Contrary Effects of the Receptor Tyrosine Kinase Inhibitor Vandetanib on Constitutive and Flow-Stimulated Nitric Oxide Elaboration in Humans

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Abstract—Vascular endothelial growth factor regulates neoplastic angiogenesis through production of endothelium-derived NO. We performed a prospective evaluation of vascular function during treatment with vandetanib, a vascular endothelial growth receptor 2 and 3 receptor tyrosine kinase inhibitor, to determine the effects of vascular endothelial growth receptor signal interruption on endothelial function in humans. Seventeen patients with stage IV breast cancer received dose-escalated vandetanib in combination with low-dose oral chemotherapy. We measured blood pressure, systemic nitrate/nitrite levels, and brachial artery vascular function. In vitro analyses of cultured endothelial cells were performed to determine the effect of vandetanib on NO production, akt\(^{473}\) phosphorylation, and endothelial NO synthesize protein content and membrane localization. Vandetanib treatment for 6 weeks significantly increased blood pressure, decreased resting brachial artery diameter, and decreased plasma systemic nitrate/nitrite levels compared with baseline. Flow-mediated vasodilatation was preserved, and no change was noted in nitroglycerin-mediated vasodilation. In vitro, endothelial cell nitrite levels and akt\(^{473}\) phosphorylation were reduced and vascular endothelial growth receptor 2 levels did not change, but endothelial NO synthesize membrane concentration doubled. Vandetanib reduces constitutive NO production and increases blood pressure, yet flow-stimulated NO bioavailability was preserved. Changes in vascular function with tyrosine kinase inhibition are complex and require further study in humans. (Hypertension. 2011;58:85-92.)

Key Words: vascular endothelial growth factor ■ VEGF receptor 2 ■ secondary hypertension ■ endothelium ■ NO
Methods

Subjects
Eligible subjects with metastatic breast cancer were recruited as part of a single-center investigator-initiated phase 1 trial. The subjects had exposure to ≤4 previous chemotherapy regimens for metastatic disease, an Eastern Cooperative Oncology Group performance status of ≥2, were postmenopausal or surgically sterile, and had normal bone marrow, hepatic, and renal function. Patients were required to have preserved cardiac function (left ventricular ejection fraction >45%), no evidence of QTC prolongation, and adequately controlled blood pressure at baseline. Patients were excluded for a requirement of >1 medication to control blood pressure to <140/90 mm Hg, therapeutic anticoagulation, or clinically significant cardiac disease.

Study Design
Three sequential cohorts, planned enrollment 8 patients each, were treated with escalating doses of daily vandetanib, an oral inhibitor of VEGFR and epidermal growth factor receptor (cohort 1: 100 mg; cohort 2: 200 mg; cohort 3: 300 mg), with continuous metronomic chemotherapy (cyclophosphamide, 50.0 mg PO once daily, and methotrexate, 2.5 mg PO twice daily, days 1 and 2 of each week). Vandetanib is a potent VEGFR2 inhibitor (inhibitory concentration: 23: 40 nmol/L) and shows additional inhibitory activity against rearranged during transfection receptor (IC50 = 100 nmol/L), Fms-related tyrosine kinase 4/VEGFR3 (IC50 = 110 nmol/L), and epidermal growth factor receptor (IC50 = 500 nmol/L).23-24
Subjects underwent vascular function testing before administration of vandetanib and after 6 weeks of protocol therapy. Because there were no differences in change in blood pressure or vascular function between cohorts, all of the subjects were studied as one group. All of the participants provided written informed consent. The protocol was approved by the human research committees of the Brigham and Women’s Hospital and Dana Farber Cancer Institute.

Blood Pressure Assessments
Blood pressure measurements were performed at each vascular study using an oscillographic device after 10 minutes of quiet recumbency before vascular measurements. The blood pressures were measured in triplicate with the value provided the average of the 3. Blood pressure was measured before vascular studies. All of the studies were performed in the morning after an overnight fast. Antihypertensive medications were held the day of study.

Assessment of Vascular Function
To assess endothelium-dependent, NO-mediated conduit artery vasodilation, brachial artery flow-mediated vasodilation after a hyperemic stimulus was measured at baseline and after 6 weeks on protocol therapy. The flow-mediated vasodilation technique was performed according to published protocol.25 We and others have demonstrated that brachial artery vasodilation 1 minute after reactive hyperemia dilation is mediated by NO.26,27
Subjects were studied in a controlled environment in the supine position after a minimum 4-hour fast. After a minimum 10-minute equilibration period, baseline 2D images of the brachial artery were obtained ∼2 cm above the antecubital fossa. A blood pressure cuff, placed proximal to the imaging transducer on the upper arm, was inflated using a Wallac 1420 Multilabel microplate reader (Perkin Elmer), with excitation at 355 nm and emission at 430 nm.

DNA Damage ELISA
The marker 8-hydroxy-2′-deoxyguanosine is an oxidized nucleoside excised from damaged DNA that increases in the setting of oxidative DNA damage. Levels of 8-hydroxy-2′-deoxyguanosine were quantified in patient plasma samples using the colorimetric DNA Damage ELISA (Assay Designs) as per the manufacturer’s instructions. Absorbances at 450 nm were measured using a Spectra Max 190 microplate reader with SoftMax Pro software (Molecular Devices).

Nitrotyrosine ELISA
Superoxides are highly reactive and can react with NO to form peroxynitrite, which reacts with tyrosines on proteins causing tyrosine nitration (tyrosine converted to 3-nitrotyrosine). Patient plasma samples were examined using a quantitative chemiluminescent nitrotyrosine ELISA to measure tyrosine nitration as per the manufacturer’s instructions (Millipore). Luminescence was measured using a Wallac 1420 Multilabel microplate reader.
In Vitro Endothelial Cell Studies

Mile Sven 1 (MS1) endothelial cells (ECs) were cultured as we described previously.29

NO Assay

Vandetanib or matched vehicle control (dimethyl sulfoxide [DMSO]) was added to MS1 EC (n=6 per group with studies done in duplicate) in phenol red-free DMEM/0.5% BSA and incubated (0.5 hours, 37°C, 10% CO2). Then, 100 μmol/L of L-arginine and 100 μmol/L of soluble N-ethylmaleimide sensitive factor attachment proteins were added, cells were incubated (1.5 hours, 37°C, 10% CO2), and the NO assay was performed as described above.

Akt Activity

The MS1 ECs were cultured in 24-well plates in low-glucose (1.0 g/L) DMEM (LG-DMEM) supplemented with 10% FCS/1% l-glutamine- penicillin-streptomycin (37°C, 10% CO2) and grown to near confluence.

Previous systemic therapy, %

Bevacizumab 41
Trastuzumab or lapatinib 12
Cetuximab 12
Cediranib 6

Statistical Considerations

Descriptive measures are reported as mean±SD. Experimental measures are reported as mean±SE. Biomarkers are reported as median (interquartile range). Basal forearm blood flow and diameter were compared by paired 2-tailed t tests. Laboratory measures were compared by Mann-Whitney U testing for 2-way comparisons. Association between vascular function and blood pressure changes was compared by Mann-Whitney U testing for 2-way comparisons. The MS1 ECs were cultured as we described previously.29 Films were scanned, and Scion Image software was used to conduct densitometric analyses to quantify signal intensity (n=4 to 6 per group, studies done in triplicate).

eNOS Protein Levels in Membrane and Cytosol

The MS1 ECs were cultured in their normal culture medium and grown to confluence. Cells were rinsed in PBS and were serum starved in culture medium diluted 1/5 with LG-DMEM (2 hours, 37°C, 10% CO2). Vandetanib (Selleck/Husker Chemicals) was dissolved in DMSO and diluted in LG-DMEM/0.5% BSA. Either 1 μmol/L of vandetanib or matched vehicle control was added to cells and incubated (1 hour, 37°C, 10% CO2). Protein lysates were prepared, and membrane and cytosol components were isolated using the Subcellular Protein Fractionation kit (Pierce). Both membrane and cytosolic fractions were run on gels and Western blotting conducted as we described.29 eNOS (rabbit monoclonal antibody, clone 49G3 at 1/1000), GAPDH (horseradish peroxidase–conjugate clone 14C10 at 1/5000), and endothelial (VE)-cadherin (rabbit polyclonal antibody, clone H72 at 1/1000) proteins levels were measured; films were scanned; and Scion Image software was used to conduct densitometric analyses to quantify signal intensity (n=3 per group, studies done in duplicate).

Results

Twenty-three patients were enrolled into the phase 1 trial. Nineteen subjects consented to participate in the vascular study, and 2 withdrew consent midprotocol. Patient and tumor characteristics are described in Table 1 for the 17 subjects who completed the investigation. All of the patients enrolled received protocol therapy.

Blood Pressure and Constitutive NO Bioavailability

Consistent with previous studies of VEGF receptor tyrosine kinase inhibitors (RTKIs), vandetanib increased mean arterial pressure from 91±8 to 102±10 mm Hg (P=0.001; Table 2). The increase in blood pressure was similar in both systolic and diastolic components. In contrast, no change in heart rate was noted. Also, subjects’ weight decreased significantly. Two laboratory measures of NO were used to determine NO bioavailability before and during vandetanib use. Nitrogen oxide (NOx) levels decreased significantly from baseline after exposure to study drugs for 6 weeks (Figure 1; P=0.036), indicating reduced NO elaboration. There was a trend between the reduction of nitrite level and increase in blood pressure (R²=0.21; P=0.068). When divided by the median blood pressure increase (10 mm Hg), the subjects with an increase of more than the median increased mean arterial pressure by 19±6 mm Hg compared with the subjects with an increase of less than the median, who had a nonsignificant change of 1±2 mm Hg (P<0.001). The subjects with an above-the-median increase in blood pressure had a 10-fold greater reduction in NOx compared with the 9 subjects whose blood pressure was below the median (−3945±5530 versus −382±2492; P=0.048). Levels of nitrotyrosine trended lower from baseline after 6 weeks of treatment (Table 2; P=0.054). Physiological evidence of reduced NO was evaluated with brachial ultrasonography. Baseline arterial diameter was 2.74±0.09 mm and decreased after 6 weeks of treatment to 2.57±0.08 mm (P=0.004; Table 2). Consistent with a reduction in NOx and increased blood pressure, forearm vascular resistance increased from 5.3±0.5 to 6.4±0.5 U (P=0.015). Shear stress did not vary significantly between study conditions (10.9±1.2 versus 11.6±1.7 poise; P=0.4).

We investigated the putative mechanism of reduced constitutive NO bioavailability in MS1 ECs. Incubation of vandetanib with MS1 EC significantly decreased nitrite production compared with the matched vehicle (DMSO;
Vandetanib reduced extracellular nitrite levels in endothelial cells. MS1 endothelial cells (ECs) were incubated with 1 μmol/L of vandetanib or matched vehicle (dimethyl sulfoxide [DMSO]), 50 ng/mL of vascular endothelial growth factor (VEGF) or matched vehicle (PBS; 0.5 hours), and l-arginine and soluble N-ethylmaleamide sensitive factor attachment protein (SNAP) added (1.5 hours). Vandetanib lowered nitrate levels in MS1 ECs (**P=0.0003). VEGF was used a positive control and increased nitrate levels (**P=0.02). These findings indicate that vandetanib lowered endothelial cell NO levels.

phosphorylation of the intermediate, AKT at serine 473. Western blotting (Figure 3) shows that vandetanib also reduced phosphorylation of Akt at serine 473 in MS1 ECs compared with vehicle controls (DMSO; Figure 3; P=0.01), indicating reduced Akt activation. Oxidative stress, as a mechanism to reduce NO bioavailability, was also evaluated. Levels of 8-hydroxy-2′-deoxyguanosine, a product of oxidative DNA damage, were stable with treatment (Table 2) and did not vary by vandetanib dose levels. In addition, nitrotyrosine levels trended lower during treatment. This may suggest a decrease in oxidative stress or a reduction in circulating nitrates from which to nitrosylate proteins.

**Vascular Function Studies and Stimulated NO Bioavailability**

We measured flow-mediated vasodilation as an index of flow-stimulated NO bioavailability. The application of a

**Figure 2.** Vandetanib reduced extracellular nitrite levels in endothelial cells. MS1 endothelial cells (ECs) were incubated with 1 μmol/L of vandetanib or matched vehicle (dimethyl sulfoxide [DMSO]), 50 ng/mL of vascular endothelial growth factor (VEGF) or matched vehicle (PBS; 0.5 hours), and l-arginine and soluble N-ethylmaleamide sensitive factor attachment protein (SNAP) added (1.5 hours). Vandetanib lowered nitrate levels in MS1 ECs (**P=0.0003). VEGF was used a positive control and increased nitrate levels (**P=0.02). These findings indicate that vandetanib lowered endothelial cell NO levels.

**Figure 3.** Vandetanib reduced phosphorylation of Akt in endothelial cells (ECs). MS1 ECs were incubated with 1 μmol/L of vandetanib or matched vehicle (dimethyl sulfoxide [DMSO]; 1 hour). Western blotting analysis showed that vandetanib decreased phosphorylation of Akt (S473) in MS1 ECs (**P=0.01; n=6 per group, studies done in triplicate). These findings show that vandetanib reduced Akt activity.

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**Table 2. Experimental Measures**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6 wk</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138±20</td>
<td>150±21</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>68±7</td>
<td>77±8</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
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<td>102±10</td>
<td>0.001</td>
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<td>Heart rate, bpm</td>
<td>74±13</td>
<td>71±10</td>
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<tr>
<td>Weight, kg</td>
<td>72.8±17.0</td>
<td>71.3±16.5</td>
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<tr>
<td>Basal brachial artery diameter, mm</td>
<td>2.74±0.09</td>
<td>2.57±0.08</td>
<td>0.004</td>
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<tr>
<td>Post-RH brachial artery diameter, mm</td>
<td>3.07±0.12</td>
<td>2.93±0.12</td>
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<tr>
<td>Absolute increase in brachial artery diameter, mm</td>
<td>0.33±0.05</td>
<td>0.36±0.06</td>
<td>0.36</td>
</tr>
<tr>
<td>Reactive hyperemic stimulus, fold increase</td>
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<td>6.8±3.0</td>
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</tr>
<tr>
<td>Flow-mediated vasodilation, %</td>
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<td>13.8±1.8</td>
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<tr>
<td>Pretnitroglycerin brachial artery diameter, mm</td>
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<td>2.63±0.1</td>
<td>0.024</td>
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<tr>
<td>Postnitroglycerin brachial artery diameter, mm</td>
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<td>3.16±0.13</td>
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<tr>
<td>Nitroglycerin-mediated vasodilation, %</td>
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<tr>
<td>Nitrites, AU</td>
<td>48 446±1264</td>
<td>46 799±1740</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrotyrosine, AU</td>
<td>259 814±26 139</td>
<td>246 157±20 501</td>
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<tr>
<td>8-Hydroxy-2′-deoxyguanosine, AU</td>
<td>1.96±0.09</td>
<td>2.0±0.15</td>
<td>0.5</td>
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</tbody>
</table>

AU indicates arbitrary units.

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**Figure 1.** Vandetanib reduced plasma nitrite levels in humans. Plasma levels of nitrates were measured in patients at baseline and after receiving vandetanib plus chemotherapy for 6 weeks. Vandetanib lowered nitrite levels after 6 weeks (**P=0.0001), suggesting that circulating levels of NO were reduced.
5-minute ischemic intervention created a significant reactive hyperemic stimulus during both study visits. Peak reactive hyperemic blood flow increased 5.8 ± 2.8-fold over basal flow at baseline and 6.8 ± 3.0-fold at 6 weeks (P = 0.02). In the whole cohort, flow-mediated vasodilation did not change significantly during the 6 weeks of treatment (12.0 ± 1.7% versus 13.8 ± 1.8%; Figure 4; P = 0.15), even when adjusted for the variation in reactive hyperemia (P = 0.26). There was no change in nitroglycerin-mediated vasodilation during treatment. To understand the mechanism of preserved flow-mediated vasodilation despite VEGF inhibition, membrane-associated eNOS protein level and VEGFR2 protein levels were assessed. Vandetanib application increased membrane eNOS protein levels 2-fold (P = 0.04; Figure 5). No changes in VEGFR2 levels were noted.

**Figure 4.** Flow-mediated and nitroglycerin-mediated vasodilation. Endothelium-dependent, flow-mediated vasodilation was preserved after 6 weeks of vandetanib therapy (12.0 ± 1.7% vs 13.8 ± 1.8%; P = 0.15). Nitroglycerin-mediated, endothelium-independent vasodilation was unchanged after 6 weeks of vandetanib treatment (22.5 ± 2.0% versus 20.0 ± 2.3%; P = 0.2).

**Discussion**

This study demonstrates that vandetanib, a VEGFR2/3, and rearranged during transfection receptor tyrosine kinase antagonist, in combination with metronomic chemotherapy, attenuates constitutive but not flow-mediated NO bioavailability in humans. Administration of this medication significantly increased mean blood pressure and decreased, in association, systemic NOx levels. These findings are bolstered by the decrease in resting conduit artery size despite the lack of change in wall shear stress and the increase in forearm vascular resistance. The mechanism of the chronic reduction in NO was tested in vitro. Vandetanib significantly reduced nitrite production and serine437 AKT phosphorylation in MS1 ECs. These analyses support the contention that vandetanib reduces phosphatidylinositol 3-kinase-AKT-mediated phosphorylation of eNOS activation sites and consequent attenuation in the constitutive production of NO. We also studied other potential mechanisms to explain this finding. Both eNOS and VEGFR2 total cellular and membrane fractions were evaluated in MS1 coronary ECs treated with vandetanib. The treated cells showed an increase in both total and membrane-associated eNOS but no change in either parameter for VEGFR2, providing more insight into the physiological effects of vandetanib.

**VEGF and NO**

The angiogenic and vasoactive effects of VEGF occur primarily via VEGFR2.30,31 Supporting this finding, the incidence of hypertension seen in clinical trials appears to correlate with the potency of the kinase inhibitors to block VEGFR2.17 VEGFR2 modulates eNOS production of NO through multiple signaling pathways. Tyrosine phosphorylation of VEGFR2 initially activates phospholipase C-γ, rapidly increasing the intracellular calcium concentration, and facilitating calmodulin-mediated eNOS dissociation from caveolin 1 and consequent NO production.32 Infusion of VEGF into patients induces immediate NO elaboration and hypotension.33 Later, VEGF activation of VEGFR2 stimulates the phosphatidylinositol 3-kinase-AKT-heat shock protein 90 pathway, which phosphorylates eNOS serine437, a positive regulator of the enzyme.32,34

Our findings of increased blood pressure, increased vascular resistance, decreased systemic NO production, and decreased basal arterial diameter are consistent with the predicted effects of a VEGFR2 inhibitor. Indeed, the significant reduction in systemic NOx production in this paired sample with VEGFR inhibition is greater than reported recently in another study of humans treated with VEGF antagonism.35 These results and our in vitro data showing that vandetanib reduces EC Akt phosphorylation and nitrite production suggest that VEGFR2 inhibition reduces constitutive eNOS-mediated NO production. Other sources of NOx are less likely to contribute to this picture, because VEGFR2 inhibition has been shown to decrease inducible NO synthase.36 Thus, our data are consistent with a mechanism of VEGFR2 inhibition disrupting the phosphatidylinositol 3-kinase-Akt heat shock protein 90 phosphorylation-dependent activation of eNOS, leading to chronically reduced NO levels and hypertension, particularly in light of other work in humans.
Receptor Tyrosine Kinase Inhibitor Specificity and Vascular Function

In contrast to our findings, in a study of the RTKI telatinib, there was an attenuation in vascular smooth muscle and possibly endothelial function.37 One explanation that may reconcile the differences in our observations with vandetanib versus telatinib is the variability of the effect of these RTKIs on phosphorylation of specific tyrosine moieties and cell types. The fact that telatinib and vandetanib produced different changes in blood pressure, vascular smooth muscle function, and endothelial function over a similar time course in intact humans makes clear that the description of an agent as a VEGFR2 inhibitor reveals only its gross function. A second variance may be the non-VEGFR–related effects. Telatinib inhibits platelet-derived growth factor receptor activity, which has shown to be an important mechanism by which vascular smooth muscle cells increase cytosolic calcium and may explain the attenuated response to nitroglycerin seen in this study.38,39 These results highlight the need for evaluation of each agent specifically.

Hypertension

Recently, several investigators have reported evidence of an association between treatment-induced hypertension and tumor responsiveness, suggesting that vascular responsiveness to therapy is a predictor of the drug’s efficacy against the cancer.40–42 This link may reflect the fact that NO mediates vascular responsiveness, as well as angiogenesis, malignant transformation, and tumorigenesis.43 These observations lead to proposals that blood pressure elevation may serve as a biomarker for efficacious VEGF signaling inhibition15 despite the observations that neither tumor expression of VEGF nor VEGFR2 nor plasma levels of VEGF have proven to be useful predictors of treatment outcome.42,44

Our study found an average increase of mean arterial pressure of 11 mm Hg. Such changes are significant and warrant clinical attention. To illustrate, the cholesteryl ester transfer protein inhibitor torcetrapib increased blood pressure by 5.4 mm Hg and was associated with a 58% increase in all-cause mortality despite marked reductions in low-density lipoprotein and increases in high-density lipoprotein.45 We surmise that vandetanib increased blood pressure by decreasing the constitutive production of NO, manifesting as a reduction in nitrite levels in our subjects. These findings are similar to other RTKIs. We cannot exclude the possibility of an increase in the production of an endogenous vasoconstrictor; however, in patients treated with the VEGFR2 inhibitor sorafenib, despite a mean increase in blood pressure of 13 mm Hg, there were no changes in catecholamines, endothelin I, urotensin II, renin, and aldosterone levels.15 Additional agent-specific mechanisms are likely present and require further study to elucidate.

Additional mechanisms of hypertension need to be considered. Vascular rarefaction has been demonstrated in response to VEGF antagonism37 and may contribute to the cause or effects of induced hypertension. Recently, Machnik et al4 demonstrated that inhibition of VEGFR3 (a described property of vandetanib) augments interstitial hypertonic volume retention, decreases eNOS expression, and increases blood pressure. Interestingly, in this experiment, inhibition of VEGF-C mediated activation of VEGFR3 was associated with a decrease in eNOS expression. Vandetanib is also an epidermal growth factor receptor antagonist and rearranged during transfection inhibitor, but blockade of these receptors has not been associated with hypertension.46 Both VEGF and eNOS contribute importantly to natriuresis,47 so the effect of renal VEGFR-2 inhibition may also mediate changes in blood pressure. Finally, the role of the metronomic therapy (methotrexate and cyclophosphamide) remains unclear. Neither is commonly associated with hypertension, but we cannot exclude any interaction. The role of these and other mechanisms need further study.

Limitations

This study would have been strengthened by inclusion of a control group; however, in the setting of this phase 1 trial in advanced breast cancer, randomization and the use of placebo were not possible. Whether the concomitant therapies, methotrexate and cyclophosphamide, contributed to vascular function remains an open question, but they have not demonstrated this tendency in past studies of subjects with rheumathal disease.48–52 Diet is an important contributor to levels of NOx. A change in diet may have participated in changing the systemic level of NOx; however, we believe the trend noted between increasing blood pressure and decreasing NOX suggests that these 2 changes were related.

Perspectives

Treatment with the VEGFR2 RTKI vandetanib in combination with metronomic chemotherapy increased blood pressure, decreased constitutive NO production, and decreased conduit artery resting diameter. In vitro, vandetanib decreased Akt phosphorylation and NO production, yet increased eNOS membrane content. Additional studies will be needed to elucidate the specific mechanisms underlying the vascular responses to different RTKIs, the effect of specific tyrosine moiety inhibition on EC signaling, and the clinical sequelae of hypertension induced by these medications.

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Disclosures

None.

References


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