprotective

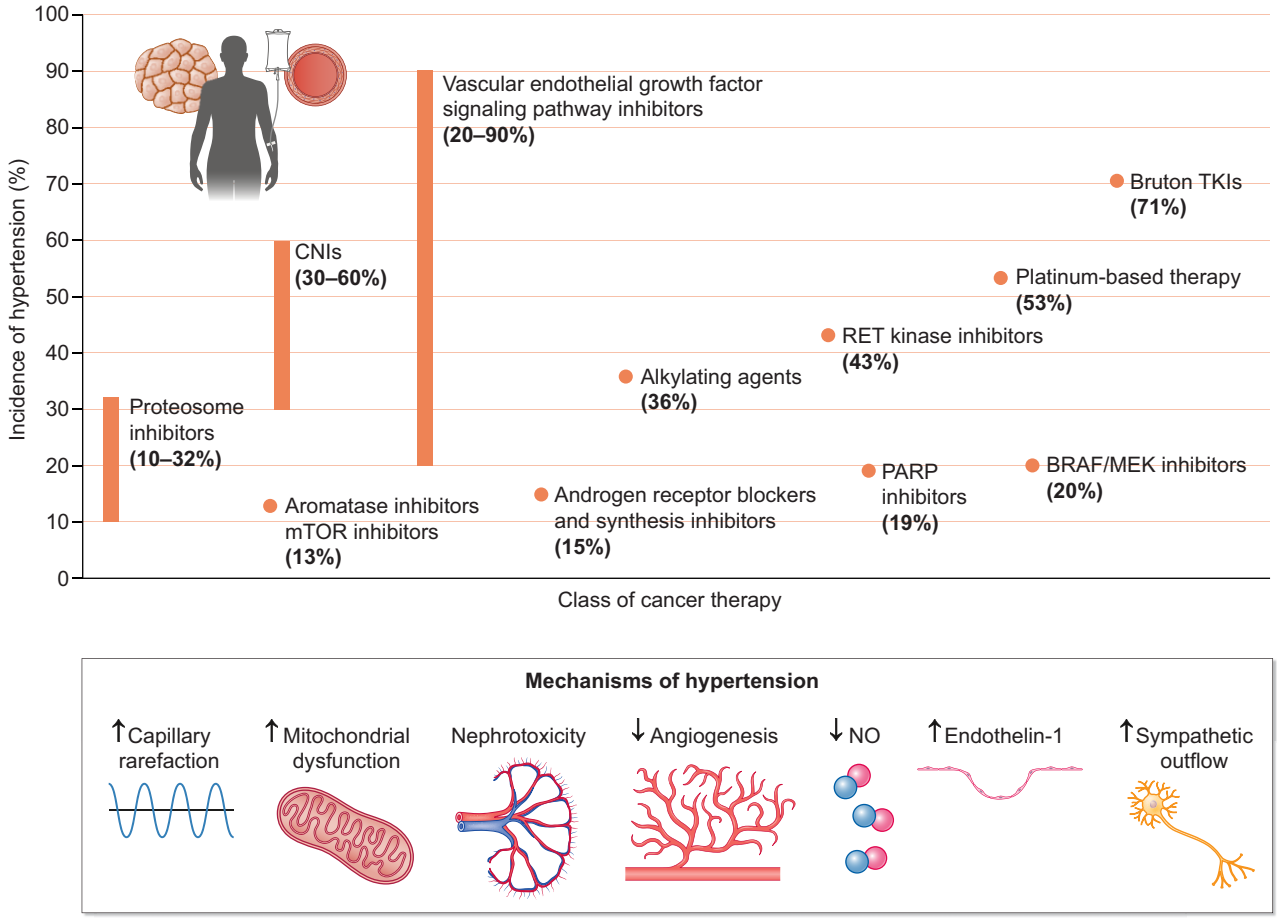


Figure 2: Incidence and mechanism of hypertension due to various classes of cancer therapy [62].

effects of tamoxifen. Similarly, there is no conclusive evidence that immunotherapy causes hypertension. A meta-analysis of 32 randomized controlled trials involving 19 000 patients did not demonstrate an association between the use of immune checkpoint inhibitors and short-term hypertension [36].

Adjunctive medications commonly administered in conjunction with chemotherapy can also raise BP. Glucocorticoids are widely used in anticancer regimens to increase the efficacy of chemotherapy and minimize therapy-related side effects. They contribute to hypertension by promoting sodium and water retention via mineralocorticoid receptor stimulation [15]. Erythropoiesis-stimulating agents (ESAs) are recommended by the American Society of Clinical Oncology/American Society of Hematology for selected patients with chemotherapy-associated anaemia [37]. Recent decades have seen a decline in their use because of increased risk of hypertension, thromboembolic events and mortality [38]. ESA-induced hypertension occurs due to increased blood viscosity, intrinsic vasoconstrictive properties, increased sensitivity to endogenous vasopressors and vascular resistance to NO [15]. ESA discontinuation is advised when antihypertensives are ineffective in managing elevated BP [38]. Frequently used in cancer patients, nonsteroidal anti-inflammatory drugs (NSAIDs) can cause or exacerbate hypertension by increased salt and water retention and diminished production of prostaglandins [39]. They should be used judiciously in patients with preexisting CV disease (CVD) or chronic kidney disease (CKD). Calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus represent another class of drugs used in cancer management, most commonly for immunosuppression following bone marrow transplantation, occasionally for cancer-associated autoimmune haemolytic anaemia and pure red cell aplasia. CNIs can cause hypertension in 30%–60% of patients [40], primarily through their effects on the renal tubules, RAAS and NO–endothelin balance [41].

Radiation therapy has been implicated in hypertension through various pathways. Carotid baroreflex denervation and failure from craniocervical irradiation can lead to labile hypertension or hypertensive crisis. Endothelial cell injury and baroreceptor dysfunction are associated with elevated sympathetic activity, increased reactive oxygen species (ROS) and reduced parasympathetic activity [42], which may also manifest as BP variability, orthostatic intolerance and tachycardia. Radiation-induced renal artery stenosis is rare; however, it should be suspected in patients who develop hypertension following abdominal radiotherapy [43]. Radiation nephropathy can occur in around 20% of patients following kidney irradiation and may present as either acute radiation nephritis (ARN) or chronic radiation nephropathy (CRN) [1]. ARN usually occurs between 6–18 months after radiation exposure. It may be associated with vague symptoms of fatigue, oedema and headaches, or symptoms due to malignant hypertension like encephalopathy and heart failure (HF). Renal biopsy shows loss of endothelial cells with subendothelial expansion and TMA. In contrast, CRN occurs after 18 months of exposure and is often asymptomatic.

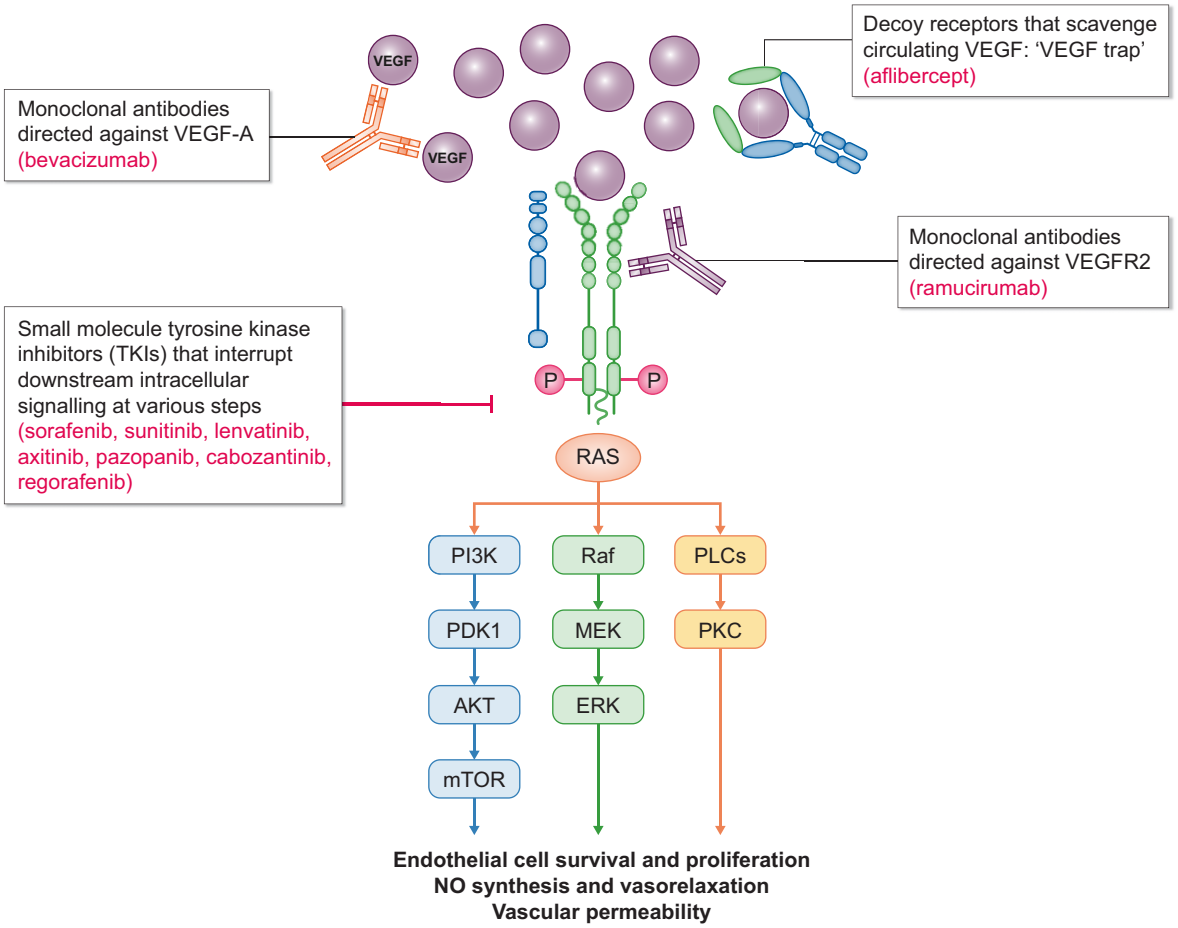


Figure 3: Different types of VEGF signalling pathway inhibitors and their actions.

Hypertension is one of the first signs of CRN, with evidence of interstitial fibrosis and arteriolar sclerosis on histopathology [44]. Hypertension due to radiation nephropathy is usually treated with ACE-I/ARBs.

There are additional nontherapy-related factors that can contribute to increased BP. Cancer patients are at a higher risk for pain, anxiety, depression and sleep problems, all of which can cause transient or chronic BP elevations. They may also have other characteristics which place them at risk for new-onset or exacerbated hypertension, including a high-sodium diet, sedentary lifestyle, tobacco or alcohol use, and weight gain, particularly seen with breast and prostate cancer. Paraneoplastic hypertension can occur due to the release of various vasoactive peptides like endothelin-1, urotensin-II and adrenomedullin (renal cell cancer) [45], renin and angiotensinogen (hepatocellular cancer) [46, 47], corticotropin-releasing hormone (small-cell lung cancer and carcinoid tumours) [48, 49] and catecholamines (phaeochromocytomas and paragangliomas) [50].

DEFINING ONCO-HYPERTENSION

Cancer patients have traditionally been excluded from large-scale hypertension trials. Therefore, there is little evidence to inform the therapeutic thresholds and BP targets in this highly specialized population. Diagnostic and treatment recommendations are based on expert opinion and extrapolation of the general hypertension guidelines to onco-hypertension. There are several limitations to this approach. The pathophysiologic pathways responsible for CTRH may differ fundamentally from those of essential hypertension. For instance, patients receiving VSPIs can develop an abrupt rise in BP within days of starting treatment, resulting in acute end-organ damage at lower BP compared with chronic hypertensives with well-conditioned autoregulatory mechanisms. In one study, 54 normotensive patients treated with sorafenib underwent 24-h ambulatory BP monitoring (ABPM); 93% had a rise in BP by Day 6, and most experienced an increase within the first 24 h of therapy [51]. This phenomenon has been recognized in the Common Terminology Criteria for Adverse Events (CTCAE), and a symptomatic increase in diastolic BP by >20 mmHg is an indication for therapy [52]. The recent International Cardio-Oncology Society (IC-OS) guidelines also define this exaggerated hypertensive response as an increase in systolic BP by >20 mmHg and in mean arterial pressure by >15 mmHg [53].

In addition, inaccurate BP measurements due to cancer-related pain and anxiety often confound hypertension diagnosis. In a small retrospective study that investigated the difference between BP measurements recorded by physicians and nurses in breast cancer patients before initiation of chemotherapy, almost 60% of the patients were noted to have a significant white coat effect [54]. Similarly, masked hypertension

Table 1: Anticancer drugs and adjunctive therapies commonly associated with hypertension. Listed are example drugs, hypothesized mechanisms of drug-induced hypertension, and suggested first-line treatment of hypertension.

Anticancer drug class	Example drugs	Putative mechanisms	Suggested first-line treatment[a]	Ref
VEGF signalling pathway inhibitors	Bevacizumab, sorafenib, sunitinib, lenvatinib, axitinib, pazopanib, regorafinib	↑ Vasoconstriction (ET-1), ↓ vasodilation (NO), endothelial dysfunction, capillary rarefaction, ↓ lymphangiogenesis, renal injury and TMA	ACE-I/ARB, dihydropyridine CCB	[3, 9, 12, 85–89]
Proteosome inhibitors	Bortezomib, carfilzomib, ixazomib	Cellular toxicity, endothelial dysfunction, ↓ NO bioavailability, TMA	ACE-I/ARB	[18, 90, 91]
Alkylating agents	Cyclophosphamide, ifosfamide, Busulfan	Oxidative stress, endothelial dysfunction, abnormal vascular remodelling, renal injury	ACE-I/ARB, dihydropyridine CCB	[92, 93]
Platinum-based compounds	Cisplatin, carboplatin	↓ NO bioavailability, endothelial dysfunction, renal injury	ACE-I/ARB, dihydropyridine CCB	[82, 94, 95]
Nucleoside analogues	Gemcitabine	Endothelial cell damage, TMA	ACE-I/ARB	[1, 30, 96]
BTK inhibitors	Ibrutinib, acalabrutinib	↓ hsp 70, ↓ NO bioavailability, endothelial dysfunction	ACE-I/ARB, BB (nebivolol or carvedilol)	[19, 97]
BRAF/MEK inhibitors	Vemurafenib, dabrafenib, encorafenib	CD47 upregulation, ↓ cGMP, ↓ NO bioavailability	ACE-I/ARB, dihydropyridine CCB	[20, 98, 99]
Androgen synthesis inhibitors	Abiraterone, leuprolide	CYP17A inhibition with diversion of steroid precursors to mineralocorticoid production → increased fluid retention	MRA (eplerenone), diuretics	[79, 100]
Androgen receptor blockers	Enzalutamide	Endothelial dysfunction, ↓ testosterone-induced vasodilation mediated by L-type calcium channels	Dihydropyridine CCB, ACE-I/ARB, MRA	[59, 101, 102]
mTOR inhibitors	Everolimus, sirolimus	↓ VEGF bioavailability	ACE-I/ARB, dihydropyridine CCB	[103, 104]
PI3K inhibitors[b]	Copanlisib	↓ NO production by inhibition of PI3K/AKT/eNOS pathway	ACE-I/ARB, dihydropyridine CCB	[26, 104]
RET kinase inhibitors	Selpercatinib, pralsetinib	Inhibition of BRAF/MEK/ERK → CD47 upregulation, ↓ cGMP, ↓ NO bioavailability	ACE-I/ARB, dihydropyridine CCB	[105–107]
PARP inhibitors[c]	Niraparib	↓ Dopamine, norepinephrine and serotonin reuptake, inhibition of DYRK1A	BB (nebivolol or carvedilol), ACE-I/ARB	[108–110]
Calcineurin inhibitors	Cyclosporine, tacrolimus	↑ Proximal tubule Na reabsorption, renal dysfunction, ↓ NO bioavailability, ↑ ET-1 and ROS, ↑ RAAS	Dihydropyridine CCB, thiazide diuretics	[41, 111–113]
Glucocorticoids	Prednisone, dexamethasone	↑ Na and water retention, ↑ vasoconstriction, ↑ sensitivity to endogenous vasopressors	MRA, diuretics, ACE-I/ARB, steroid dose reduction or discontinuation	[114]
Erythropoiesis-stimulating agents	Erythropoietin, darbopoietin	↑ Blood viscosity, ↑ vasoconstriction, ↑ sensitivity to endogenous vasopressors	Dihydropyridine CCB, EPO discontinuation	[38]

[a]In the absence of contraindication.
[b]Idelalisib does not typically cause hypertension.
[c]Olaparib may have antihypertensive and cardioprotective effects.
ET-1, endothelin 1; hsp, heat shock protein; CD47, cluster of differentiation; cGMP, cyclic guanosine monophosphate; CYP17A, cytochrome 17A; DYRK1A, dual-specificity tyrosine phosphorylated and regulated kinase 1A; Na, sodium; EPO, erythropoietin.

is also quite prevalent among cancer patients and can cause underdiagnosis in an office-based setting. This is especially true for hypertension caused by VSPIs and proteasome inhibitors, which can be dose-dependent and transient. Azizi *et al*. examined home BP monitoring (HBPM) in 14 patients receiving sunitinib; BP increased by Week 1 of treatment initiation and decreased within 1–2 weeks after discontinuing therapy [55]. Another prospective observational study by Mir *et al*. noted that twice daily HBPM was associated with more than two times higher detection rates of early hypertension compared with in-clinic measurements (55% versus 24%, $P < .001$) [56]. As a result, most guidelines recommend ABPM or HBPM, especially when initiating or titrating medications like VSPIs, which can potentially cause a rapid rise in BP and hypertensive emergency if undetected.

Another controversy in the management of CTRH involves the use of BP as a biomarker of antineoplastic efficacy. Several studies have demonstrated that patients who develop hypertension with VSPIs have better overall and progression-free survival compared with those who remain normotensive [57, 58]. This observation has established hypertension as a favourable sign of effective VSPI therapy and encouraged the practice of dose titration guided by changes in BP. The package insert for axitinib suggests that the dose may be increased for patients who have tolerated therapy for 2 weeks and remained normotensive without the need for antihypertensive medications [59]. Current data suggest that treating hypertension does not negate the survival benefits conferred by VSPIs [14, 60] and may, in fact, prevent cancer therapy interruption or dose reduction due to the sequelae of severe uncontrolled hypertension.

Lastly, the treatment of CTRH should be guided by the cancer prognosis in an individualized manner. The 2022 European Society of Cardiology (ESC) guidelines on cardio-oncology acknowledge this need and suggest more lenient treatment thresholds (>160/100 mmHg) for asymptomatic patients with metastatic cancer who have an expected survival of less than 1 year [61].

APPROACH TO MANAGEMENT

Diagnosis, evaluation and monitoring

Before starting prohypertensive cancer therapy, patients should be counselled about the risk of developing new or worsening hypertension so that they can participate in BP monitoring and understand the potential need for rapid institution and escalation of antihypertensive therapy. In addition, a thorough assessment of CV risk should be performed at the first visit, as this initial risk stratification drives BP management and targets.

Baseline BP must be obtained in all patients. Not only is this necessary to detect an exaggerated hypertensive response with chemotherapy, but it also helps identify patients with preexisting hypertension who could benefit from early BP management. A recent study that evaluated BP trends after initiation of various VSPIs found that patients receiving treatment for known hypertension had three times lower odds of developing VSPI-induced BP rise compared with baseline normotensive patients [14].

BP should be measured in both arms after being seated for 5 min, without any exercise, smoking or caffeine consumption in the previous 30 min [62]. The patient should be seated comfortably with legs uncrossed and the arm resting at the level of the heart. Elevated BP should be confirmed on at least two occasions before diagnosing hypertension. ABPM is more accurate and carries a stronger association with CV outcomes than office-based monitoring, and it should be performed in all patients when available. Some centres have established remote patient monitoring (RPM) programs to closely monitor the response to cancer therapy [63]. Home BP self-monitoring is an acceptable alternative to ABPM and RPM. In general, BP should be checked at least every week in the clinic when receiving the first cycle of chemotherapy and every 2–3 weeks during the remaining cycles [64]. This should be supplemented by twice-daily BP monitoring at home with a validated device [65].

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Clinical Practice Guidelines and the 2018 ESC/European Society of Hypertension guidelines are generally used for the diagnosis and grading of hypertension in patients with cancer. Hypertension is diagnosed if the appropriately measured office-based or average home BP is ≥130/80 mmHg [65] or the average BP on ABPM is ≥125/75 mmHg [66]. Subsequent evaluation is like that of noncancer patients. Workup includes ECG, echocardiography and evaluation for secondary causes of hypertension, including hyperaldosteronism, pheochromocytoma, hypercortisolism, CKD, renal artery stenosis and obstructive sleep apnea, as indicated.

Therapeutic goals

Patients with preexisting CVD [coronary artery disease (CAD); peripheral vascular disease; HF or stroke], proteinuric CKD, diabetes mellitus or atherosclerotic CVD (ASCVD) risk >10% should receive antihypertensive therapies if BP is ≥130/80 mmHg. Patients without known CVD and low ASCVD risk can be treated at a higher BP threshold of ≥140/90 mmHg [62]. BP should be controlled before starting cancer therapy to minimize the risk of cardiotoxicity. The presence of hypertension, particularly poorly controlled hypertension, increases the risk of anthracycline- and trastuzumab-associated cardiomyopathy and HF [67]. A recent study by Kaneko *et al*. confirmed an association between hypertension and an increased risk of heart failure and other CVD in cancer patients, with an odds ratio of 1.24 for ACC/AHA stage 1 hypertension (130–139/80–89 mmHg) and 1.99 for stage 2 hypertension (>140/90 mmHg) [68]. Effective treatment of hypertension also helps patients tolerate maximum doses of the planned anticancer therapies, yielding better control of the tumour.

Once started on antihypertensive therapy, the goal BP is <130/80 mmHg in most individuals [62]. A goal BP of <140/90 mmHg may be reasonable [61], especially for patients who are unable to either tolerate or achieve stricter BP control due to ongoing chemotherapy. For asymptomatic patients with metastatic cancer with an expected survival of 1–3 years, the target may be relaxed further to 140–159/90–99 mmHg [61]. BP >160/100 mmHg should be treated in all patients, irrespective of the oncologic prognosis, to prevent life-threatening complications, hospitalizations and interruptions to cancer therapy due to uncontrolled hypertension. An acute BP rise (diastolic BP increase >20 mmHg) caused by agents like VSPIs may also benefit from treatment [52].

Prohypertensive anticancer agents should be held if BP rises above 180/110 mmHg and should not be restarted until BP is controlled to <160/100 mmHg. Once BP is better controlled, a multidisciplinary team should assess the competing risks of cancer and CVD and determine whether to rechallenge with dose reduction or switch to an alternative agent [53, 61].

Hypertensive emergency is defined by IC-OS as ‘very high BP elevations associated with acute hypertension-mediated organ damage’ and is an indication for hospital admission for immediate BP-lowering therapy [53]. The occurrence of acute or-

gan damage, including pulmonary oedema, cardiac ischaemia, acute renal failure, papilledema, hypertensive encephalopathy, neurologic deficits or posterior reversible encephalopathy syndrome, may warrant permanent discontinuation of cancer therapy [4, 69].

There are insufficient data to determine a BP threshold predictive of an increased risk of hypertensive emergency with VSPIs. Plummer *et al*. have reported that VSPI may be safe to start if BP is <160/100 mmHg in the office and <150/95 mmHg at home [69]. However, all efforts must be made to control BP to a level <140/90 mmHg while on VSPI. It is not necessary to delay cancer therapy to achieve this BP goal; instead, BP-lowering and cancer treatment goals can be attained in parallel. Patients with uncontrolled BP despite three antihypertensive medications may benefit from referral to a specialized onco-hypertension clinic.

In addition to BP monitoring, patients should be screened for proteinuria before and during VSPI therapy. Treatment with VSPIs can be continued in most cases of non–nephrotic range proteinuria and can also be managed with ACE-I/ARBs. The implications of more significant proteinuria during VSPI therapy are poorly understood, which is reflected in the lack of consensus and guidance regarding management strategies. A suggested approach includes holding therapy for proteinuria >2 g/day [70, 71]. Proteinuria often disappears upon stopping VSPI therapy; however, persistence beyond 3 months, high-grade proteinuria >3 g/day or microscopic hematuria should prompt a renal biopsy to evaluate for chemotherapy-induced TMA and may require permanent discontinuation of VSPI [70, 72]. A biopsy may also help to identify paraneoplastic glomerular diseases, such as membranous nephropathy, as the cause of proteinuria, which may instead require escalation of chemotherapy.

Choosing antihypertensive medications

There are no randomized controlled trials that prove the superiority of one antihypertensive agent over the rest. As in non-cancer patients, antihypertensive medications should be tailored to comorbidities (Table 2). ACE-I/ARBs and dihydropyridine CCBs are the most frequently used agents for the treatment of CTRH because of their vasodilatory effect. While both are believed to have equal BP-lowering effect [14], ACE-I/ARBs are preferred as the first choice because of their beneficial role in concomitant cancer therapy–related cardiac dysfunction [61, 65]. Additionally, some data suggest that the use of ARBs in patients receiving VSPIs has been associated with improved overall and progression-free survival [45, 73]. It has been postulated that ARBs may augment the antitumour efficacy of VSPIs [64, 74]. ACE-I/ARBs may also be beneficial for VSPI-induced proteinuria and vasoreactivity [63]. There are insufficient data pertaining to the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with VSPI-induced proteinuria.

Patients with BP >160/100 mmHg should be treated with a combination therapy of ACE-I/ARBs and dihydropyridine CCBs [61]. Thiazide diuretics may also be used, although caution must be exercised in patients at risk for chemotherapy-induced diarrhoea and electrolyte loss, as they can result in volume depletion and QT prolongation, respectively [62]. For resistant CTRH, spironolactone, nitrates and/or hydralazine are effective agents [61]. Beta-blockers are typically reserved for coexisting indications of CAD, HF and arrhythmias. They may be a good choice for BTK inhibitors which cause both hypertension and atrial fibrillation. They may also be useful for hypertension caused by high sympathetic tone, often associated with pain and stress.

Table 2: Suggested choice of antihypertensive drugs by comorbidity.

Comorbidity	Suggested antihypertensive medication
DM, diabetic nephropathy, proteinuria, CKD	ACE-I/ARB SGLT2i
CHF, LV systolic dysfunction	ACE-I/ARB/ARNI SGLT2i BB MRA Loop diuretic
CAD	BB ACE-I/ARB Nitrates
Arrhythmia	BB
Resistant HTN	MRA Nitrates and/or hydralazine
Elderly, isolated systolic HTN	Dihydropyridine CCB

DM, diabetes mellitus; CHF, congestive heart failure; HTN, hypertension; LV, left ventricular; ARNI, angiotensin receptor/neprilysin inhibitor; BB, beta blocker.

Nebivolol is the preferred beta-blocker because it promotes NO bioavailability. Carvedilol may also be a reasonable choice because of its alpha-blocking action. Mineralocorticoid receptor antagonists (MRAs) and other potassium-sparing diuretics are effective agents for hypertension caused by androgen blockers and glucocorticoids, as they counter the effects of sodium-water retention and hypokalemia associated with mineralocorticoid excess. In case of persistent steroid-induced hypertension, loop diuretics or steroid discontinuation may be needed. Table 1 summarizes the preferred antihypertensive medications based on the mechanism of CTRH.

Providers must exercise caution to avoid choosing antihypertensive agents that have a known drug interaction with cancer therapy [63]. For example, non-dihydropyridine CCBs (verapamil, diltiazem) inhibit CYP3A4 enzymes which increase plasma levels of TKIs. In addition, verapamil decreases the excretion of doxorubicin, paclitaxel and irinotecan, and worsens cardiotoxicity. Amlodipine should not be used in patients with VEGF-induced hepatotoxicity. ACE-I have a higher risk of angioedema with mammalian target of rapamycin (mTOR) inhibitors. Loop diuretics have a higher risk of causing ototoxicity and nephrotoxicity with platinum-based therapy. Thiazide diuretics may potentiate cyclophosphamide-induced myelosuppression. Certain TKIs cause QT prolongation, which can be worsened by beta-blocker use, increasing the risk of pause-dependent torsades. Certain non-VEGF TKIs, such as imatinib and gefitinib, increase metoprolol levels and worsen bradycardia. This effect is even more pronounced with crizotinib and ceritinib, which can cause additional bradycardia. Spironolactone should not be used for abiraterone-induced hypertension as it interferes with the antiandrogen effect of abiraterone and can cause an increase in prostate cancer growth. While spironolactone typically carries anti-androgenic properties and is believed to be protective against prostate cancer [75], in an androgen-deprived environment created by androgen synthesis inhibitors, it behaves as a selective androgen receptor modulator and exerts a paradoxical pro-androgenic effect [76–78]. Eplerenone is a safe alternative to spironolactone [79].

Lifestyle modifications

The benefits of lifestyle modifications, such as dietary sodium restriction and exercise, cannot be overemphasized and should be encouraged in all patients [62, 63]. Patients receiving VSPIs are more sensitive to sodium load due to impaired natriuresis, and a sodium-restricted diet has been shown to reduce the risk of VSPI-induced hypertension [80]. Patients should be counselled to avoid substances that can exacerbate hypertension, including caffeine, smoking, alcohol and NSAIDs, especially when receiving cancer therapy.

LONG-TERM FOLLOW-UP

After discontinuation of VSPIs or proteasome inhibitors, BP may decrease in a matter of days [55] and may require a rapid dose reduction of antihypertensive medications. Therefore, these patients should be closely monitored on ABPM or daily HBPM to avoid rebound hypotension and ischaemic events. There is insufficient evidence to identify the risk factors that predispose to this phenomenon.

In contrast, hypertension due to BTK inhibitors can occur several months after treatment initiation [19] and can be persistent [81], especially as the treatment for CLL may continue for several years. Similarly, cisplatin can persist in the bloodstream for up to 20 years after drug exposure, leading to late-onset hypertension due to chronic endothelial dysfunction [82, 83]. Cancer survivors have a higher prevalence of hypertension compared with the general population, accompanied by a higher incidence of CVD if untreated [15, 84]. A meta-analysis revealed that the incidence of HF was 12 times higher in childhood cancer survivors who developed hypertension compared with their normotensive counterparts [84]. Therefore, these patients should be closely followed long after the discontinuation of anticancer therapy. Larger prospective studies are needed to identify the agents that can cause persistent or late-onset hypertension.

CONCLUSION

In summary, the burden of hypertension in patients with cancer is exceedingly high. Many of these patients have underlying CV risk factors; various anticancer therapies can exert prohypertensive effects; and direct cardiac, renal and/or vascular toxicity of cancer treatment can further exacerbate hypertension. All these effects can increase the risk of CV disease and mortality in this vulnerable patient population. The concurrent management of cancer and CV comorbidities, including hypertension, is critical to allow the successful completion of optimal cancer therapy while minimizing adverse effects (Graphical Abstract). The joint efforts of the oncologist, cardio-oncologist, onco-nephrologist, speciality pharmacist and other players are vital to providing optimal care for these patients, especially with new cancer therapeutics being discovered every day. Timely screening, early diagnosis and effective treatment of hypertension are key components of preventing end-organ damage and minimizing cancer therapy dose reduction or interruption. The overarching goal is to prevent short-term and late CV events while achieving the maximum benefits of cancer treatment.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

A.S.K. is supported by the Letts O'Brien Fund for Breast Cancer Research. K.D.J. is a founder and co-president of the American Society of Onco-Nephrology; and reports consultancy agreements with Secretome, George Clinicals, PMV pharmaceuticals and Calliditas. K.D.J. reports honoraria from the American Society of Nephrology and UpToDate.com; reports serving on the editorial boards of *American Journal of Kidney Diseases*, *Clinical Journal of the American Society of Nephrology*, *Clinical Kidney Journal*, *Journal of Onconephrology*, *Kidney International* and *Nephrology Dialysis Transplantation*; and reports serving as Editor-in-Chief of ASN Kidney News and section editor for onconephrology for *Nephrology Dialysis Transplantation*. All the authors declared no competing interests. S.M.H. is supported by the National Institute of Health (K08 DK118120).

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