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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 rectum.[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 are therefore required.

PQI Process: Before initiating VEGFIs, patients should be evaluated for:
Cardiovascular risk factors:[5]

- History of cardiovascular disease (CVD), diabetes, prior documentation of left ventricular hypertrophy, age, smoking, family history of early CVD[6]
- Physical examination: blood pressure, waist circumference[6]
- Labs: serum creatinine, fasting blood glucose, lipid profile, urine albumin[6]
- Screening for end-organ damage[7]
- 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.

Drug-Specific Recommendations

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). If appropriate, avoid medications which increase risk of HTN and encourage avoidance of alcohol, cigarettes, and caffeine.
- Psychological distress can lead to BP increases.[22] Connect patients to stress-reduction resources, or consider pharmacologic therapy for stress if necessary.[23]

Antihypertensives [6,24]

Class	Examples	Application	Caution/Contraindications
ACEs	*Lisinopril, enalapril, quinapril, ramipril, fosinopril, benazepril, captopril*	Pre-existing/high risk of left ventricular dysfunction Preferred first line in diabetes, proteinuria	Coadministration of renally-cleared medications (cisplatin, pemetrexed, etc.) or in patients with hyperkalemia Renovascular disease, peripheral vascular disease, renal impairment
ARBs	*Valsartan, irbesartan, losartan, olmesartan, telmisartan, candesartan*		
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)	Risk of hypercalcemia or hypokalemia Concomitant QT_C-prolonging drugs

		Favorable for isolated systolic HTN	Sulfa allergy

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