Inhibition of Vascular Endothelial Growth Factor-A Signaling Induces Hypertension: Examining the Effect of Cediranib (Recentin; AZD2171) Treatment on Blood Pressure in Rat and the Use of Concomitant Antihypertensive Therapy

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Abstract

Purpose: Inhibition of vascular endothelial growth factor-A (VEGF) signaling is a key therapeutic approach in oncology given the role of VEGF in angiogenesis and vascular permeability in solid tumors. Clinical trials examining VEGF signaling inhibitors commonly report hypertension. We examined the effect of cediranib, a highly potent VEGF signaling inhibitor, on the blood pressure of rats and the ability of standard antihypertensive agents to modulate the consequences of VEGF signaling inhibition.

Experimental Design: The ability of cediranib to induce hypertensive changes and the effect of giving antihypertensive therapy were investigated in conscious, unrestrained telemetered rats. Two antihypertensive agents were studied: captopril, an angiotensin-converting enzyme inhibitor, and nifedipine, a dihydropyridine calcium channel blocker. The antitumor activity of cediranib, alone and in combination with nifedipine, was also evaluated in a LoVo human colorectal tumor xenograft model in nude rats. All treatments were given orally.

Results: Administration of 0.1 to 1.5 mg/kg/d of cediranib for 4 consecutive days induced a relatively mild hypertensive effect, elevating diastolic blood pressure by 10 to 14 mmHg. Dosing 3 mg/kg/d cediranib for 4 days induced a marked hypertension of 35 to 50 mmHg. Captopril (30 mg/kg, qd) was effective at lowering a 10 mmHg increase in blood pressure but not a 35 to 50 mmHg increase. However, the latter was rapidly reversed by administration of nifedipine (10 mg/kg, bd). Coadministration of nifedipine did not negatively affect the antitumor activity of cediranib (1.5 mg/kg/d).

Conclusions: Hypertension is a direct consequence of inhibiting VEGF signaling but can be controlled with appropriately selected, standard antihypertensive medication.

Vascular endothelial growth factor-A (VEGF) signaling is considered a key stimulant of the neovascular growth that is required to support solid tumor progression (1). Although the angiogenic phenotype is a complex, multistep process, VEGF alone can induce the varied signaling responses required for formation of a primitive vascular network, including endothelial cell proliferation, via focal adhesion kinase stimulation of the mitogen-activated protein kinase pathway (2), migration, through FAK and paxillin phosphorylation (3), and survival, through activation of protein kinase B/Akt (4). VEGF also has a profound permeabilizing effect on the endothelium, initially being termed vascular permeability factor (5). The underlying mechanism for increased permeability and vascular leakage, at least in part, involves VEGF-stimulated phosphorylation of the endothelial cell-cell adhesion molecule VE-cadherin, resulting in its rapid internalization and the disassembly of intercellular junctions (6).

Given its apparent ubiquity in assisting solid tumor progression, inhibition of VEGF signaling is being pursued avidly as a therapeutic strategy. VEGF binds to the endothelial cell–associated receptors VEGFR-1 (Flt-1) and VEGFR-2 (KDR) and initiates intracellular signaling by inducing receptor homodimerization or heterodimerization. These events activate intrinsic receptor tyrosine kinase activity, leading to a sequence of phosphorylation events that collectively propagate cytoplasmic signaling. VEGF activation of VEGFR-2 is the predominant driver of the angiogenic and permeability responses (7, 8), with VEGFR-1 having more limited cellular effects (9). Consequently, technical approaches to inhibit VEGF signaling have focused on preventing VEGFR-2 activation, through VEGF ligand sequestration (1, 10), blocking the ability of VEGFR-2 to...
directly bind VEGF (11), or use of small-molecule receptor tyrosine kinase inhibitors, such as cediranib (Recentin; AZD2171; ref. 12), which prevent VEGFR-2 from eliciting a signaling response.

In addition to its angiogenic and permeabilizing properties, VEGF is also known to have a vasodilatory effect; a variety of reports indicate that exogenous VEGF administration can affect vascular tone and hence blood pressure (13, 14). This effect is thought to be mediated principally via nitric oxide (NO) signaling because a VEGF-induced dilation can be prevented by pretreatment with a NO synthase inhibitor (13–15). Other studies indicate that, although NO seems the most important regulator of vascular tone downstream of VEGF signaling, prostacyclin (PGI₂) may play an additional, smaller functional role (16). Vasodilation, like the angiogenic and permeability effects of VEGF, is also predominantly dependent on signaling through VEGFR-2 (17). However, PGI₂ synthesis in bovine aortic endothelial cells has been shown to specifically require heterodimerization of VEGFR-2 with VEGFR-1 (18).

Although large doses of exogenous VEGF induce vasodilation, the role of physiologic levels of VEGF in regulating normal vascular tone is less clear. However, recent clinical trials examining bevacizumab, a humanized antibody that binds VEGF-A (19), or structurally distinct small molecules with inhibitory activity against the VEGF receptor tyrosine kinases (20–23), have reported an incidence of hypertension. This suggests that the vasodilatory properties of VEGF can play a role in normal vascular tone and that inhibition of this pathway for therapeutic benefit may require hypertension management in some oncology patients.

Here, we show that cediranib, a highly potent VEGF signaling inhibitor, can reverse a hypertensive change induced by acute administration of exogenous VEGF in anesthetized rats. We also show that administration of cediranib to conscious telemetered rats, in a dose range that is known to affect pathologic (24) and physiologic VEGF signaling (12) in rat, can elevate blood pressure. These blood pressure increases can be reversed completely with standard antihypertensive agents, although homeostatic regulation determines the magnitude of hypertension encountered and dictates the effectiveness of the class of antihypertensive agent used. Finally, in a human tumor xenograft model in athymic rats, we show that coadministration of the calcium channel blocker nifedipine does not affect the antitumor activity of cediranib.

Materials and Methods

VEGF and basic fibroblast growth factor. Human VEGF-A (165 isoform) was expressed in Sf21 insect cells using the baculovirus expression system and purified from cell lysates using heparin-Sepharose affinity chromatography followed by C2-C18 mixed bed reversed-phase chromatography. Human basic fibroblast growth factor (bFGF) was expressed in Escherichia coli [BL21(DE3)pLySS strain] and purified from cell lysates by heparin-Sepharose affinity chromatography.

Cediranib. [(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (cediranib, Recentin, Astra-Zeneca) was synthesized in house at AstraZeneca as described previously (12).

Growth factor–induced hypotension in anesthetized rats. Male Alderley Park Wistar strain rats (125-175 g body weight) were anesthetized by administration of Intraval (30 mg/kg; thiopentone sodium, 2.5%; May and Baker) via the i.p. route. Once surgical anesthesia was established, confirmed by the absence of both the blink and foot withdrawal reflexes, the carotid artery and jugular vein were cannulated to enable blood pressure recording and growth factor administration, respectively. Blood pressure was measured using a Bell and Howell 4-422-001 transducer attached to a Lectromed MT8P amplifier (Lectromed UK Ltd.) and chart recorder (Lectromed MTF8). The body temperature of each animal was maintained via a thermistor covered heated blanket coupled to a CFP 8185 recital thermometer (Bioscience Ltd.). Once a stable blood pressure was attained, VEGF (6 μg), bFGF (12 μg), or vehicle alone (physiologic saline with 0.5% bovine serum albumin) was given via the venous cannula. In some studies, the resultant hypotensive response was allowed to return to baseline over a period of 40 min before administration of the same growth factor, and then an alternative growth factor was given 5 min later. In other studies, cediranib (0.125 and 0.25 mg/kg) was formulated as a solution in 25% hydroxypropyl-β-cyclodextrin and given i.v. (0.1 mL volume) at the peak of the growth factor–induced hypotension, typically between 2 and 4 min, and the subsequent blood pressure was recorded 1 to 2 min later.

Measurement of blood pressure in conscious unrestrained rats. The radiotelemetry system (Data Sciences International) and associated methodology used has been described previously (25). Briefly, in this instance, male Alderley Park Wistar strain rats (175-200 g body weight) were anesthetized with the inhalation anesthetic isoflurane (Abbott Laboratories). Once surgical anesthesia was confirmed, the abdominal cavity was opened and the descending abdominal aorta was located. The vessel was cleared of connective tissue using blunt dissection techniques and a tie was placed underneath (2.0 silk suture; Ethicon). This tie was lifted to occlude the vessel while the catheter of a DSI TA11PA-C40 implant was inserted into the aorta along the bevel of a bent 21-gauge needle. Once in the vessel, the catheter was fixed with medical-grade adhesive (Vetbond, 3M Animal Care Products). The body of the transmitter implant was then fixed in place by suturing to the inside of the abdominal wall. The surgical wound in the abdomen was closed with dissolving sutures (Mersilk 5.0, Ethicon) and autoclips (Clay Adams) used to close the outer skin. Animals were treated before the end of surgery with the analgesic buprenorphine (0.4 mg/kg s.c.; Schering-Plough) and monitored closely to ensure good recovery. The autoclips were removed 1 wk after surgery.

Telemetered rats were dosed with 1% (w/v) aqueous polysorbate vehicle, once daily, to acclimate them to handling and dosing. Once stable blood pressure and heart rate baselines were obtained, typically after a period of 7 d, cediranib [suspended in 1% (w/v) aqueous polysorbate 80 (polyoxyethylene (20) sorbitan monoleate in deionized water] was given orally (at 5 mL/kg body weight), once daily, for up to 4 d. The cediranib dose range examined (0.1-3 mg/kg/d) had been previously shown to inhibit human tumor xenograft growth in athymic rats dose-dependently (24). In a subsequent set of experiments, cediranib was given for 3 to 5 d until the level of hypertension began to plateau. Daily administration of cediranib was then continued, either alone or in combination with captopril (30 mg/kg, q.d) or nifedipine (10 mg/kg, bd; both obtained from Sigma-Aldrich). The first daily dose of nifedipine was given in combination with cediranib and the second daily dose of nifedipine was given after an interval of 8 h using a separate suspension prepared in 1% polysorbate vehicle.

Human tumor model. Human LoVo colorectal carcinoma tumor cells (American Type Culture Collection) were maintained as exponentially growing monolayers in DMEM (Life Technologies) + 10% FCS (Labtech International) + 2 mmol/L l-glutamine (Sigma-Aldrich). Tumors were established in female Alderley Park athymic (nu/nu genotype) rats by s.c. injection of LoVo cells (1 x 10^7 in serum-free medium) into the left hind flank. When tumors reached a volume of 0.1 to 0.5 cm³, 7 d after cell inoculation, rats were randomized into groups (12 rats in the control group and 8 per treated group). To power
the study so that a 30% change in tumor volume could be detected and be statistically significant, group sizes were determined by statistical analysis of accrued historical data on the growth variability of this tumor. Cediranib, captopril, and nifedipine were suspended in 0.5% (w/v) hydroxypropyl methylcellulose solution containing 0.1% (w/v) aqueous polysorbate 80 and dosed to adult rats by oral gavage at 5 mL/kg of body weight. Vehicle, cediranib (1.5 mg/kg, qd), nifedipine (10 mg/kg, bd), or the combination of cediranib and nifedipine was given by oral gavage (0.1 mL/10 g), as in telemetered rat studies.

Tumor volumes were assessed by bilateral Vernier caliper measurement at least twice weekly and calculated using the formula \( \frac{\text{length} \times \text{width} \times \text{length} \times \text{width}}{3} \), where length was taken to be the longest diameter across the tumor and width the corresponding perpendicular. Growth inhibition was calculated from the start of treatment by comparison of the mean change in tumor volume for control and treated groups. To remove any size dependency before statistical evaluation (the variance in mean tumor volume data increases proportionally with volume and is therefore disproportionate between groups), data were log transformed before statistical evaluation using a one-tailed, two-sample \( t \) test.

**Results**

Acute hypotensive effects of VEGF and inhibition with cediranib. Growth factor administration was examined in anesthetized rats where homeostatic reflexes are reduced, making the animals more sensitive to the effects of hypotensive stimuli than when conscious. Consistent with previous literature reports (e.g., 14), we found that a bolus injection of VEGF into the jugular vein of anesthetized rats causes large, acute reductions in blood pressure. A second injection of VEGF 40 min later had no effect on blood pressure, indicating that desensitization (tachyphylaxis) has been induced (Fig. 1A). Using another vasoactive growth factor, bFGF, we found that the tachyphylaxis induced by VEGF does not affect the ability of bFGF to induce hypotension and, similarly, a tachyphylaxis to bFGF does not influence the hypotensive response induced by subsequent VEGF administration (Fig. 1B and C). These findings support the hypothesis that VEGF and bFGF induce hypotension by distinct signaling responses that are mediated...
by binding to their respective growth factor receptors but with both having a downstream signaling dependency on NO production (13–16, 26). A VEGF-induced hypotensive response was reversed instantly by i.v. administration of cediranib (0.25 mg/kg; Fig. 2). These additional data indicate that the hypotensive response that follows exogenous VEGF administration is dependent on continual VEGF receptor kinase signaling.

Cediranib induces hypertension in conscious rats. Single oral doses of 3 mg/kg cediranib induced mild hypertension (~15 mmHg) in the animals (Fig. 3A), the onset and duration of which was dependent on the dose used (data not shown). The hypertension was associated with occasional findings of bradycardia in some rats, which is a predictable compensatory response to a sudden increase in blood pressure. When cediranib was given orally, once daily, for 4 consecutive days, greater increases in blood pressure were observed (Table 1; Fig. 3B). The magnitude of hypertension was related to dose and reached a plateau of approximately 10 to 14 mmHg (diastolic) between the second and fourth day of treatment with 0.1 to 1.5 mg/kg of cediranib (Table 1). A subtle but reproducible dose response was observed in the time taken to reach this plateau, with larger doses resulting in 10 to 14 mmHg increases more rapidly than smaller doses (e.g., 0.1 versus 0.5 mg/kg/d cediranib; Fig. 3B). When doses of ≥1.75 mg/kg were used, the hypertension induced after 4 days of treatment greatly exceeded the 10 to 14 mmHg plateau (Table 1), with diastolic blood pressure increases ranging between 35 and 50 mmHg in different studies following continuous administration of 3 mg/kg/d cediranib. An example of a more marked hypertensive response, induced by 3 mg/kg/d cediranib, is shown in Fig. 3B. When cediranib dosing was discontinued, all hypertensive responses returned to a normal baseline within 2 days, irrespective of the dose given or magnitude of blood pressure increase induced. These data indicate that a VEGF signaling inhibitor induces dose-dependent hypertension in conscious rat, although the dose response is complex.

Effect of antihypertensive therapies on cediranib-induced hypertension. Because VEGF causes hypotension by vasodilation rather than a direct cardiac mechanism (14), hypertension induced by VEGF signaling inhibition is likely to be attributable to an effect on physiologic vasodilatory tone, resulting in a simple vasoconstrictive response. With this probable mechanism in mind, two antihypertensive agents, captopril and nifedipine, were selected for combination studies with cediranib. Both agents decrease blood pressure by reducing peripheral vascular resistance. Captopril is an inhibitor of angiotensin-converting enzyme, which produces angiotensin II, a potent endogenous vasoconstrictive agent, from the less vasoactive precursor angiotensin I. The formation of angiotensin II represents the final step in the renin-angiotensin system, which...
acts as an important homeostatic regulator of blood pressure. Captopril (30 mg/kg) completely reversed the hypertensive change of 10 mmHg established by 3 days of dosing of 0.25 mg/kg/d cediranib (Fig. 4A). However, the same captopril treatment regimen failed to modulate a much larger hypertensive response of 35 mmHg established by three daily doses of 3 mg/kg cediranib (Fig. 4B). That a range of cediranib concentrations between 0.1 and 1.5 mg/kg all induce a similar magnitude of blood pressure increase (10-14 mmHg) suggests that homeostatic mechanisms in rat may limit blood pressure rises up to the observed 10 to 14 mmHg threshold. This may also explain why cediranib doses of ≥1.75 mg/kg/d induced disproportionately greater increases in blood pressure (Table 1) that were unaffected by captopril treatment, marked hypertension being presumably evident when the degree of VEGF signaling inhibition is too high for the animal to compensate any further. A marked hypertensive response of ~35 mmHg, induced by treatment with 3 mg/kg/d cediranib for 5 days, was reversed completely by administration of the direct vasodilator nifedipine (Fig. 4B). Nifedipine is a calcium channel blocker that acts as an antihypertensive by selectively inducing vasodilation in the blood vessels responsible for resistance to blood flow, therefore working independently of mechanisms that regulate normal blood pressure homeostasis. Nifedipine was also shown to reverse a marked hypertension induced by cediranib in rats, with a 40 to 45 mmHg increase in diastolic blood pressure that had been refractory to captopril treatment for 4 days (Fig. 4B). Collectively, these data indicate that hypertension induced by a VEGF signaling inhibitor can be reversed with antihypertensive medication but that careful selection of the antihypertensive is required, dependent on the magnitude of blood pressure increase encountered.

### Discussion

The vasodilatory properties of VEGF have been shown previously in preclinical experiments that involved administration of exogenous VEGF to a range of mammalian species (14, 27, 28). Similarly, clinical trials examining VEGF administration, which aim to promote angiogenesis in ischemic conditions, have confirmed that VEGF has vasodilatory and hypotensive effects in man (29). The magnitude of hypotension

<table>
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<tr>
<th>Cediranib dose (mg/kg/d)</th>
<th>Diastolic blood pressure increase (mmHg ± SE)</th>
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<td>0.1</td>
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<td>0.25</td>
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<td>0.5</td>
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<td>1.5</td>
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<td>1.75</td>
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Fig. 4. Effects of different antihypertensive therapies on cediranib-induced hypertension. A, administration of captopril (30 mg/kg, orally, qd) reverses a 10 mmHg increase in blood pressure induced by cediranib (0.25 mg/kg qd). B, a more significant hypertension (30-45 mmHg) induced by chronic administration of 3 mg/kg/d cediranib is not modulated significantly by concomitant captopril (30 mg/kg orally, qd) administration over a 4-d period but is subsequently reversed by nifedipine (10 mg/kg, orally, bd). Nifedipine (10 mg/kg, orally, bd) also normalized the blood pressure of rats that received cediranib (3 mg/kg/d) alone.
induced is dependent on the rate of i.v. VEGF administration: slower infusions gave a significantly attenuated response in comparison with rapid infusions or bolus injection (30, 31). VEGF was found to induce a profound hypotension in anesthetized rats in our experiments, dropping diastolic blood pressure from basal levels (typically between 80 and 110 mmHg) to ~40 mmHg. This change is larger than has been reported in conscious rats (14) and is likely to result from the reduced effectiveness of homeostatic reflexes in the anesthetized setting. Studies with selective VEGFR-1 and VEGFR-2 ligands indicate that VEGF-induced vasodilation involves a specific VEGF receptor response and that VEGFR-2 is the predominant mediator (17). Data from our experiments, examining the differential hypotensive effects of VEGF and bFGF in vivo, and the ability of cediranib to reverse a VEGF-induced hypotension, also support the premise that VEGF mediates vasodilation through binding to VEGF receptors and activation of VEGF receptor kinase signaling.

Although exogenous VEGF administration imparts a significant effect on blood vessel tone in the adult, this knowledge does not permit assumptions to be made about the role of endogenous VEGF signaling in the normal physiologic control of vessel tone and blood pressure. Indeed, the fact that exogenous VEGF induces relatively short-term hypotensive effects, and that these effects are accompanied by an acute tachyphylaxis, may be taken to suggest that VEGF signaling is unlikely to act as significant homeostatic regulator of blood pressure. However, we found cediranib, a highly potent VEGF receptor tyrosine kinase inhibitor (12), to induce significant and reproducible hypertensive responses in conscious telemetered rats. Administration of 0.1 to 1.5 mg/kg/d of cediranib elevated diastolic blood pressure by approximately 10 to 14 mmHg within 2 to 4 days. Cediranib is known to affect physiologic and pathologic VEGF signaling within this dose range when given chronically for 28 days; the growth of Calu-6 human lung tumor xenografts in athymic rats was inhibited by 75% (P < 0.05 by one-tailed, two-sample t test) following administration of 1 mg/kg/d cediranib (24) and 1.25 mg/kg/d cediranib induced a statistically significant hypertrophy in the femorotibial growth plates of growing immunocompetent rats (12) by inhibiting endochondral ossification that is dependent on VEGF signaling and angiogenesis (32). Whereas these doses of cediranib resulted in comparatively mild hypertensive effects, administration of 1.75 to 3 mg/kg/d of cediranib for 4 days induced more profound increases in blood pressure of 35 to 50 mmHg. Hypertension has recently emerged as one of the most frequently reported findings in oncology clinical trials examining VEGF signaling inhibitors. Elevated blood pressure has been documented in patients receiving cediranib (23), as well as other structurally distinct small-molecule inhibitors that have activity against the VEGF receptor tyrosine kinases (20–22), or with bevacizumab or VEGF-Trap, which sequesters VEGF ligand (19, 33). Furthermore, naturally occurring increases in soluble VEGFR-1, which sequesters VEGF, are known to contribute to the pathogenesis of preeclampsia, a disease in pregnancy that involves hypertension (34). Collectively, these observations indicate that VEGF signaling does indeed play an important role in the maintenance of normotension in the adult. Given that VEGFR-2 signaling is central to mediating both the vasodilatory and angiogenic properties of VEGF, the desired therapeutic aim of preventing angiogenic signaling through this receptor will inevitably involve some perturbation of blood pressure homeostasis. Consequently, any therapeutic approach that inhibits VEGF signaling appreciably will incur a hypertensive liability that must be monitored for patient safety and, if necessary, controlled with appropriate comedication.

Our subsequent experiments, which examined concomitant antihypertensive therapy with cediranib treatment, suggest that the successful reversal of a hypertension induced by VEGF signaling inhibition will be dependent on the magnitude of blood pressure increases encountered and the mechanism of action of the antihypertensive agent selected. The angiotensin-converting enzyme inhibitor captopril was highly effective at reversing a 10 mmHg increase in blood pressure induced by cediranib but was unable to modulate more profound blood pressure increases of 30 to 50 mmHg. That captopril exerts an antihypertensive effect by affecting the renin-angiotensin system, a key homeostatic regulator of blood pressure, suggests that such homeostatic compensatory mechanisms are operative in rats when a comparatively mild (i.e., 10-14 mmHg) blood pressure increase is evident. The inability of captopril to modulate much greater blood pressure increases, induced by a more substantial inhibition of VEGF signaling, suggests that the renin-angiotensin system has already been down-regulated under these conditions in an attempt to maintain normotension. This hypothesis is further supported by a trend toward reduced renin levels, observed in a limited number of blood samples from rats treated with cediranib at 3 mg/kg for 4 days (56% median decrease, n = 7; data not shown). Consequently, a directly acting vasodilator, nifedipine, was required to reverse the more significant hypertensive responses encountered. Encouragingly, chronic concomitant administration of nifedipine did not reduce the antitumor activity of cediranib in athymic rats. This suggests that if anti-hypertensive therapy is required, it can be given concomitantly.
for prolonged periods without affecting the potential therapeutic benefits that should be derived from inhibiting VEGF signaling.

However, further consideration must be given to the selection of alternative antihypertensive medication, as there are other agents that could affect negatively the efficacy of VEGF signaling inhibitors or have reduced success in managing a resultant hypertension. The angiogenic responses induced by VEGF have been shown to have a dependency on downstream NO production in several experimental systems (35, 36) and VEGF-driven angiogenesis is found to be impaired in eNOS−/− mice (37, 38). Thus, antihypertensive agents, such as nitrates that induce vasodilation by the NO signaling pathway (i.e., via direct release of NO or stimulation of NO-sensitive second messengers), are likely to be highly effective at treating a marked hypertension induced by inhibition of VEGF signaling but may perhaps compromise the antiangiogenic benefits. Given there are alternative options available for hypertension management, it may be prudent to avoid this class of antihypertensive for chronic administration with a VEGF signaling inhibitor. Use of some loop diuretics such as furosemide, which blocks renal chloride and sodium reabsorption, should also be avoided as their efficacy is impaired by inhibitors of NO (39). Inhibition of VEGF signaling decreases NO activation acutely, as well as the synthesis of NO synthase chronically (40), which would significantly reduce the effectiveness of furosemide. Furosemide can also increase the levels of renin (41), which could further exacerbate a hypertension induced by a VEGF signaling inhibitor. Nifedipine, a calcium channel blocker, was effective at reversing a marked hypertension induced by cediranib; however, calcium channel blockers can reduce the contractility of arterial smooth muscle in the peripheral vasculature and/or reduce the force of contraction of the heart to differing extents. The dihydropyridine calcium channel blockers, such as nifedipine, have much greater potency on peripheral blood vessels than any direct cardiac effect, making them suitable for inducing direct vasodilation. However, other calcium channel blockers that show selectivity for cardiac tissue (e.g., verapamil from the phenylalkylamine class) may be less effective at reversing hypertension induced by VEGF signaling inhibitor given that homeostatic mechanisms may have already decreased cardiac output.

It has been suggested recently that hypertension could be a useful biomarker for dose setting when examining anti-VEGF signaling approaches (42). We showed a complex but reproducible response between cediranib dose and hypertensive outcome in rat, which was influenced by homeostatic mechanisms. Although this response was reproducible in healthy, inbred rats, significantly more variation would be anticipated in oncology patients as a consequence of their diverse genotypes, age, varying levels of underlying cardiovascular disease, and treatment with disparate forms of additional medication. These factors would influence the ability to maintain an effective homeostatic response and are likely to lead to appreciable interpatient variability in the magnitude of hypertension encountered for a given level of VEGF signaling blockade. Hence, although increases in blood pressure should be evident across a cohort of patients treated with a VEGF signaling inhibitor over a period of time, it is unlikely that this would be a useful biomarker for individual patients at a specific time point.

In summary, these preclinical data indicate that hypertension is a frequent consequence of VEGF signaling inhibition but that this can be managed optimally with selected antihypertensive medication. Although angiotensin-converting enzyme inhibitors were shown to be effective at overcoming mild hypertension, this was not sufficient to overcome more severe hypertension where use of a direct vasodilator is warranted. If the direct vasodilator is to be used chronically in combination with a VEGF signaling inhibitor, selection of a non–nitrate-based therapy, such as nifedipine, is recommended, as this should control blood pressure and not affect antitumor efficacy.

Such a hypertension management protocol using a stepwise approach to the management of hypertension is currently in place and being examined across all trials with cediranib in oncology patients (23).

References


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