

# Angiogenesis Inhibitors and Hypertension: An Emerging Issue

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Any of a number of therapeutic agents or chemical substances can induce transient or more long-lasting forms of hypertension. Drugs that cause hypertension do so by either stimulating pressor responses, increasing extracellular volume, and/or by decreasing vascular compliance. In the process, the effects of numerous anti-hypertensive therapies can be overridden.<sup>1</sup> The list of compounds capable of increasing blood pressure (BP) is quite extensive and continues to grow.<sup>2</sup> It would seem that vascular endothelial growth factor (VEGF) antagonists (or angiogenesis inhibitors) can now be added to an already lengthy list of compounds linked to the onset of a hypertensive state.<sup>3-5</sup>

Several angiogenesis inhibitors have now been implicated in the development of hypertension.<sup>3,6-11</sup> Early studies with bevacizumab offered the first clue as to the prevalence of hypertension with angiogenesis inhibitors. In the study of Hurwitz et al, 402 patients were treated with bevacizumab (5 mg/kg every 2 weeks) and hypertension was seen in 22% of cases (control population rate, 8.3%). Grade 3 hypertension (or that requiring therapy) was noted in 11% of the bevacizumab-treated cohort.<sup>8</sup> Yang et al evaluated two different doses of bevacizumab (3 and 10 mg/kg) in patients with metastatic renal cell carcinoma.<sup>3</sup> Hypertension and asymptomatic proteinuria were associated with bevacizumab therapy, particularly in the high-dose group. Among all bevacizumab-treated patients who required therapy for newly diagnosed hypertension (for whom the dates of onset could be most accurately determined), the median interval from the first dose of bevacizumab to the onset of hypertension was 131 days (range, 7 to 316). Hypertension and proteinuria uniformly decreased with the cessation of therapy; however, documentation of complete resolution of these adverse effects was not possible because of multiple confounders relating to death and commencement of other therapies.<sup>3</sup>

In a phase III trial conducted by Miller et al in metastatic breast cancer patients grade 3 hypertension was observed in 17.9% of those receiving capecitabine and bevacizumab (15 mg/kg given intravenously on day 1 of every 3-week cycle) compared to capecitabine alone.<sup>9</sup> Preinfusion systolic and diastolic BP values fell by a mean of 2.6 and 0.7 mmHg, respectively, in the capecitabine alone group, while increasing by 5.5 and 4.6 mmHg in the capecitabine and bevacizumab combination group; no relationship was observed with duration of bevacizumab therapy or pre-existing hypertension. In these studies, four patients had bevacizumab stopped as a result of hypertension. An apparent association between hypertension and proteinuria was noted in the combination

arm of this study: patients who developed proteinuria were more likely to become hypertensive (47.1% v 16.9%;  $P \leq .001$ ) than patients who did not happen to develop proteinuria.<sup>9</sup>

Several lines of reasoning would suggest a likelihood of BP decreasing initially with angiogenic growth factor therapy and increasing with angiogenesis inhibitor therapy. First, a number of studies in animals and humans have noted a drop in BP with angiogenic growth factor administration.<sup>7</sup> In the VEGF in Ischemia for Vascular Angiogenesis Trial (VIVA), both intracoronary and intravenous infusions of recombinant human VEGF were accompanied by falls in systolic BP of up to 22% at the highest doses.<sup>12</sup> Second, VEGF both enhances endothelial nitric oxide synthase (eNOS) activity and upregulates the message and protein levels of VEGF in human endothelial cells; thus, nitric oxide generation is an essential component of the response pattern to angiogenic growth factors.<sup>13</sup> Finally, angiogenic growth factors offer a strong stimulus for the construction of new capillaries and the recruitment of endothelial progenitor cells.<sup>14,15</sup> This enhancement of angiogenesis/arteriogenesis can be expected to decrease vascular resistance. It has been recognized for some time that small arteries and precapillary arterioles are critical determinants of vascular resistance and a reduction in their density—so-called capillary and arteriolar rarefaction—is observed in many animal models of hypertension.<sup>16</sup>

In this issue of the *Journal of Clinical Oncology*, Veronese et al carefully describe the BP changes observed with BAY 43-9006.<sup>17</sup> BAY 43-9006 is a novel bi-aryl urea initially developed as a specific inhibitor of C-Raf and B-Raf. Subsequent studies have shown this compound to also inhibit several important tyrosine kinases involved in tumor progression including VEGF.<sup>18-19</sup> More recently, the apoptotic potential of this compound has been described to at least, in part, relate to a down-regulation of myeloid cell leukemia-1.<sup>20</sup> These investigators have observed significant increases in BP in a large proportion of patients receiving BAY 43-9006. To this end, 12 of 20 (60%) of those studied experienced a systolic BP increase of 20 mmHg or more after 3 weeks of BAY 43-9006 at a dose of 400 mg twice daily. Further, these investigators gathered strong supporting evidence suggesting that activation of hypertension-producing neurohumoral pathways and/or overt volume expansion are not major contributing factors to BAY 43-9006-related hypertension. These studies, did on the other hand, note a rise in vascular stiffness although it could not be established whether this was a cause or an effect of the BP elevation.<sup>17</sup>

Veronese et al show quite nicely that BAY 43-0096 treated patients more likely than not will experience a rise in BP if exposed to this compound in sufficient amounts. The frequency with which BP elevations were observed in these studies is higher than that previously observed with both BAY 43-0096 and other angiogenesis inhibitors, in part, because these investigators were specifically and carefully observing for BP changes.<sup>18-19,21</sup> In other studies, no doubt the gravity of the illness, confounding hemodynamic and volume factors, and limited monitoring precluded an accurate assessment of BP changes.

What is the future with angiogenesis inhibitors? No doubt, these compounds will be important tools in the management of various malignancies. Can and should the likelihood of their increasing BP be a deterrent to their continued development? The answer is probably not. The risk-benefit ratio for any new therapy should always be carefully addressed. This is no different for angiogenesis inhibitors. If one undertakes such an exercise, it is clear that success in stabilizing or remitting solid tumor activity would strongly outweigh the presumably temporary risk of any developed hypertension.

Questions do remain, however, and should apply to the future assessment of BAY 43-9006 as well as other angiogenesis inhibitors. First, it is unclear as to the best dosing regimen (once or twice daily, on-off cycle of administration) for BAY 43-9006 to minimize the risk of developing significant hypertension while still providing a best therapy exposure; moreover, it is unclear as to which patients are most susceptible to the development of significant hypertension with BAY 43-0096 and thus in whom it should possibly be withheld. Another important consideration with angiogenesis inhibitors is the way in which BP change is identified. Future descriptions of hypertension in patients treated with angiogenesis inhibitors should endeavor to report absolute BP and/or 24-hour ambulatory BP monitoring values compared to baseline readings. Reliance on toxicity grading systems standardizes the description of tumor therapy-related side effects, but lacks the descriptive precision provided by absolute value changes of a physiologic measure such as BP.

A final consideration is whether there are specific antihypertensive drug therapies better suited for BAY 43-9006-related hypertension. BAY undergoes some metabolism by the cytochrome P450 system, especially by CYP3A4, and therefore is a candidate for drug-drug interactions involving this isozyme. For that reason, until more formal studies are undertaken it should be used cautiously with antihypertensive compounds, such as verapamil and diltiazem that are inhibitors of CYP3A4. Dihydropyridine calcium channel blockers do not inhibit CYP3A4, although they are substrates for CYP3A4; thus, they would be preferred agents if a calcium-channel blocker is selected for antihypertensive therapy. Alternatively, compounds that improve microcirculatory structure and function, such as ACE inhibitors and angiotensin-receptor blockers, can be con-

sidered for empiric use in patients with angiogenesis inhibitor-related hypertension.<sup>22</sup>

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