Malignant Hypertension in Patients Treated With Vascular Endothelial Growth Factor Inhibitors

Jara Caro, MD; Enrique Morales, MD, PhD; Eduardo Gutierrez, MD; Luis Miguel Ruilope, MD, PhD; Manuel Praga, MD, PhD

From the Nephrology Department, Hospital 12 de Octubre, Madrid, Spain

The development of drugs capable of modulating angiogenesis has created a significant improvement in the survival associated with metastatic tumors. This group of drugs includes anti-vascular endothelial growth factor (VEGF) monoclonal antibodies (bevacizumab), intracellular VEGF receptor inhibitors (sorafenib, sutinib, pazopanib), and the small VEGF inactivating molecules (VEGF trap).[1] The most frequent renal side effect involvement is arterial hypertension, proteinuria, and thrombotic microangiopathy (TMA).[1–4] However, there is little information available regarding the relationship between these drugs and the development of malignant hypertension (MHT).[2,3] Here we present two patients with clear cell renal carcinoma treated with VEGF inhibitors who developed MHT.

The first case was a 46-year-old woman diagnosed with clear cell renal carcinoma treated with a left radical nephrectomy. Five months after surgery she began treatment with pazopanib because of the appearance of metastasis. Three weeks after starting treatment she presented to the emergency department with blurry vision and headache. Physical examination revealed a blood pressure (BP) of 220/110 mm Hg and retinal examination revealed multiple cotton-wool spots, retinal hemorrhages, and swelling of the optic disk (grade IV hypertensive retinopathy). Results of laboratory tests revealed a serum creatinine (SCr) level of 1.3 mg/dL and proteinuria of 1.5 g/24 hours with normal sediment, and hemogram results showed a thrombopenia of 99,000 platelets, with a hemoglobin level of 12 g/dL. To control BP the following were used: a β-blocker, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and α-blockers, which achieved a BP of 120/60 mm Hg. Pazopanib was suspended until BP was controlled and re-introduced without complications. Renal function improved with creatinine of 0.9 mg/dL upon hospital discharge and negative proteinuria in the 24-hour analysis.

The second case was a 53-year-old woman with a history of hypertension and clear cell renal carcinoma with pleural metastases treated with a left radical nephrectomy. After surgery she began treatment with sunitinib. Two months later the patient was admitted to the nephrology department for a hypertensive crisis and acute renal failure. Upon arrival, her BP was 180/100 mm Hg, she revealed grade III hypertensive retinopathy, and hemogram showed a hemoglobin level of 8.4 g/dL, 53,000 platelets, and schistocytes in the peripheral blood. The biochemical studies showed lactate dehydrogenase 798 U/L, SCr 4.3 mg/dL, and proteinuria 5 to 6 g/24 hours. The patient was prescribed valsartan, enalapril, and amlodipine to control BP. With the clinical diagnosis of MHT and TMA, and in view of the seriousness of acute renal failure, she was taken off the drug and started on hemodialysis and plasmapheresis (5 sessions) without satisfactory results, continuing a program of chronic renal replacement treatment.

VEFG is a powerful promoter of angiogenesis and is produced by different tumors. In the glomerulus, under normal conditions, VEFG is produced in the epithelial cells, diffuses across the basal membrane, and arrives at the glomerular capillary lumen where the receptors are found. The ligand-receptor union allows for the fenestration of the endothelium, maintains the capillary integrity, intervenes in the remodeling of the mesangial matrix, and favors vasodilatation by the nitric oxide pathway.[4–6] There have been reports of the occurrence of hypertension (higher than 30%–40%) with different anti-VEFG, but none of them mentions the development of MHT.[7–10] The possible pathogenic pathways to explain this particular propensity of patients who received VEFG inhibitors to MHT could rely on the already known higher incidence of TMA among these patients. BP control can be achieved by using the majority of available drugs. ACE inhibitors and the angiotensin II receptor blockers are useful because of their antiproteinuric effect.[11] Derivatives of nitrate and dihydropyridine calcium antagonists are advantageous because of the increase in concentration of nitric oxide. Nondihydropyridine calcium antagonists should be avoided because they increase the production of VEGF and stimulate angiogenesis.

To summarize, the increase in the use of VEFG inhibitors conditions the necessity to pay special attention to the occurrence of hypertension, proteinuria, or renal failure. It is necessary to monitor proteinuria and perform a funduscopic examination in all patients who develop hypertension or whose hytertension worsens.

Address for correspondence: Enrique Morales, MD, PhD, Nephrology Department, Hospital 12 de Octubre, Madrid, Spain
E-mail: emoralesr@senefro.org

Manuscript received: October 9, 2012; **revised:** October 20, 2012; **accepted:** October 27, 2012
DOI: 10.1111/jch.12052

Disclosure: None.

References

1. Gurevich F, Perazella MA. Renal effects of anti-angiogenesis therapy: update for the internist. *Am J Med*. 2009;122:322–328.
2. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis*. 2007;49:186–193.
3. Müller-Deile J, Broker V, Grünwald V, et al. Renal side effects of VEGF-blocking therapy. *NDT Plus*. 2010;3:172–175.
4. Kelly RJ, Billemont B, Rixe O. Renal toxicity of targeted therapies. *Target Oncol*. 2009;4:121–133.
5. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF Inhibition and renal thrombotic microangiopathy. *N Engl J Med*. 2008;358:1129–1136.
6. Izzedine H, Ederhy S, Goldwasser F, et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol*. 2009;20:807–815.
7. Izzedine H, Rixe O, Billenout B, et al. Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. *Am J Kidney Dis*. 2007;50:203–218.
8. Patel TV, Morgan JA, Demetri GD, et al. A preclampsia like syndrome caracterized by reversible hypertension and proteinuria induced by the multitargeted kinase inhibitors sunitinib and sorafenib. *J Natl Cancer Inst*. 2008;100:282–284.
9. Veronese ML, Mosenkis A, Flaherty KT, et al. Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol*. 2006;24:1363–1369.
10. Robinson ES, Matulonis UA, Ivy P, et al. Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clin J Am Soc Nephrol*. 2010;5:477–483.
11. González R, Morales E, Segura J, et al. Long-term renal survival in malignant hypertension. *Nephrol Dial Transplant*. 2010;25:3266–3272.