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 re-
store 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 an-
giogenesis (7). Such an antihypertensive strategy could theoreti-
cally 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 antitumorefficacy in a
rodent model (8).

The results presented by Maitland and colleagues raise a
number of interesting questions. What explains the wide vari-
ability in blood pressure response to VSP inhibition? Some pa-
tients experienced a blood pressure rise of more than 20 mmHg
systolic and 15 mmHg diastolic, whereas others experienced al-
most no elevation in blood pressure at all, and this variability
did not correlate with clinical variables or total plasma sorafe-
nib levels. Although the complexity of blood pressure regulato-
ry mechanisms in humans may account for a large part of this
variability, the VEGF gene is highly polymorphic, and two re-
cent studies identified a VEGF genotype (VEGF-634 C/C) that
protects against the development of VSP inhibitor-induced hy-
pertension (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 sus-
ceptible to VSP inhibition. How variants in VEGF genotype as-
soociate 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 col-
leagues 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. Despite these interesting results, it is currently un-
certain 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. Al-
though much less well characterized, proteinuria is likely a
mechanism-dependent toxicity of VSP inhibition, and it is eas-
ily quantified. Fewer patients develop overt proteinuria on VSP
inhibitors, and whether proteinuria might also serve as an anti-
cancer efficacy biomarker requires investigation (12). Finally, the
possible relationship between VSP inhibitor-induced hyper-
tension 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 devel-
opment of ventricular dysfunction on these agents.

Understanding exactly how VSP inhibitors induce cardio-
vascular 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 an-
giogenesis 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.

6B. Rini, personal communication.

Disclosure of Potential Conflicts of Interest

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Novartis; consultant, Bayer, Onyx, Pfizer, Genentech, Novartis, Wyeth.
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Rapid Development of Hypertension by Sorafenib: Toxicity or Target?

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