Rapid Development of Hypertension by Sorafenib: Toxicity or Target?

Commentary on Maitland et al., p. 6250

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Blood pressure elevation is likely a pharmacodynamic marker of VEGF signaling pathway (VSP) inhibition and could be useful for optimizing safe and effective VSP inhibitor dosing. Blood pressure rises on the first day of treatment, facilitating design and interpretation of future trials aiming to correlate blood pressure changes with clinical outcomes. (Clin Cancer Res 2009;15(19):5947–9)

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. Although VEGF signaling is critical for tumor angiogenesis, VEGF also plays important roles in homeostasis of normal vasculature. Early trials reported the development of hypertension in a significant fraction of patients receiving antiangiogenic therapies, particularly those targeting the VSP, but it is becoming clear that nearly all patients experience a rise in blood pressure during therapy, even if they are not diagnosed with hypertension. Despite a growing appreciation of this cardiovascular toxicity, our knowledge of the risk factors for and the mechanisms underlying the development of hypertension on VSP inhibitors, its optimal management, and its 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 elevation on the first day of sorafenib therapy. They detected a mean increase of 8.2 mmHg systolic and 6.5 mmHg diastolic blood pressure within the first 24 h of therapy. The close temporal relationship of blood pressure elevation with sorafenib administration, coupled with the observation that all other VSP inhibitors are capable of inducing hypertension, suggests that this toxicity is a consequence of the VEGF receptor inhibitory property of sorafenib. There was substantial variation in the blood pressure response to sorafenib—from no increase to more than double the mean increase—and this variation was not explained by baseline blood pressure, 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 blood pressure variation in patients receiving VSP inhibitors than can be accomplished with routine office-based measurements. This ability to accurately measure blood pressure response to VSP inhibitors suggests that incorporation of ABPM should facilitate the interpretation of future clinical studies aiming to correlate blood pressure changes with laboratory results and clinical outcomes.

The acute rise in blood pressure 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 blood pressure is through acute inhibition of endothelial-derived vasodilatory factors such as nitric oxide (Fig. 1). Indeed, direct VEGF infusion induces rapid hypotension, through upregulation of endothelial nitric oxide synthase by PI3k/Akt- and MAPK-dependent pathways, resulting in enhanced nitric oxide production and subsequent vasodilation (2). The observation that the majority of blood pressure 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 blood pressure elevation. However, preclinical and human evidence indicates that endothelial cell apoptosis, leading to a reduction in capillary density and increased afterload, could also play an important role. Autocrine VEGF provides a survival signal to endothelial cell (3), and in murine renal cancer xenograft models, endothelial cell loss within tumors can be seen as early as day three of VSP inhibitor therapy (4). Furthermore, VSP inhibitors have been noted to induce endothelial cell apoptosis and capillary rarefaction in humans (5), and skin biopsies in patients receiving sorafenib suggest that necrosis at the basal layer occurs, indicating that endothelial cell apoptosis is not just restricted to tumor vasculature (6). Clearly, additional data addressing the mechanism of hypertension in humans treated with VSP inhibitors are needed.

Understanding the biologic mechanism that underlies VSP inhibitor-induced hypertension may enable treatment of this toxicity that minimizes potential detrimental antitumor effects. For example, if nitric oxide inhibition plays a primary role in VSP inhibitor-induced hypertension, then restoration of nitric oxide signaling through nitrates or phosphodiesterase
Inhibitors would be rational antihypertensive therapies to restore the vasodilatory balance in patients with this toxicity. However, nitric oxide 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. Treatment of hypertension with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers is effective and does not alter antitumor 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 blood pressure response to VSP inhibition? Some patients experienced a blood pressure rise of more than 20 mmHg systolic and 15 mmHg diastolic, whereas others experienced almost no elevation in blood pressure at all, and this variability did not correlate with clinical variables or total plasma sorafenib levels. Although the complexity of blood pressure 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 the development of VSP inhibitor-induced hypertension (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 associated with risk of hypertension on VSP inhibitor therapy may be relevant to our understanding of hypertension in the general population and also could suggest new strategies for identifying patients at risk for cardiovascular toxicities from VSP inhibition.

As indicated by the investigators, another critical unresolved question is whether blood pressure elevation might predict outcome. Two studies examined this topic. Schneider and colleagues 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 mo in patients with renal cell carcinoma treated with axitinib who developed a diastolic blood pressure ≥90 mmHg on treatment, compared to a median overall survival of 9.7 mo in patients with a diastolic blood pressure <90 mmHg (11). A randomized trial, utilizing ABPM and dose escalation of axitinib in patients with renal carcinoma, will directly address this question.6 Despite these interesting results, it is currently uncertain whether similar associations between hypertension 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 antitumor efficacy biomarker requires investigation (12). Finally, the possible relationship between VSP inhibitor-induced hypertension 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.

Fig. 1. Mechanisms of VSP inhibitor-induced hypertension. Polymorphisms in the VEGF gene might alter VEGF expression or signaling, thereby determining risk of hypertension, antitumor 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 nitric oxide, causing vascular smooth muscle cell constriction. Both capillary rarefaction and vasoconstriction lead to increased systemic vascular resistance and elevated blood pressure.

Disclosure of Potential Conflicts of Interest

B.D. Humphreys, commercial research grant, Genzyme; consultant, Surface Logix. M.B. Atkins, commercial research grant, Bayer, Onyx, Novartis; consultant, Bayer, Onyx, Pfizer, Genentech, Novartis, Wyeth.

6B. Rini, personal communication.
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