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VEGF kinase inhibitors: how do they cause hypertension?

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Bhargava P. VEGF kinase inhibitors: how do they cause hypertension?. Am J Physiol Regul Integr Comp Physiol 297: R1–R5, 2009. First published May 13, 2009; doi:10.1152/ajpregu.90502.2008.—Neoangiogenesis is a critical phenomenon enabling the growth and metastasis of tumors, and inhibitors of neoangiogenesis have been recently added to the armamentarium of anticancer therapies available for clinical use. Dysregulated signaling through the vascular endothelial growth factor (VEGF) pathway has been implicated as a key mediator of neoangiogenesis in tumors. Agents that block signaling through the VEGF pathway demonstrated tumor shrinkage in preclinical models and were therefore developed as anticancer therapies for use in humans. VEGF kinase inhibitors are being used in the treatment of a wide variety of cancers, and recent studies have shown that patients will likely require long-term treatment with these agents. Hypertension has emerged as a frequent side effect associated with agents that block signaling through the VEGF pathway. A thorough understanding of the mechanisms underlying hypertension is crucial to developing appropriate therapeutic strategies for treating hypertension associated with VEGF kinase inhibitors. Several recent studies have advanced our understanding of the pathophysiology of hypertension associated with VEGF kinase inhibitors and will be the subject of this review.

neoangiogenesis; side effects; cancer

NEOANGIOGENESIS IS A CRITICAL phenomenon enabling the growth and metastasis of tumors, and inhibitors of neoangiogenesis have been recently added to the armamentarium of anticancer therapies available for clinical use (13). Dysregulated signaling through the vascular endothelial growth factor (VEGF) pathway has been implicated as a key mediator of neoangiogenesis in tumors (19). Agents that block signaling through the VEGF pathway demonstrated tumor shrinkage in preclinical models and were therefore developed as anticancer therapies for human use. The first agent to demonstrate efficacy in human studies was bevacizumab, a monoclonal antibody that predominantly binds to the VEGF-A isoform (12, 24). However, the emerging complexity of the VEGF pathway, with multiple isoforms of VEGF (five naturally occurring isoforms derived from alternate splicing of the same gene) and three known VEGF receptors (VEGF-R1, -R2, and -R3) has led to the development of broad-spectrum VEGF inhibitors to achieve maximal inhibition of this pathway (44). One strategy to achieve broad-spectrum inhibition of the VEGF pathway involves targeting the intracellular tyrosine kinase domains of multiple VEGF inhibitors using small-molecule kinase inhibitors. These VEGF kinase inhibitors block signaling through all three VEGF receptors to varying degrees, and several agents in this class are being tested in the clinic.

Hypertension has emerged as a frequent side effect associated with inhibition of the VEGF pathway (45). Hypertension has been observed in 20% to 30% of patients treated with bevacizumab and 15% to 60% of patients treated with VEGF kinase inhibitors (51). While there is no clear association with age, patients with an underlying history of hypertension appear more prone to developing hypertension with VEGF kinase inhibitors. Several recent studies have advanced our understanding of the pathophysiology of hypertension associated with VEGF kinase inhibitors and will be the subject of this review.

Several studies have shown that VEGF can modulate vascular contractility and blood pressure in humans. A study conducted by Ku et al. (26) demonstrated that VEGF induces nitric oxide (NO)-dependent relaxation in coronary arteries, providing the initial clues to the association between VEGF and blood pressure regulation. In a study by Hood and colleagues (22), it was demonstrated that VEGF upregulates the endothelial nitric oxide synthase (eNOS) enzyme leading to upregulation of NO production in HUVEC in vitro. Subsequent studies showed that VEGF induction of eNOS is mediated by PI3K/Akt and MAPK pathways (15) and that VEGF plays an important role in maintaining baseline vascular tone by regulation of NO synthesis (23). The presence of another pathway involved in mediating the vasoactive effects of VEGF through prostacyclin (PGI2) release in HUVEC was demonstrated by Wheeler-Jones and colleagues (53). Subsequently, He and colleagues (18) showed that VEGF binding to flk-1/KDR (VEGF-R2) leads to activation of c-Src and downstream production of prostacyclin. In a clinical trial using VEGF to treat ischemia, a rapid decline (8–12 mmHg) in mean arterial pressure was observed in patients receiving an intravenous infusion of recombinant human VEGF165 (7). These data suggest that inhibition of signaling through the VEGF pathway would lead to a decrease in NO and prostacyclin production, resulting in an increase in vascular resistance and blood pressure, although direct evidence to validate this hypothesis is lacking. Preclinical studies to establish a direct link between VEGF and hypertension have been limited by a lack of VEGF-deficient mouse models, since the loss of a single VEGF allele is lethal in a mouse embryo. Using receptor-selective VEGF mutants, Li et al. (28) showed that the vasoactive effects of
VEGF are primarily mediated through VEGF-R2. Consistent with this observation, the incidence of hypertension observed in clinical trials appears to correlate with the potency of the VEGF kinase inhibitor against VEGF-R2, such that agents with higher potency are associated with a higher incidence of hypertension (Fig. 1) (1, 3, 4, 6, 8, 9, 11, 14, 20, 21, 30, 34–41, 43, 46, 47, 49, 50). Additional study details of these clinical trials are provided in Table 1. It should be noted that some of the VEGF kinase inhibitors may also have inhibitory effects on other kinases such as cKit-, PDGF-, RAF-kinase, etc. These nonselective effects on other kinases result in clinical toxicities such as stomatitis, fatigue, dermatological toxicities, and myelosuppression, without any noticeable effects on hypertension.

Another possible mechanism causing hypertension relates to a decrease in the number of small arteries and arterioles (rarefaction) in response to treatment with VEGF kinase inhibitors. Studies in spontaneously hypertensive rats have shown a rarefaction of arterioles and capillaries at 6 to 8 wk of age (2, 25), and rapid microvascular rarefaction (after 3 days) was observed in rats fed a high-salt diet (16), suggesting that rarefaction is an early event during hypertension. Microvascular rarefaction has been consistently demonstrated in adults with hypertension (17, 33). Noon et al. (32) demonstrated capillary rarefaction in young adults with a familial predisposition to hypertension, suggesting that rarefaction (as a result of defective angiogenesis) was a cause rather than a consequence of hypertension. In a recent study, Lee et al. (27) showed that in vivo autocrine VEGF signaling is required for endothelial cell survival under nonpathological conditions. Activation of VEGF-R2 by endogenous VEGF enables endothelial cell survival, indicating that the homeostatic function of VEGF signaling within endothelial cells is of considerable biological significance. Therefore, inhibition of signaling with VEGF kinase inhibitors would be expected to cause endothelial cell apoptosis and vascular rarefaction in nontumor tissues.Emerging clinical data support the occurrence of rarefaction in patients treated with VEGF inhibitors. In a clinical study in patients treated with BAY 57–9352, Steeghs et al. (48) provided the first evidence of capillary rarefaction associated with a VEGF kinase inhibitor in humans (48). In this small study (7 patients), all patients had a marked decrease in the number of capillary loops (measured using sidestream dark-field imaging of the buccal mucosa) after 5 wk of treatment with BAY 57–9352. In another study, Mourad et al. (31) demonstrated capillary rarefaction in the skin of patients treated with bevacizumab and chemotherapy for 6 mo using a technique called acizumab and chemotherapy for 6 mo using a technique called

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**Table 1. Details for studies reporting the incidence of hypertension with vascular endothelial growth factor tyrosine kinase inhibitors**

<table>
<thead>
<tr>
<th>Drug (IC&lt;sub&gt;50&lt;/sub&gt; for VEGF-R2)</th>
<th>HTN, All Grades, %</th>
<th>Patients, n</th>
<th>Cancer Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGI1736 (0.25 nM)</td>
<td>61</td>
<td>36</td>
<td>Solid tumors</td>
<td>Rugo et al. (40)</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>25</td>
<td>Solid tumors</td>
<td>Rini et al. (37)</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>32</td>
<td>Melanoma</td>
<td>Fruhauf et al. (14)</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>307</td>
<td>Solid tumors</td>
<td>Rini et al. (38)</td>
</tr>
<tr>
<td>AMG706 (3 nM)</td>
<td>42</td>
<td>71</td>
<td>Solid tumors</td>
<td>Rosen et al. (39)</td>
</tr>
<tr>
<td>AV-951 (0.16 nM)</td>
<td>56</td>
<td>41</td>
<td>Solid tumors</td>
<td>Eskens et al. (9)</td>
</tr>
<tr>
<td>AZD2171 (0.5 nM)</td>
<td>35</td>
<td>83</td>
<td>Solid tumors</td>
<td>Drevs et al. (6)</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>26</td>
<td>Reproductive</td>
<td>Ryan et al. (41)</td>
</tr>
<tr>
<td>GW786034 (30 nM)</td>
<td>28</td>
<td>37</td>
<td>Solid tumors</td>
<td>Sutte et al. (49)</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>111</td>
<td>STS</td>
<td>Sleijfer et al. (46)</td>
</tr>
<tr>
<td>PTK/ZK (37 nM)</td>
<td>16</td>
<td>43</td>
<td>Solid tumors</td>
<td>Thomas et al. (50)</td>
</tr>
<tr>
<td>Sunitinib (90 nM)</td>
<td>43</td>
<td>202</td>
<td>RCC</td>
<td>Ratain et al. (54)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>384</td>
<td>RCC</td>
<td>Escudier et al. (8)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>29</td>
<td>RCC</td>
<td>Shepard et al. (43)</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>58</td>
<td>RCC</td>
<td>Riechelmann et al. (36)</td>
</tr>
<tr>
<td>Sunitinib (10 nM)</td>
<td>18</td>
<td>28</td>
<td>Solid tumors</td>
<td>Faurie et al. (11)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>63</td>
<td>RCC</td>
<td>Motzer et al. (30)</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>17</td>
<td>Thyroid</td>
<td>Ravaud et al. (35)</td>
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<td></td>
<td>42</td>
<td>17</td>
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<td>Cohen et al. (4)</td>
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<td></td>
<td>30</td>
<td>10</td>
<td>Glioma</td>
<td>Chakravarty et al. (7)</td>
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<td></td>
<td>23</td>
<td>22</td>
<td>SCCN</td>
<td>Choong et al. (3)</td>
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<td></td>
<td>11</td>
<td>63</td>
<td>NSCLC</td>
<td>Socinski et al. (47)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>77</td>
<td>Solid tumors</td>
<td>Holden et al. (21)</td>
</tr>
</tbody>
</table>

These studies were selected based on treatment at maximum tolerated doses of each agent to minimize the effects of dose and exposure within different studies of individual agents. All studies used the National Cancer Institute Common Toxicity Criteria for the definition and grading of hypertension. The incidence of hypertension shown in the table refers to all grades (grades 1–4) of hypertension. HTN, hypertension; RCC, renal cell cancer; HRPC, hormone-refractory prostate cancer; STS, soft tissue sarcoma; SCCN, squamous cell carcinoma of the head and neck; NSCLC, nonsmall cell lung cancer; VEGF-R2, vascular endothelial growth factor-receptor 2.
intravital video capillaroscopy. These authors also demonstrated the presence of endothelial dysfunction in these patients using laser-Doppler flowmetry and iontophoresis of pilocarpine to study endothelial-dependent vasodilatation. Despite the fact that it is unclear whether the rarefaction is structural (disappearance of capillaries), functional (nonperfusion of capillaries), or a combination of both, it is likely that this phenomenon contributes to the hypertension observed in patients treated with VEGF kinase inhibitors.

An increase in arterial stiffness, either in the proximal vessels (the aorta and its main branches) or the distal vessels (small arteries and arterioles), has been associated with hypertension (42). Veronese et al. (52) demonstrated a significant increase in the stiffness of the proximal vessels, measured using central aortic augmentation index and aortic pulse wave velocity, in patients treated with sorafenib for 3 to 6 wk, suggesting that vascular stiffness may contribute to the hypertension seen in patients treated with VEGF kinase inhibitors. These investigators also showed that serum renin, aldosterone, and catecholamine levels were not affected, indicating that renovascular mechanisms and/or volume expansion were not major contributors to the etiology of hypertension in patients receiving sorafenib. Matsuura et al. (29) demonstrated a stimulatory interaction between VEGF and endothelin (ET-1) on each other’s gene expression in bovine aortic endothelial cells and vascular smooth muscle cells, suggesting an interplay between these two important pathways that regulate vascular tone. Therefore, it is possible that treatment with a VEGF kinase inhibitor could cause an imbalance between ET-1 (a potent vasoconstrictor) and VEGF, thus contributing to hyper-tension.

A recent study by Curwen et al. (5) used telemetered rats to demonstrate that cediranib, a VEGF kinase inhibitor, can reverse hypertension caused by VEGF. The authors also demonstrated that cediranib induced significant and reproducible hypertension in conscious telemetered rats and that the rise in blood pressure directly correlated with the dosing interval of this agent. A clinical study with AV-951, an inhibitor of all three VEGF receptor kinases, in patients with advanced solid tumors showed that the incidence of hypertension increased with dose and that the rise in blood pressure correlated with plasma levels of AV-951 (9). Hypertension was observed across all dose levels, regardless of the underlying cancer or the extent of metastasis, indicating that hypertension was a drug related rather than a tumor-related phenomenon.

Although the studies reviewed here provide possible mechanisms linking hypertension to VEGF kinase inhibitors, a full understanding of this important side effect will require additional preclinical studies and carefully conducted clinical trials. The mechanisms proposed in this review include increased vascular resistance (due to decreased NO and prostacyclin production), vascular rarefaction and increased arterial stiffness; however, it is possible that other unrecognized mechanisms may be contributing to the development of hypertension associated with VEGF kinase inhibitors. VEGF kinase inhibitors are being used in the treatment of a wide variety of cancers, and recent studies have shown that patients will likely require long-term treatment with these agents. A thorough understanding of the mechanisms underlying hypertension is crucial to developing appropriate therapeutic strategies for treating hypertension associated with VEGF kinase inhibitors.

**Perspectives and Significance**

Drugs that block the VEGF receptor-linked tyrosine kinase have recently demonstrated anticancer activity and are now being used for the treatment of a wide variety of cancers. Hypertension is a frequent side effect of VEGF kinase inhibitors, and several mechanisms have been proposed for hypertension associated with VEGF kinase inhibitors. This review summarizes our current understanding of this intriguing phenomenon, and suggests directions for future research.

**DISCLOSURES**

I am an employee of Aveo Pharmaceuticals, Inc., holding stock options in the company.

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R4  VEGF KINASE INHIBITORS: HOW DO THEY CAUSE HYPERTENSION?

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