Management of VEGF TKI-Induced HTN

AMERICAN COLLEGE of CARDIOLOGY

PROBLEM

- Anti-vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) (i.e., axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib) are associated with cardiotoxicity, leading to:
  - Hypertension (HTN) (up to 80%)
  - Left ventricular systolic dysfunction (3-15%)
  - Symptomatic heart failure (HF) (1-10%)
  - QTc prolongation (4.4%)
  - Myocardial ischemia (MI) (1.4-1.7%)
  - Thromboembolism (1-3%)
- HTN attributed to VEGF TKI is at least partially related to inhibition of nitric oxide, decrease in capillary density, and increased production of vasoconstrictors.
- The highest incidence of HTN is in initial stages of therapy (within hours to days).

SOLUTION

- Initial evaluation
  - Baseline blood pressure (BP), left ventricular ejection fraction (LVEF), electrocardiogram, and assessment of cardiac risk factors (i.e., pre-existing cardiac disease, diabetes mellitus, hyperlipidemia)
- Monitoring
  - HTN: Frequent BP monitoring (including ambulatory home BP) and adjustment of anti-hypertensive therapies with VEGF TKI initiation, dosage adjustments and discontinuation.
- HF: LVEF assessment every 3-6 months, measurement of cardiac biomarkers at onset of new symptoms
- Treatment
  - HTN: As per treatment table
  - HF: Hold VEGF TKI when >10% drop in ejection fraction to a value below the lower limit of normal and initiate HF medications as per ACC guidelines

HTN Definition			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Systolic BP 120-139 mmHg or Diastolic BP 80-89 mmHg	Systolic BP 140-159 mmHg or Diastolic BP 90-99 mmHg and recurrent or persistent (≥24 hours) or Symptomatic increase by >20 mmHg (diastolic) or Symptomatic increase to >140/90 mmHg if previously normal	Systolic BP ≥160 mmHg or Diastolic BP ≥100 mmHg	Hypertensive crisis* (elevated BP with life-threatening consequences)
HTN Treatment			
Manage risk factors	• Evaluate for proteinuria. • If >1 g/dL, hematuria, or acute kidney injury, consult a nephrologist		
Assess for alternative causes of elevated BP	• Optimize or initiate anti-hypertensive agent. • Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and dihydropyridine calcium channel blockers are anti-hypertensive agents of choice. • If desired BP not achieved, add carvedilol or nebivolol, thiazide diuretic, or mineralocorticoid receptor antagonist. • **AVOID** diltiazem and verapamil due to CYP3A4 inhibition drug interaction.		
		Risk-benefit discussion between cardiologist and oncologist to **consider holding VEGF TKI if resistant to treatment with at least 3 anti-hypertensives**	Risk-benefit discussion between cardiologist and oncologist **to hold VEGF TKI until blood pressure is controlled** Consider VEGF TKI dose reduction

** Hypertensive crisis may require intravenous antihypertensive medications. Refer to HTN guidelines.*

BEST PRACTICES:

- **Establish cardio-oncology clinic in collaboration with oncology**
- **Rule out secondary causes of HTN**
- **Educate patients on appropriate home BP-monitoring technique**
- **Monitor for hypotension upon discontinuation of VEGF TKIs**

To download the infographic and see citations visit
ACC.org/Infographics

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