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## Rapid Development of Hypertension by Sorafenib: Toxicity or Target?

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### Summary

Blood pressure (BP) elevation is likely a pharmacodynamic marker of VEGF signaling pathway (VSP) inhibition and could be useful for optimizing safe and effective VSP inhibitor dosing. BP rises on the first day of treatment, facilitating design and interpretation of future trials aiming to correlate BP changes with clinical outcomes.

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Inhibition of angiogenesis by targeting the VEGF signaling pathway (VSP) has proven to be a successful anticancer strategy in a growing number of solid tumors. While VEGF signaling is critical for tumor angiogenesis, VEGF also plays important roles in homeostasis of normal vasculature. Early trials reported the development of hypertension (HTN) in a significant fraction of patients receiving anti-angiogenic therapies, particularly those targeting the VSP, but it is becoming clear that nearly all patients experience a rise in BP during therapy, even if they are not diagnosed with HTN. Despite a growing appreciation of this cardiovascular toxicity, our knowledge of the risk factors for and mechanisms underlying the development of HTN on VSP inhibitors, its optimal management and potential role as a cancer biomarker is far from complete.

In this issue of *Clinical Cancer Research*, Maitland and colleagues (1) report significant blood pressure (BP) elevation on the first day of sorafenib therapy. They detected a mean increase of 8.2 mmHg systolic and 6.5 mmHg diastolic within the first 24 hours of therapy. The close temporal relationship of BP elevation with sorafenib administration, coupled with the observation that all other VSP inhibitors are capable of inducing HTN, suggests that this toxicity is a consequence of the VEGF receptor inhibitory property of sorafenib. There was substantial variation in the BP response to sorafenib – from no increase to more than double the mean increase – and this variation was not explained by baseline BP, other clinical variables or plasma sorafenib levels. Among other things, this study highlights the use of ambulatory blood pressure monitoring (ABPM) as an investigational tool to more accurately measure BP variation in patients receiving VSP inhibitors than can be accomplished with routine office-based measurements. This ability to accurately measure BP response to VSP inhibitors suggests that incorporation of ABPM should facilitate the interpretation of future clinical studies aiming to correlate BP changes with laboratory results and clinical outcomes.

The acute rise in BP measured by Maitland and colleagues on the first day of therapy with sorafenib – even before steady-state drug levels are reached – suggests that a primary

mechanism by which VSP inhibitors elevate BP is through acute inhibition of endothelial-derived vasodilatory factors such as nitric oxide (NO) (Figure 1). Indeed, direct VEGF infusion induces rapid hypotension, through upregulation of endothelial NO synthase by PI3k/Akt and MAPK dependent pathways, resulting in enhanced NO production and subsequent vasodilation (2). The observation that the majority of BP rise was noted in the first week of sorafenib therapy and normalizes quickly when treatment is held is consistent with the notion that endothelial-dependent vasoconstriction accounts for most of the observed BP elevation. However, preclinical and human evidence indicates that endothelial cell (EC) apoptosis, leading to a reduction in capillary density and increased afterload, could also play an important role. Autocrine VEGF provides a survival signal to EC (3), and in murine renal cancer xenograft models, EC loss within tumors can be seen as early as day three of VSP inhibitor therapy (4). Furthermore, VSP inhibitors have been noted to induce EC apoptosis and capillary rarefaction in humans (5) and skin biopsies in patients receiving sorafenib suggest that necrosis at the basal layer occurs, indicating that EC apoptosis is not just restricted to tumor vasculature (6). Clearly additional data addressing the mechanism of HTN in humans treated with VSP inhibitors is needed.

Understanding the biologic mechanism that underlies VSP inhibitor-induced HTN may enable treatment of this toxicity that minimizes potential detrimental antitumor effects. For example, if NO inhibition plays a primary role in VSP inhibitor-induced HTN, then restoration of NO signaling through nitrates or phosphodiesterase inhibitors would be rational antihypertensive therapies to restore the vasodilatory balance in patients with this toxicity. However NO is critical for angiogenesis and the eNOS knockout mouse is characterized by deficient VEGF-induced angiogenesis (7). Such an antihypertensive strategy could theoretically blunt antitumor efficacy by promoting angiogenesis. On the other hand, treatment of HTN with angiotensin converting enzyme inhibitors, angiotensin receptor blockers or calcium channel blockers is effective and does not alter anti-tumor efficacy in a rodent model (8).

The results presented by Maitland and colleagues raise a number of interesting questions. What explains the wide variability in BP response to VSP inhibition? Some patients experienced a BP rise of more than 20 mmHg systolic and 15 mmHg diastolic, whereas others experienced almost no elevation in BP at all and this variability did not correlate with clinical variables or total plasma sorafenib levels. While the complexity of BP regulatory mechanisms in humans may account for a large part of this variability, the VEGF gene is highly polymorphic, and two recent studies identified a VEGF genotype (VEGF-634 C/C) that protects against development of VSP inhibitor-induced HTN (9,10). Because this polymorphism is located in the VEGF 5' untranslated region, it could alter VEGF transcription or translation with a net effect of rendering the patient less susceptible to VSP inhibition. How variants in VEGF genotype associate with risk of HTN on VSP inhibitor therapy may be relevant to our understanding of HTN in the general population and also could suggest new strategies for identifying patients at risk of cardiovascular toxicities from VSP inhibition.

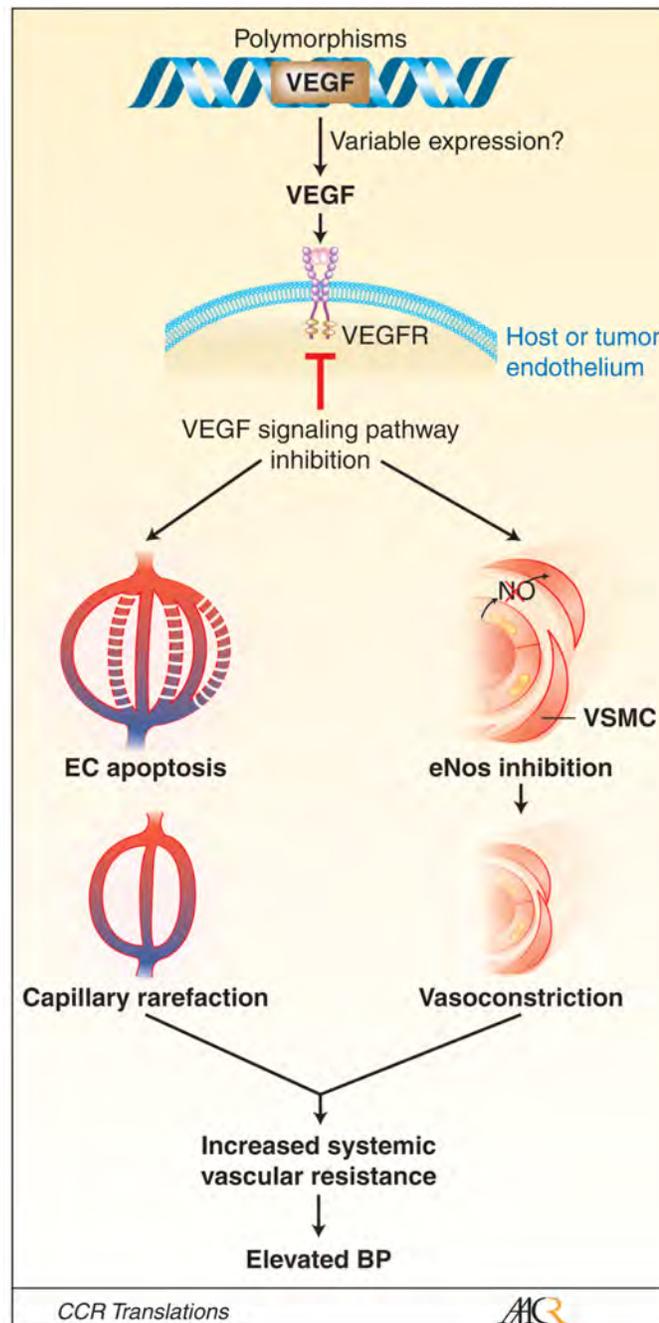
As indicated by the authors, another critical unresolved question is whether blood pressure elevation might predict outcome. Two studies examined this topic. Schneider *et al.* have reported improved overall survival associated with a specific VEGF genotype in metastatic breast cancer treated with combined paclitaxel and bevacizumab (9). Furthermore, in a pooled analysis, Rini and colleagues have reported a median overall survival of 30.1 months in patients with renal cell carcinoma treated with axitinib who developed a diastolic BP  $\geq$  90 mmHg on treatment, compared to a median overall survival of 9.7 months in patients with a diastolic BP  $<$  90 mmHg (11). A randomized trial, utilizing ABPM and dose escalation of axitinib in patients with renal carcinoma, will directly address this question (B. Rini, personal communication). Despite these interesting results, it is currently uncertain whether similar associations between HTN and clinical benefit will occur with sorafenib and other less potent VSP inhibitors or in

cancers other than renal cell or breast. Although much less well characterized, proteinuria is likely a mechanism-dependent toxicity of VSP inhibition and it is easily quantified. Fewer patients develop overt proteinuria on VSP inhibitors, and whether proteinuria might also serve as an anticancer efficacy biomarker requires investigation (12). Finally, the possible relationship between VSP-inhibitor induced HTN and ventricular dysfunction associated with use of these agents remains uncharacterized. While increased afterload might predispose to the development of reduced ejection fraction, not all VSP-inhibitors have been associated with this toxicity and non-VEGF-dependent signaling, such as inhibition of the PDGF and Raf signaling pathways, may be more important in the development of ventricular dysfunction on these agents.

Understanding exactly how VSP inhibitors induce cardiovascular toxicity will be critical for optimizing the safety, tolerability and perhaps efficacy of this very promising class of cancer therapeutics while providing clues on the biology of angiogenesis in humans, and the results presented by Maitland and colleagues are an important step toward this goal.

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**Figure 1. Mechanisms of VSP inhibitor-induced hypertension**

Polymorphisms in the VEGF gene might alter VEGF expression or signaling, thereby determining risk of HTN, anti-tumor efficacy or both during treatment with VSP inhibitors. VSP inhibition by sorafenib removes an endothelial cell survival signal, leading to apoptosis and capillary rarefaction. It also decreases eNOS expression and activity, inhibiting endothelial cell-derived NO, causing vascular smooth muscle cell constriction. Both capillary rarefaction and vasoconstriction lead to increased systemic vascular resistance and elevated BP.