VEGF Pathway Inhibitors–Induced Hypertension: Next Step in Therapy

To the Editor:

Li and colleagues[1] presented a systematic review and meta-analysis of the incidence and risk of hypertension conferred by sorafenib based on 13,555 patients enrolled in double-blind randomized studies (7013 patients), single-arm phase 2 studies (2881 patients), and expanded-access programs (3661 patients).

I would like to provide some comments regarding hypertension induced by inhibitors of angiogenesis.

Angiogenesis is critical to tumor growth as well as to metastases. This process is tightly regulated by proangiogenic and antiangiogenic growth factors and their receptors. Some of these factors are highly specific for the endothelium (eg, vascular endothelial growth factor [VEGF]), while others have a wide range of activities in different cells (eg, matrix metalloproteinases). Dysregulation of the VEGF-signaling pathway was suggested as a key mediator of tumor neoangiogenesis.[2] Consequently, a variety of drugs that target VEGF or its receptors have been developed for the treatment of different tumor types. Increased use of VEGF pathway inhibitors (VPIs) lead to their cardiovascular side effects, most notably hypertension and heart failure but also arterial and venous thrombotic events.[3] Hypertension is the most common adverse effect of the inhibitors of VEGF pathway–based therapy (VPI therapy) in cancer patients. In the combined treatment of bevacizumab and sunitinib in patients with advanced solid tumors or renal cell carcinoma, the incidence of hypertension was 92%.[4] The incidence of high-grade hypertension in patients receiving bevacizumab ranged between 2.4% and 14.8%.[5,6] High-grade hypertension is associated with a significant increase in morbidity and may subsequently result in dose reduction or discontinuation of VPI therapy. Although the mechanism underlying the development of hypertension induced by ngiogenesis inhibition still remains to be elucidated, decreased nitric oxide (NO) bioavailability is thought to be a critical factor. Kruzliak and colleagues[3,5] described the existence of two major pathophysiological mechanisms resulting in hypertension induced by VPI: (1) direct inhibition of NO production with reduced vasodilatation and increased vasoconstriction; and (2) NO deficiency–mediated increase in vascular medial cells proliferation, leading to the fixation of hypertension. Considering these two mechanisms, they suggest that administration of NO donors in VPI-treated patients will prevent the occurrence of hypertension and its associated complications.[2,6] Administration of NO donors before chemotherapy with angiogenesis inhibitors and/or during chemotherapy could reduce the incidence and severity of this type of hypertension. This new therapeutic approach is based only on case reports and case-control studies and future prospective studies are needed to verify it.

Acknowledgment: This work was elaborated within the grant of European Regional Development Fund—Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123).

Disclosures: The author declares no conflict of interest.

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doi: 10.1111/jch.12348