

Positive Quality Intervention: VEGF Inhibitor-Induced Hypertension

Description: This document will address effective practices for the management of vascular endothelial growth factor inhibitors (VEGFIs) induced hypertension (HTN).

Background: VEGFIs are a growing therapeutic class that targets tumor angiogenesis to prevent metastasis and tumor progression.¹ It has wide applicability in a variety of cancers including, brain, breast, colon, kidney, liver, lung, and rectal.² Due to its mechanism of action, the VEGFIs are known to cause HTN. The activation of VEGF exerts a multifaceted effect on the vasculature, including enhanced endothelial permeability, vasodilation through the production of nitric oxide, and angiogenesis in physiologic processes like wound repair. VEGFIs clinically targets this process, often leading to a dose-dependent blood pressure (BP) increase as a side effect.³ A similar effect has also been observed in tyrosine kinase inhibitors with VEGFI activity.² Incidence of VEGFI-related HTN varies from 30-80%, depending on the medication.^{1,3,4} Uncontrolled HTN and hypertensive crisis can necessitate dose reductions or therapy discontinuation, worsening patient outcomes.³ Strict blood pressure control and monitoring is required as BP can rise rapidly (within the first 24 hours of therapy initiation).¹

PQI Process: Before initiating VEGFIs, patients should be evaluated for:

- Cardiovascular risk factors⁵⁻⁷
 - History of cardiovascular disease (CVD), diabetes, prior documentation of left ventricular hypertrophy, age, smoking, family history of early CVD
 - Physical examination: controlled blood pressure, waist circumference
 - Labs: serum creatinine, fasting blood glucose, lipid profile, urine albumin
 - Screening for end-organ damage
 - Socioeconomic barriers (health literacy, access to proper fitting cuff, ability to perform self-monitoring)
- Medications/drugs that may worsen HTN
 - Prescription Medications: NSAIDs, adrenal steroid hormones, erythropoietin, hormonal contraceptives, sympathomimetics
 - OTC: oxymetazoline, pseudoephedrine, phenylephrine, NSAIDs
 - Supplements: saw palmetto, St John's wort, ephedra, DHEA, bitter orange, green coffee extract, kava
- During Treatment

Monitoring BP	Weekly clinic visits or documentation with a certified cuff device for at-home use in the first cycle; after that, check BP every 2-3 weeks. ⁸ If antihypertensives are initiated, monitor for efficacy and adverse effects (see Table 2)
Initiate Antihypertensives	Initiate antihypertensives if BP >140/90 (>130/80 if high risk), or if DBP increases by >20 mmHg from baseline. ⁶ HTN management should be guideline-directed, taking into account comorbidities and potential drug interactions (Table 2) ^{6,9}
Hold or D/C VEGFI	Refer to the package insert for drug-specific recommendations (Table 1), but in general, hold/discontinue (D/C)VEGFI if HTN is uncontrolled or if patient has malignant HTN or hypertensive crisis

IMPORTANT NOTICE: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual's sole responsibility to seek guidance from a qualified healthcare professional. *Updated 5.28.24*

Agent	Package Insert Recommendations (HTN and proteinuria)
Bevacizumab	Routine blood pressure monitoring every 2-3 weeks, hold if SBP>160 mmHg or DBP>100 mmHg, and watch for signs of proteinuria ¹⁰
Ramucirumab	Routine blood pressure monitoring every 2 weeks or more as indicated ¹¹
Ziv-aflibercept	Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend if hypertension is not controlled and permanently reduce dose to 2 mg/kg for subsequent cycles. Withhold for more than 2 g of proteinuria in 24 hrs and D/C for nephrotic syndrome or thrombotic microangiopathy ¹²
Sorafenib	Monitor blood pressure weekly for the first 6 weeks, EKG and electrolytes for those at high risk of arrhythmias. If HTN: hold until symptoms resolve and DBP<90 mm Hg, then resume at reduced dose by 1 dose level. If needed, reduce another dose level. ¹³
Sunitinib	Monitor blood pressure and suspend administration in severe hypertension until controlled, monitor for proteinuria, signs of CHF ¹⁴
Pazopanib	Blood pressure should be well-controlled prior to initiating and D/C if hypertension is severe and persistent despite anti-hypertensive therapy, monitor urine protein and D/C for Grade 4 proteinuria, EKG for risk of QTc prolongation ¹⁵
Axitinib	Monitor for hypertension and reduce dose or D/C in the case of persistent hypertension despite medications or in the case of hypertensive crisis, monitor for proteinuria before initiation and periodically throughout and reduce dose or temporarily D/C if moderate to severe ¹⁶
Regorafenib	Monitor blood pressure weekly for the first 6 weeks and then every cycle or more frequently if indicated and temporarily or permanently hold for severe or uncontrolled hypertension ¹⁷
Ponatinib	Monitor and manage blood pressure elevations, monitor for signs of CHF, monitor for fluid retention and interrupt, reduce, or D/C if present ¹⁸
Vandetanib	Hypertension should be monitored and drug should not be restarted if blood pressure cannot be controlled, monitor for signs of HF, EKG for risk of QTc prolongation ¹⁹
Cabozantinib	Routine blood pressure monitoring and withhold if hypertension is not adequately controlled with antihypertensive therapy and restart at a lower dose. D/C if hypertensive crisis or severe hypertension that cannot be controlled, monitor urine protein and D/C for nephrotic syndrome ²⁰
Lenvatinib	Check blood pressure at 1 week, then every 2 weeks for the first 2 months, then monthly. Withhold, dose-reduce, or D/C if hypertension is severe. Monitor for proteinuria prior to treatment and periodically. Withhold for more than 2 g of proteinuria in 24 hrs, and D/C for nephrotic syndrome ²¹

Patient-Centered Activities:

- Provide [Oral Chemotherapy/Intravenous Cancer Treatment Education](#) Sheets (Table 1 links)
- Record BP readings in a [journal](#); include contingency plan in case of emergency
- Lifestyle modifications: exercise, dietary approaches to stop hypertension (DASH), avoid alcohol, cigarettes, and caffeine
- Connect patients to stress-reduction [resources](#) as needed^{22, 23}

Class	Examples	Application	Caution/Contraindications
ACEs	Lisinopril, enalapril, quinapril, ramipril, fosinopril, benazepril, captopril	Pre-existing/high risk of left ventricular dysfunction	Coadministration of renally-cleared medications (cisplatin, pemetrexed, etc.) or in patients with hyperkalemia
ARBs	Valsartan, irbesartan, losartan, olmesartan, telmisartan, candesartan	Preferred first line in diabetes, proteinuria	Renovascular disease, peripheral vascular disease, renal impairment
β-blockers	Atenolol, bisoprolol, nadolol, propranolol (LA), metoprolol	Pre-existing/high risk of left ventricular dysfunction or history of MI, anxiety	Asthenia, malaise, fatigue, concomitant QTc-prolonging drugs Bradycardia/heart block, diabetes, asthma/COPD, decompensated CHF
CCB	Amlodipine, felodipine, nifedipine LA	Preferred in CKD on alkylating agents Favorable for isolated systolic HTN	Lower extremity edema Avoid non-dihydropyridine CCBs (diltiazem and verapamil) with CYP3A4-metabolized chemotherapy (ex. sunitinib and sorafenib)
Thiazide diuretics	Chlorthalidone HCTZ (± triamterene)	Patient on glucocorticoids (+ mineralocorticoid antagonists) Favorable for isolated systolic HTN	Risk of hypercalcemia or hypokalemia Concomitant QTc-prolonging drugs Sulfa allergy Acute kidney injury due to CINV dehydration

References:

1. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension Induced by VEGF Signaling Pathway Inhibition: Mechanisms and Potential Use as a Biomarker. *Semin Nephrol.* 2010;30(6):591-601. doi:10.1016/j.semnephrol.2010.09.007.

2. Kidoguchi S, Sugano N, Tokudome G, et al. New Concept of Onco-Hypertension and Future Perspectives. *Hypertension*. 2021;77(1):16-27. doi:10.1161/HYPERTENSIONAHA.120.16044.
3. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. *Semin Nephrol*. 2010;30(6):591-601. doi:10.1016/j.semnephrol.2010.09.007.
4. Touyz RM, Lang NN. Hypertension and Antiangiogenesis. *JACC CardioOncology*. 2019;1(1):37-40. doi:10.1016/j.jacc.2019.08.010.
5. Donald C. Moore, PharmD, BCPS, BCOP; Margaret M. Kientzel, PharmD; and Adenike Fasan, BPharm. Hypertension Caused by VEGF-Signaling Pathway Inhibitors. *Journal of Hematology Oncology Pharmacy*. 2017;7(4):141-143.
6. de Jesus-Gonzalez N, Robinson E, Moslehi J, Humphreys BD. Management of Antiangiogenic Therapy-Induced Hypertension. *Hypertension*. 2012;60(3):607-615. doi:10.1161/HYPERTENSIONAHA.112.196774.
7. Cameron AC, Touyz RM, Lang NN. Vascular Complications of Cancer Chemotherapy. *Can J Cardiol*. 2016;32(7):852-862. doi:10.1016/j.cjca.2015.12.023.
8. Abi Aad S, Pierce M, Barmaimon G, Farhat FS, Benjo A, Mouhayar E. Hypertension induced by chemotherapeutic and immunosuppressive agents: a new challenge. *Crit Rev Oncol Hematol*. 2015;93(1):28-35. doi:10.1016/j.critrevonc.2014.08.004.
9. US Department of Health & Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Published online November 27, 2017. Accessed February 7, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
10. [Avastin. Prescribing Information. Genentech.](#)
11. [Cycrima. Prescribing Information. Eli Lilly.](#)
12. [Zaltrap. Prescribing Information. Sanofi-Aventis.](#)
13. [Sorafenib. Prescribing Information. Bayer.](#)
14. [Sutent. Prescribing Information. Pfizer.](#)
15. [Votrient \(pazopanib\). Prescribing Information. GlaxoSmithKline.](#)
16. [Inlyta. Prescribing Information. Pfizer Labs.](#)
17. [Stivarga. Prescribing Information. Bayer Healthcare Pharmaceuticals Inc.](#)
18. [Iclusig \(ponatinib\) tablets. Prescribing Information. Ariad Pharmaceuticals.](#)
19. [Vandetanib. Prescribing Information. AstraZeneca Pharmaceuticals LP.](#)
20. [Cabometyx. Prescribing Information. Exelixis Inc.](#)
21. [Lenvima. Prescribing Information. Eisai.](#)
22. Ojike N, Sowers JR, Seixas A, et al. Psychological Distress and Hypertension: Results from the National Health Interview Survey for 2004-2013. *Cardiorenal Med*. 2016;6(3):198-208. doi:10.1159/000443933.
23. Psychological Stress and Cancer - National Cancer Institute. Published December 17, 2012. Accessed February 9, 2022. <https://www.cancer.gov/about-cancer/coping/feelings/stress-fact-sheet>.
24. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010;102(9):596-604. doi:10.1093/jnci/djq091.