



Tyrosine Kinase Inhibitor-Induced Hypertension

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Abstract

Purpose of Review The purpose of this paper is to identify commonly used tyrosine kinase inhibitors (TKIs) that are associated with hypertension, primarily, vascular endothelial growth factor (VEGF) signaling pathway (VSP) inhibitors. We review the incidence, mechanism, and strategies for management of TKI-induced HTN. We hope to provide clinicians with guidance on how to manage similar clinical scenarios.

Recent Findings Many of the newer VSP inhibitors are reviewed here, including cediranib, axitinib, pazopanib, and ponatinib. Trials utilizing prophylactic treatment with angiotensin system inhibitors (ASIs) are discussed as well as recent data showing an improvement in overall survival and progression-free survival in patients on ASIs and TKI-induced hypertension.

Summary The incidence of TKI-induced HTN among the VEGF inhibitors ranges from 5 to 80% and is dose dependent. Newer generation small-molecule TKIs has a lower incidence. The mechanism of action involves VSP inhibition, leading to decreased nitric oxide and increased endothelin production, which causes vasoconstriction, capillary rarefaction, and hypertension. ASIs and calcium channel blockers are first-line therapy for treatment and are associated with improved overall survival. Nitrates and beta-blockers are associated with in vitro cancer regression; however, there is a paucity of trials regarding their use as an anti-hypertensive agent in the TKI-induced HTN patient population.

Keywords VEGF inhibitor · Hypertension · Tyrosine kinase inhibitor · Anti-hypertensive therapy · Nitric oxide · Incidence

Introduction

The recent 2017 AHA/ACC guidelines define hypertension (HTN) as a systolic blood pressure (SBP) over 130 mmHg and a diastolic blood pressure (DBP) over 80 mmHg based on two or more measurements on two separate visits [1]. In an observational study of > 1 million adults ≥ 30 years old, elevated SBP and DBP were associated with increased risk of cardiovascular disease (CVD) incidence and angina, myocar-

dial infarction, heart failure, stroke, peripheral arterial disease, and abdominal aortic aneurysm [2]. In the USA, HTN is the leading modifiable risk factor that causes CVD death [3].

With a prevalence of 37%, HTN is also the most common CVD comorbidity in cancer registries [4]. The etiology of HTN is vast and novel cancer therapies, such as tyrosine kinase inhibitors (TKIs) are associated with HTN. In fact, many physicians suggest that TKI-induced HTN is a surrogate for drug efficacy against tumor cells and the 2017 AHA/ACC guidelines specifically cite this class of drugs as a precipitant of HTN [1]. The TKIs most notorious for causing HTN are drugs that target the vascular endothelial growth factor (VEGF) signaling pathway (VSP). Both small-molecule and antibody VEGF inhibitors are well-tolerated first-line agents that have been shown to increase overall survival in a multitude of different cancers. VEGF inhibition primarily affects angiogenesis of tumor cells leading to tumor death; however, inhibition of angiogenesis can also result in HTN through endothelial-dependent pathways, alterations in capillary density, and even micro-emboli.

While guidelines recommend treatment of HTN for long-term mortality risk reduction, most patients that receive VSP

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inhibitor therapy receive the drug for a short period and have limited life expectancy, calling into question the need to treat their HTN. However, serious adverse events, discontinuation of therapy, and decrease in overall survival can occur with untreated TKI-induced HTN. New data suggests that treating TKI-induced HTN can lead to improved overall survival as well as cancer progression-free survival due to control of a modifiable CVD risk factor and the ability to stay on life-saving cancer therapy for longer periods [5]. Besides HTN, VSP inhibition can lead to other serious adverse cardiac events such as arterial thrombotic disease, cardiomyopathy, and ischemic heart disease with varying incidence; however, discussion of these adverse events are beyond the scope of this article. The incidence, mechanism, and management of TKI-induced HTN via VSP inhibition will be reviewed here.

Incidence

HTN in earlier studies using TKIs was defined most commonly by using the Common Terminology Criteria for Adverse Events (CTCAE) versions 2.0 or 3.0 as described in Table 1 [6]. Some studies also used the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 (JNC 7) guidelines that defined HTN as BP \geq 140/90. The CTCAE version 4.0 was modified to parallel the JNC 7 guidelines in an effort to achieve more consistency. The recent change in HTN guidelines published by the ACC/AHA in 2017 is thus not reflected in these studies.

TKIs have been associated with increased incidence of HTN but the incidence can vary depending on the drug, pre-existing conditions, dose, and type of tumor. Some of the risk factors include pre-existing HTN with SBP \geq 160 mmHg or DBP \geq 100 mmHg, diabetes, established cardiac or renal disease, older age, cigarette smoking, dyslipidemia, family history of premature CVD, obesity, and elevated fasting plasma glucose levels [7]. The incidence of HTN for some of the commonly used TKIs are discussed below and summarized in Table 2.

Table 2 Incidence of hypertension with tyrosine kinase inhibitors [Adapted from [11]]

Chemotherapeutic agent	Incidence (%)
Monoclonal antibody-based TKIs	
Bevacizumab	4–35
Small-molecule-based TKIs	
Pazopanib	42
Ponatinib	68
Sorafenib	7–43
Sunitinib	5–24
Axitinib	40
Regorafenib	30–59
Cediranib	43–87

Bevacizumab

Bevacizumab is a monoclonal antibody that binds VEGF and has been used to treat colon cancer, lung cancer, glioblastoma, renal cell carcinoma (RCC), and age-related macular degeneration. It has been studied in several trials with an overall incidence of HTN from 4 to 35%. Grade 3 HTN developed in 11 to 18%. Severe HTN requiring discontinuation of therapy or hospitalization was noted in 1.7% of patients treated with bevacizumab [8]. HTN can occur with drug initiation within the first year of treatment. A median interval from first dose of bevacizumab to the onset of HTN was 131 days (range of 7–316 days) as reported by Yang et al. [9].

Studies have also shown a possible association between increased risk of developing HTN with dose and tumor type. In a meta-analysis of 19 randomized control trials done by An et al. that included 12,949 cancer patients with various solid tumors, the relative risk ratios of significantly elevated BP in patients receiving 5 and 2.5 mg/kg per week were 7.17 (95% CI, 3.91–13.13) and 4.11 (95% CI 2.49–6.78) respectively. It was also noted that the risk of developing HTN was higher in the patients with RCC (RR 13.77, 95% CI 2.28–83.15) and breast cancer patients (RR 18.83, 95% CI 1.23–292.29) who received bevacizumab at 5 mg/kg per week [10].

Table 1 Grading of hypertension according to the Common Terminology Criteria for Adverse Events v. 3.0 (similar to v. 2.0) [6]

Grade	Description
1	Asymptomatic, transient (<24 h) increase by > 20 mmHg (diastolic) or to > 150/100 if previously within normal limits; intervention not indicated
2	Recurrent or persistent (\geq 24 h) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 if previously within normal limits; monotherapy may be indicated
3	Requiring more than one drug therapy or more intensive therapy than previously
4	Hypertensive crisis
5	Death

Sunitinib

Sunitinib is a TKI used more commonly in the treatment of metastatic RCC and gastrointestinal stromal tumor (GIST). The incidence of HTN in patients treated with sunitinib has ranged from 5 to 24% in various trials [11]. In a meta-analysis done by Zhu et al., a total of 4999 patients with RCC and other malignancies from 13 clinical trials were included for analysis. The incidence of all-grade and high-grade HTN in patients treated with sunitinib were 21.6% (95% CI 18.7–24.8%) and 6.8% (95% CI 5.3–8.8%) respectively. There was an increased risk of high-grade HTN (RR = 22.72, 95% CI 4.48 to 115.29, $p < 0.001$) noted when compared to controls. There was also a significant difference detected between RCC and non-RCC in terms of all-grade HTN (RR 1.32, 95% CI 1.18–1.48%, $p < 0.001$) and high-grade HTN (RR 1.57, 95% CI 1.22–2.02%, $p = 0.001$) which may in part be related to renal dysfunction caused by sunitinib [12]. Azizi et al. showed that BP levels may increase as early as a week after initiating treatment with sunitinib [13].

Sorafenib

Sorafenib is a multi-kinase inhibitor and has several targets including the VEGF-receptor. It is most commonly used for RCC, hepatocellular carcinoma, and advanced thyroid carcinoma. The incidence of HTN in various trials has ranged from 7 to 43% for sorafenib [11]. In a meta-analysis done by Wu et al. that included 4599 patients in nine studies with RCC or other solid tumors, the overall incidence of all-grade HTN was 23.4% (95% CI 16.0–32.9%) and 5.7% (2.5–12.6%) for high-grade HTN (grade 3 or 4). The RR for increased risk of all-grade HTN was 6.11 (2.44–15.32, $p < 0.001$) compared with control subjects. No significant difference was detected in the incidence of sorafenib-associated HTN between patient with RCC and non-RCC cancer [14]. Maitland et al. noted BP elevations from sorafenib as early as within 1 day and more readily detected when steady state of sorafenib reached in a week [15].

Pazopanib

The overall incidence of HTN in patients who underwent therapy with pazopanib is around 42% in various trials [11]. It is most commonly used for advanced RCC or soft tissue sarcoma. In a small retrospective study of 35 patients with metastatic RCC at a single medical center, Pinkhas et al. noted an incidence of pazopanib-induced HTN in 57% of patients. New-onset HTN was noted in 43% of patients. The overall median time to development of pazopanib-induced HTN was 24.5 days. A baseline SBP > 130 mmHg was associated with a higher risk of developing HTN with pazopanib [16].

Axitinib

The overall incidence of HTN in patients treated with axitinib was 40% [11]. It is most commonly used for treatment of RCC as well. A recent analysis by Qin et al. looked at 26 trials, including 4790 patients diagnosed with RCC and treated with axitinib or sorafenib monotherapy and noted a higher incidence of HTN (24.9 vs. 7.9%) in patients receiving axitinib versus sorafenib [17].

Cediranib

Cediranib is an oral small-molecule TKI of VEGF-receptor 1 (VEGFR-1), VEGFR-2, VEGFR-3 among others, and is being explored in the treatment of ovarian, non-small cell lung cancer, glioblastoma, and colon cancer. A phase II trial done by Robinson and colleagues of 46 women, 31 women (67%) developed HTN by day 3; 87% developed HTN by end of study and 43% developed higher grade HTN (grade 3 or more) [18].

Ponatinib

Ponatinib is a third-generation TKI that is a potent chemotherapeutic agent used most often against resistant cases of chronic myeloid leukemia (CML), especially in patients with the BCR-ABL1^{T3151} mutation [19]. Unlike other BCR-ABL TKIs, ponatinib has a significant inhibitory effect on VEGFR-2 similar to molecules specifically designed to inhibit VSP [19]; therefore, it is no surprise that there is a significant association with HTN. Overall incidence of various degrees of HTN in various studies was as high as 68% [11]. A dose-dependent cardiovascular toxicity is noted with ponatinib as well as less tolerance of higher doses in older patient with history of diabetes or ischemic events [19].

Of note, ponatinib trials showed a significant incidence of arterial thrombotic events at 12 months, as high as 14%. Patients with traditional cardiovascular risk factors had a greater predisposition to these adverse outcomes. Due to continuing high incidence at 24 months and similar trends in subsequent studies, there was transient suspension of the drug in the US market and a restricted FDA use label [19].

Dasatinib

Dasatinib is a second-generation TKI approved for front-line therapy of CML based on superior results over imatinib [20]. Initial safety reviews isolated pleural effusions as a common therapy side effect and source of shortness of breath (SOB) [21]. At 36-month follow-up in the same study, however, there was a 3% incidence pulmonary arterial hypertension (PAH), which increased to 5% at 5 years [22]. The findings triggered an FDA warning for evaluation of signs and symptoms of

cardiopulmonary disease in patients before and during dasatinib treatment, with notation that pleural effusion and anemia were still the most common etiology of SOB symptoms [19].

VEGF Therapeutic Mechanism of Action

Aberrant activation of receptor tyrosine kinases (RTKs) are implicated in multiple cancers making them an ideal therapeutic target. With the advent of VEGF inhibitors, oncologists can employ another targeted pathway to battle cancer with more manageable adverse effects. Currently, these antibodies and small molecules are utilized as first-line treatment, and beyond, in the metastatic setting with improvement in overall survival and progression-free survival. These agents are very well tolerated and have demonstrated an improvement in quality of life.

Human RTKs are cell surface receptors that span the cell membrane consisting of an extracellular domain along with an intracellular tyrosine kinase domain. There are 58 human RTKs which are further sub classified into 20 families and function as key regulators of critical cellular function [23]. The extracellular portion has binding sites for growth factors, which are endogenous molecules that promote cell proliferation and induce neovascularization [24, 25]. In general, growth factor binding activates the receptor by inducing structural changes to the extracellular domain and causing a cascade of signals downstream that activate the intracellular domain via phosphorylation [24, 25].

There are three primary growth factors that may bind to the RTKs and the ensuing effects on the cell are dependent on the type of growth factor. Vascular endothelial growth factor (VEGF) is the dominant growth factor in controlling angiogenesis. Epidermal growth factor (EGF) is responsible for differentiation and apoptosis. Platelet-derived growth factor (PDGF) plays a role in cell growth, cell division, and angiogenesis [26].

VEGF-A is the dominant growth factor that mediates angiogenesis by binding to VEGFR on the endothelial cells stimulating cell proliferation, migration, and survival [27]. VEGFRs are expressed on both normal endothelium and tumor cells. There are both anti-VEGF antibodies as well as anti-VEGFR antibodies that target the cell surface receptor for VEGF and also block VEGF signaling. Both types of antibodies are currently utilized as targets for cancer therapy [28, 29].

The upregulation of both VEGF-A mRNA and VEGFR has been demonstrated in majority of human tumor cells. In order for malignant cells to progress and metastasize, the tumor must recruit its own blood supply by increasing angiogenesis and forming blood vessels into avascular tumor masses [30]. VEGF inhibition by anti-VEGF antibodies such as bevacizumab exert their action by neutralizing VEGF,

causing regression of existing blood vessels, and depleting the tumor vascular supply causing the cells to die. There is evidence that the remaining blood vessels are then normalized which allows traditional chemotherapy delivery to tumor cells. Chronic VEGF inhibition by bevacizumab also inhibits new and recurrent blood vessel growth [31, 32].

VEGF-Induced Hypertension Mechanism of Action

Regression of blood vessels by VEGF signaling leads to tumor death, but also has untoward consequences on the normal vasculature: HTN, proteinuria, and arterial thromboemboli.

VEGF signaling normally enhances endothelial-derived nitric oxide (NO) production, which then acts on smooth muscle cells to vasodilate (Fig. 1) [6]. VSP inhibitors interfere with NO production in the arteriolar walls which then leads to vasoconstriction, increased vascular resistance, and ultimately, HTN [33]. In mice studies done by Facemire and colleagues, an anti-VEGFR2 antibody caused a rapid and sustained increase in BP of ≈ 10 mmHg. The HTN in response to the anti-VEGFR2 antibody was associated with significant reductions in the expression of endothelial and neuronal NO synthases in the kidney [34]. These findings were replicated in Bevacizumab trials [35].

Normal VEGF signaling mediates endothelial homeostasis. VSP inhibition leads to endothelial dysfunction, stimulating the release of Endothelin-1 (ET-1), a potent vasoconstrictor that may also play a role in mediating HTN [36]. Kappers et al. have reported a parallel rise in ET-1 and HTN in both human and rodents treated with sunitinib [37]. Regorafenib has been shown to drastically increase ET-1 levels, while co-administration of an endothelin receptor antagonist blunts the hypertensive response triggered by other anti-angiogenic therapies [38, 39]. While the distinct pathway linking ET-1 and VEGF inhibition continues to be studied, ET-1 has been suggested to act in a paracrine or autocrine manner [37].

When VSP is inhibited, NO is suppressed and ET-1 is stimulated, promoting vasoconstriction and subsequent hypertension. Another aspect of endothelial dysfunction that has a minor role in the development of hypertension has to do with micro-capillary rarefaction. VEGF maintains capillary network integrity, thus when inhibition occurs, rarefaction or reduction of the density of capillary beds can occur. Mouse models reveal a 30% regression of tracheal mucosal capillary networks by 21 days when treated with VEGF inhibitors, which then reverses with anti-angiogenic therapy discontinuation [40]. In patients with metastatic colorectal carcinoma receiving bevacizumab, the capillary density of the dorsum of the finger was reduced by 10% after 6 months of treatment, which was associated with increase in BP [41].

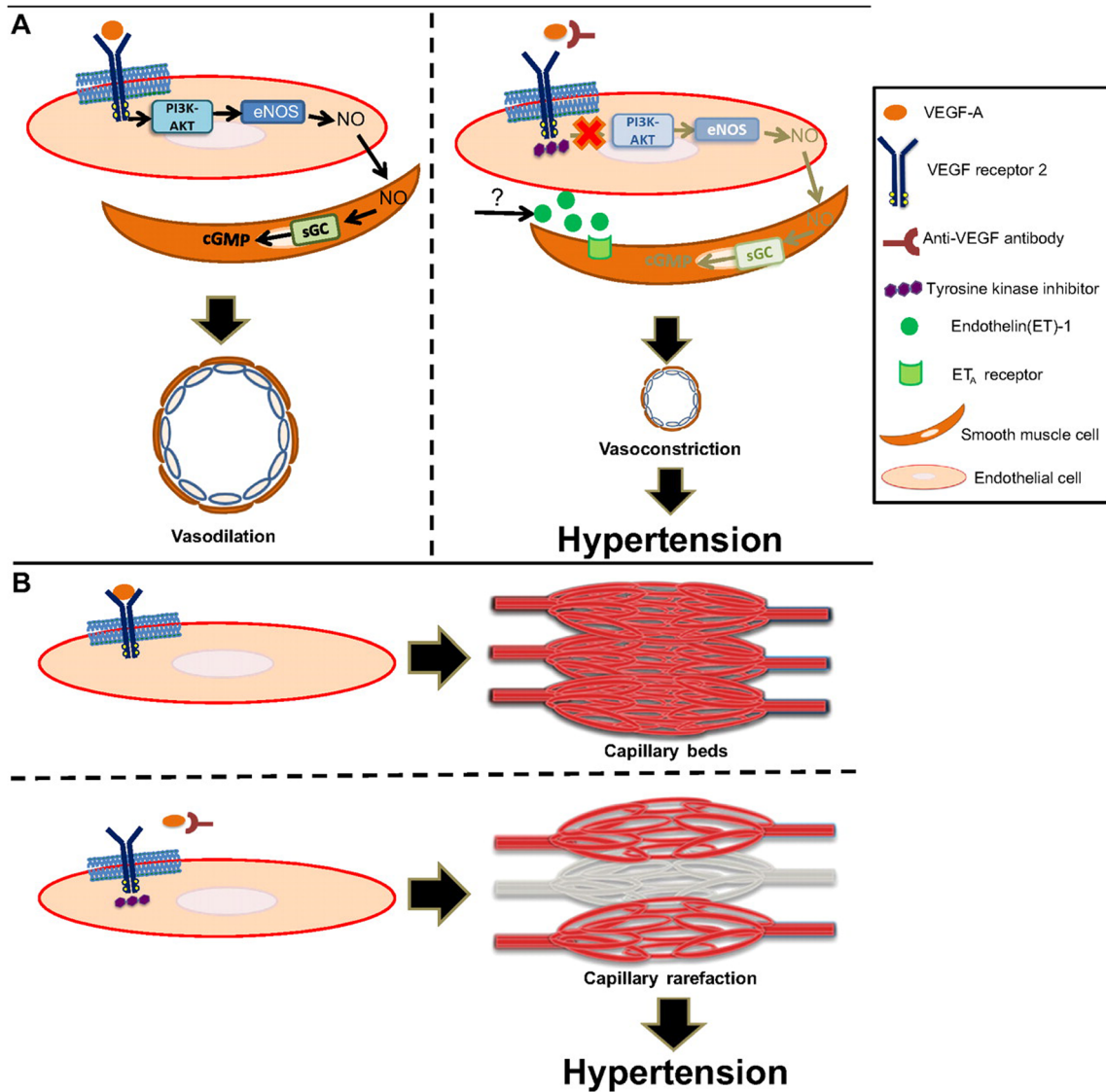


Fig. 1 Pathophysiology of hypertension induced by inhibition of vascular endothelial growth factor (VEGF) signaling pathway inhibition. Proposed mechanisms leading to vascular endothelial growth factor (VEGF) signaling pathway inhibitor-induced hypertension. **a** Activation of VEGF-receptor 2 by VEGF-A leads to subsequent activation of multiple pathways including phosphatidylinositol-3-kinase (PI3K)-AKT. PI3K-AKT phosphorylates and activates endothelial nitric oxide synthase (eNOS), increasing NO production. NO migrates to adjacent vascular smooth muscle cells and binds soluble guanylate cyclase (sGC), leading to cGMP generation and subsequent vasodilation mediated by cGMP-dependent kinases. When VEGF signaling pathway

is inhibited, NO pathway is suppressed and endothelin (ET)-1 pathway is stimulated, promoting vasoconstriction and subsequent hypertension. The source of ET-1 is unknown. **b** VEGF maintains capillary network integrity. When VEGF signaling pathway is inhibited, rarefaction or reduction of the density of capillary beds, may occur; however, this is likely a minor contributor to antiangiogenic therapy-induced hypertension. From de Jesus-Gonzalez N, Robinson E, Moslehi J, Humphreys BD. Management of antiangiogenic therapy-induced hypertension. *Hypertension*, Vol. 60, Issue 3, pages 607–15, accessible at <http://hyper.ahajournals.org/content/60/3/607>. Reproduced with kind permission from Wolters Kluwer Health, Inc.

Subsets of patients who develop anti-angiogenic therapy-induced HTN also develop proteinuria and micro-angiopathic hemolysis, which can lead to acute kidney injury. Glomerular endotheliosis represents a specific variant of thrombotic micro-angiopathy that is characterized by glomerular endothelial swelling with loss of endothelial fenestrae and occlusion of the capillary lumens. Associated thrombosis is unusual. Recent evidence suggests that this unusual glomerular lesion is mediated by a soluble VEGFR that deprives glomerular

endothelial cells of the VEGF that they require, leading to cellular injury and disruption of the filtration apparatus with subsequent proteinuria [42].

In a study by Patel et al, seven patients developed a preeclampsia-like syndrome characterized by HTN and proteinuria after starting therapy with TKI, identified clinically after developing edema, HTN, proteinuria, and/or hypoalbuminemia [43]. A possible mechanism of the renal effects is the inhibition of glomerular VEGFR signaling by TKI.

Bevacizumab is associated with a dose-dependent risk of proteinuria and HTN [44]. The effects of bevacizumab and other VEGF inhibitors are thought to be from delayed development of glomerular endotheliosis and slow rise of BP, similar to the pathophysiology of preeclampsia in pregnancy.

Management

The incidence of TKI-induced HTN may actually be a biomarker for the drug's efficacy in the treatment of cancer. In a meta-analysis of metastatic RCC patients receiving sunitinib, sunitinib-induced HTN was associated with improved overall survival and progression-free survival; however, there was a small but statistically significant increase in adverse renal events [45•]. Based on these findings, close monitoring and treatment of HTN is important to prevent serious adverse events that are known to occur with unmanaged HTN in patients on VSP inhibitors [46, 47]. Acceptable BP control would allow patients to receive the most effective dose of TKI, remain on therapy for the duration of their oncologic treatment, and improve their overall survivorship [48].

The National Cancer Institute (NCI) recommends identification of those patients at highest risk for TKI-induced HTN with a pre-treatment CVD health assessment [7]. This includes a detailed history and physical where concomitant clinical risk factors and subclinical organ damage are identified. Characteristics such as age, smoking and second-hand smoke exposure history, sleep apnea, psychological stress, family history of HTN, chronic kidney disease, unhealthy diet, obesity, diabetes, and hyperlipidemia will help identify those patients at greater risk of developing HTN during course of therapy. Additional measurements of left ventricular hypertrophy on 2D echocardiogram, carotid wall thickness, electrocardiogram, serum creatinine, 24-h urine protein, fasting blood glucose, and lipid panel may help characterize severity of comorbidities prior to initiation of therapy and help guide medical management [1, 7].

Patients with one or more clinical CVD risk factors are considered high risk and, per NCI clinical trial protocols, should have weekly BP monitoring with first cycle of VSP inhibitor and then every 2–3 weeks for duration of treatment [7]. This corresponds with clinical trials that suggest onset of HTN occurs after first or second doses of VSP inhibitors [49]. During this time, BP assessment should be performed in office. If elevated, repeat assessment and elevation is required during a second visit for diagnosis of TKI-induced HTN. For patients with white coat HTN (SBP \geq 120 mmHg and \leq 160 mmHg), home BP recordings can be used to support or negate the diagnosis. Reversible causes of HTN, such as poor pain control and high sodium diet, should be ruled out and appropriately managed [7].

Because the primary goal in the oncology setting is to prevent HTN related adverse events, BP should be reduced to a goal of < 140/90 mmHg (130/80 mmHg in chronic kidney disease and diabetic patients), as recommended by the Cardiovascular Toxicities Panel of the NCI in 2010 [7]. Stringent BP control is not recommended and may lead to less-effective VSP inhibitor dosing and/or polypharmacy [49]. If BP goal is not achieved, VSP inhibitor therapy can still be initiated given there is improvement in BP and values are below those associated with adverse cardiac events [7]. Finally, once TKI therapy is completed, patients need adjustments in their anti-hypertensive regimens to prevent hypotension.

Pharmacotherapy

Agents available for treatment of TKI-induced HTN are the same as for treatment of essential HTN. The proposed mechanism of action of TKI-induced HTN as well as clinical experience guide specific drug selection and are reviewed below. A summary of commonly used anti-hypertensive drugs, as discussed below, are provided in Table 3.

It has been suggested that angiotensin system inhibitors (ASIs) (angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs)) may be the preferred anti-hypertensive agent in the management of TKI-induced HTN, due to their beneficial effects on plasminogen activator inhibitor-1 expression and proteinuria [35]. ASIs also increase the release of endothelial NO, the production of which is reduced by treatment with VSP inhibition as discussed above [7]. Blood pressure lowering is relatively rapid producing changes within 24–48 h. Most importantly, ASIs have been shown to improve overall survival and progression-free survival. Izzedine et al. conducted a retrospective study on 213 patients receiving sunitinib and/or ASIs for metastatic RCC and associated pre- and therapy-related HTN. Through multivariate COX analysis, they found that patients who received the drug before or within one cycle of sunitinib, had a significant increase in overall survival (median, 26.4 months; $p < 0.0001$), and in progression-free survival (median, 8.1 months; $p < 0.0001$) than patients who were not on ASIs [5]. The authors hypothesize whether these findings are due to interactions between the ASI pathway and cancer proliferation or if HTN serves as a biomarker of drug efficacy. Similar findings were observed in a large meta-analysis of 4736 patients with metastatic RCC who underwent therapy with a small-molecule TKI. McKay et al. showed that ASIs were associated with improved survival ([50•]). It is our practice to use this drug as first-line therapy, given the patient does not have stage 4 or 5 chronic kidney disease.

Due to their primary vasodilatory mechanism, dihydropyridine calcium channel blockers are attractive agents in the management of TKI-induced HTN particularly

Table 3 Commonly used medications for the treatment of hypertension [Adapted from [1]]

Class	Drug	Usual dose, range (mg/day)	Daily frequency	Comments
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril	10–40	1 or 2	<ul style="list-style-type: none"> • Contraindicated in combination with ARB • Risk of hyperkalemia in patients with CKD, or simultaneous use of K⁺ supplements or K⁺-sparing drugs • Risk of acute kidney injury in patients with bilateral renal artery stenosis • Contraindicated if history of angioedema with ACE inhibitors • Teratogenic in pregnancy
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Lisinopril	10–40	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–10	1 or 2	
Angiotensin receptor blocker (ARB)	Candesartan	8–32	1	<ul style="list-style-type: none"> • Contraindicated in combination with ACE inhibitors • Risk of hyperkalemia in patients with CKD or with simultaneous use of K⁺ supplements or K⁺-sparing drugs. • Risk of acute kidney injury in patients with bilateral renal artery stenosis. • Contraindicated if history of angioedema with ARBs. If history of angioedema with an ACE inhibitor, or to initiate an ARB beginning 6 weeks after discontinuation of ACE inhibitor. • Teratogenic in pregnancy
	Irbesartan	150–300	1	
	Losartan	25–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
Calcium channel blocker (CCB)—dihydropyridines	Amlodipine	2.5–10	1	<ul style="list-style-type: none"> • Avoid in patients with HFrEF. • Dose-related pedal edema (women > men)
	Felodipine	5–10	1	
	Nicardipine SR	5–20	1	
	Nifedipine LA	60–120	1	
CCB—non-dihydropyridines	Diltiazem SR	180–360	2	<ul style="list-style-type: none"> • Avoid concomitant use of beta-blockers due to risk of bradycardia and heart block. • Avoid in patients with HFrEF. • Drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor).
	Diltiazem ER	120–480	1	
	Verapamil IR	40–80	3	
	Verapamil SR	120–480	1 or 2	
	Verapamil- delayed onset ER (various forms)	100–480	1 (in the evening)	
Diuretics—thiazide	Chlorthalidone	12.5–25	1	<ul style="list-style-type: none"> • Chlorthalidone is preferred due to prolonged half-life. • Monitor for hyponatremia and hypokalemia, uric acid, and calcium levels. • Caution in patients with gout unless patient is also on uric acid-lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Metolazone	2.5–10	1	
Diuretic—aldosterone antagonists	Eplerenone	50–100	1 or 2	<ul style="list-style-type: none"> • Preferred agents in primary aldosteronism and resistant hypertension. • Spironolactone is associated with gynecomastia and impotence compared to eplerenone. • Common add-on therapy in resistant hypertension. • Avoid use with K⁺ supplements, other K⁺-sparing diuretics, or chronic kidney disease. • Eplerenone often requires twice-daily dosing for adequate BP lowering.
	Spironolactone	25–100	1	
Beta-blockers (BB)—cardioselective	Atenolol	25–100	1 or 2	<ul style="list-style-type: none"> • Not recommended as first-line agents unless coexisting IHD or HF. • Preferred beta-blockers in patients with bronchospastic airway disease. • Bisoprolol and metoprolol succinate are preferred in HFrEF. • Avoid abrupt cessation.
	Bisoprolol	2.5–10	1	
	Metoprolol tartrate	25–400	2	
	Metoprolol succinate	25–200	1	
BB—cardioselective and vasodilatory	Nebivolol	5–40	1	<ul style="list-style-type: none"> • Nebivolol induces nitric oxide-induced vasodilation. • Avoid abrupt cessation.
BB—combined alpha- and beta-receptor	Carvedilol	6.25–50	2	<ul style="list-style-type: none"> • Carvedilol preferred in HFrEF. • Avoid abrupt cessation.
	Labetalol	200–800	2	
BB—non-cardioselective	Nadolol	40–120	1	<ul style="list-style-type: none"> • Avoid in patients with reactive airway disease. • Avoid abrupt cessation.
	Propranolol IR	160–480	2	
	Propranolol LA	80–320	1	

Table 3 (continued)

Class	Drug	Usual dose, range (mg/day)	Daily frequency	Comments
Direct vasodilators	Hydralazine	50–200	2 or 3	<ul style="list-style-type: none"> • Sodium and water retention and reflex tachycardia can occur; use with a diuretics and/or beta-blocker. • Hydralazine can cause drug-induced lupus-like syndrome at high doses. • Minoxidil is associated with hirsutism and requires a loop diuretic. • Minoxidil can induce pericardial effusion.
	Minoxidil	5–100	1–3	
Nitrates	Isosorbide dinitrate	10–40	2 or 3	
	Isosorbide mononitrate IR	20–40	2	
	Isosorbide mononitrate ER	30–120	1	

in patients with severe HTN requiring multi-drug therapy. In the study reported by Mir et al., amlodipine 5 mg daily resulted in control of HTN in 80–90% of patients who developed de novo or worsening HTN while on bevacizumab for metastatic non-small cell lung cancer, colorectal cancer, and ovarian cancer [51]. Unfortunately, the use of nifedipine had come into question due to early studies showing nifedipine-induced VEGF-secretion [52]. However, rat models evaluating cediranib in colorectal cancer showed nifedipine was more effective than captopril in reducing diastolic BP without affecting the anti-tumor activity [53]. Due to anti-hypertensive effectiveness with dihydropyridine CCBs, a trial on prophylactic use of CCBs in patients receiving cediranib was conducted and found to be effective for the management of HTN; this has influenced all ongoing cediranib trials to include similar protocols [54].

Non-dihydropyridine CCBs such as verapamil and diltiazem are CYP3A4 inhibitors, which may lead to drug-drug interactions with chemotherapeutic agents metabolized by the cytochrome P450 pathway such as sunitinib and sorafenib. Bevacizumab is metabolized via a different pathway and therefore these drugs may be considered [55].

Nitrate therapy might be considered attractive given the effect of VSP on nitric oxide production in the mechanism of inducing HTN. A 3-patient series of TKI-induced resistant HTN showed that short-acting isosorbide dinitrate effectively controlled blood pressure when three other medications would not, including ASI and dihydropyridine [56]. There is, however, data that suggests nitrate therapy may compromise anti-angiogenic benefits since VSP-induced angiogenesis is dependent on downstream NO production [57].

Although thiazide diuretics are standard therapy in the treatment of essential hypertension, they may be less effective than calcium channel blockers or ASIs in treating VSP-induced hypertension [49]. However, if there is limited success with many of the agents discussed above, thiazide diuretics, such as chlorthalidone and hydrochlorothiazide, should be considered.

There is little clinical data looking at beta-blocker therapy in VSP inhibition-induced HTN. Mouse models suggest nebivolol stimulates NO production, which induces an endothelial dependent vasodilation and reduction in blood pressure [58]. Additional mouse models have been able to demonstrate an anti-tumor effect with beta-blocker use [59]. Future studies should look at beta-blockers in the VSP inhibitor-induced HTN population for its effectiveness as an anti-hypertensive and its anti-cancer properties. It is still an ideal agent to use in patients with known coronary artery disease and/or chest pain.

Based on the elevated circulating levels of ET-1 observed in clinical and experimental studies with TKI-induced HTN, endothelin receptor blockade may be considered to mitigate the rise in BP [60]. The side effects of salt and water retention and peripheral edema likely will limit the applicability of these drugs to the treatment of HTN. Additionally, endothelin receptor antagonists are currently indicated only for the treatment of pulmonary hypertension. One final consideration for management of TKI-induced HTN is discontinuation or decrease in dose of the offending TKI. This is usually reserved for refractory HTN, hypertensive crises, or severe HTN (e.g., proteinuria and acute kidney injury). After discontinuation, it is recommended to use a different VSP inhibitor when re-challenging the patient [55].

Conclusion

In summary, aberrant RTK function is implicated in a multitude of cancers making it an ideal therapeutic target. TKIs target many receptors to varying degrees, but it is a specific drug's affinity for the VEGFR that drives its association with HTN. The incidence of some degree of clinically significant HTN in clinical trials ranges from 5 to 80%; however, the "real life" incidence is likely higher given many trials may exclude patients with difficult-to-control HTN. The pathophysiologic mechanism driving the HTN is likely complex and multifactorial. A decrease in endothelial dependent

production in nitric oxide, an increase in circulating ET-1, and a decrease in capillary density all likely play a role in increased peripheral vasoconstriction, which then results in HTN. Based on the mechanism of action, nitrate therapies and ET-1 antagonists seem like likely therapeutic agents; however, only case reports exist demonstrating their benefit. The most robust data exists for ASIs and CCBs, which allow for improved endothelial function and result in vasodilation and drop in BP. It is the practice of this writing group to use them as first-line agents. ASIs in particular are nephro-protective and have been associated with improved overall survival. Non-dihydropyridine CCBs are avoided due to potential drug-drug interactions. Use of anti-hypertensives is theorized to allow patients to tolerate higher effective doses of their TKIs, prevent disruption of therapy, and prevent serious adverse events from TKIs. Prospective randomized clinical trials are needed to test these theories in the future, which would provide valuable data to allow the most effective, life-saving, management in this patient population.

Compliance with Ethical Standards

Conflict of Interest Megha Agarwal, Nidhi Thareja, Melody Benjamin, Andre Akhondi, and George D. Mitchell declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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