Hypertension Secondary to Anti-angiogenic Therapy: Experience with Bevacizumab

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Abstract. *Background: Hypertension (HT) is a common complication of anti-angiogenic therapy. Its incidence, treatment and complications are undefined. Patients and Methods: Retrospective review of patients treated with bevacizumab (BV) from 2003-5. Common toxicity criteria (CTC) for adverse events version 3.0 were used. Results: Fifty-five out of the 154 patients treated with BV (35%) experienced HT. Eleven (20%) developed a new onset HT and 44 (80%) experienced an exacerbation of pre-existing HT. HT developed after a median of 11 weeks at a median BV dose of 10 mg/kg. HT severity was grade 1 (n=1), grade 2 (n=29) or grade 3 (n=22); 3 experienced hypertensive complications. HT was controlled in 47 (85%); BV was discontinued in 3. The angiotensin-converting enzyme inhibitor (ACE-I), quinapril was commonly used and resulted in better HT control than ACE-II, calcium channel or beta antagonists. Conclusion: HT associated with bevacizumab therapy is a manageable toxicity with the use of ACE-I.*

Angiogenesis is a biological process necessary for the progression from benign to malignant tumors, growth and metastasis of malignant cells. The most important angiogenic factors are vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and hepatocyte growth factor (1). Increased angiogenesis occurs when the growth promoting factors dominate in conditions such as cancer, rheumatoid arthritis, diabetes and cardiovascular diseases, and anti-angiogenic treatment restrains tumor growth and metastasis in pre-clinical models.

Several anti-angiogenic agents are currently under evaluation in clinical trials (Table I). Their mechanisms of action differ (Figure 1) and they are being investigated as single agents or in combination with cytotoxic chemotherapy and radiotherapy so as to achieve synergistic or additive effects. Hypertension is a consistent toxicity of patients treated with anti-angiogenic agents and the incidence of this complication is likely to increase with increasing use of anti-angiogenic therapy. No current guidelines exist regarding the management of hypertension in this situation. The widest experience with anti-angiogenic therapy is with bevacizumab (BV), a recombinant humanized monoclonal antibody. BV binds to and inhibits the activity of VEGF which results in failure of interaction between VEGF and its receptor on the vascular endothelial cells. This in turn inhibits the proliferation of endothelial cells and new blood vessel formation. BV is approved for the treatment of metastatic colorectal cancer (2).

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Patients and Methods

We conducted a retrospective review of patients treated with BV at Roswell Park Cancer Institute to determine the incidence, treatment and complications of BV-induced hypertension. Medical records of patients treated with BV for colon cancer, pancreatic cancer, small cell lung cancer and renal cell carcinoma from Oct. 2003 to Sep. 2005 were reviewed. Medical records were reviewed for demographic information, types of cancers (diagnoses), chemotherapy type, BV dose, baseline and highest blood pressure, antihypertensive drugs used, serum creatinine and proteinuria. Blood pressure recorded at pre-study screening was considered as baseline and compared with the blood pressure readings during following visits. Grading of hypertension was as per NCI common toxicity criteria for adverse events version 3.0 (CTCAEv3.0). Institutional Review Board consent was obtained for this review.

Results

During the study period, 154 patients with colon, pancreatic, small cell lung and renal cell carcinoma were treated with BV with chemotherapy. Fifty-five (35%) patients (44 with colon, 8 with pancreatic cancer, 2 with renal cell and 1 with small cell lung carcinoma) experienced hypertension. Thirty-three were men and 22 were women, the median age was 62

Table I. *Classification of anit-angiogenic agents: targets.*

Target	Mechanism of action	Agent
VEGF	Binds and inhibits VEGF activity	Bevacizumab
	Inhibits VEGF gene transcription	Interferon-α
	Blocks binding of VEGF with its receptors	AE 941 (Neovastat)
	Monoclonal antibody to VEFG	Anti-VEGF Ab
	Blocks VEGF	VEGF-Trap
VEGF receptor (VEGFR)	Blocks VEGFR-1 and VEGFR2 tyrosine kinase signaling in endothelial cells	SU011248 (Sunitinib)
	Blocks VEGFR, PDGFR and c-kit protein tyrosine kinase signaling	PTK787/ZK2284
	Blocks VEGF, bFGF & PDGF receptor signaling	SU6668
	VEGFR-2 tyrosine kinase inhibitor	SU5416 (Semaxanib)
	Blocks VEGFR, PDGFR and c-kit protein tyrosine kinase signaling	AG-013736
	Inhibits VEGFR-2	BAY 43-9006
	VEGFR and EGFR tyrosine kinase inhibitor	ZD6474
Matrix metalloproteinase (MMP)	Synthetic MMP inhibitor	BAY12-9566, BMS 275291, COL-3, CGS-27023, Marimastat, AG3340 AE 941 (Neovastat)
	Blocks binding of growth factor to its receptor	Suramin
Integrin	Small molecule blocker of integrin antagonist	EMD121974
	Antibody to integrin on endothelial surface	Vitaxin
Endothelial cells	Inhibits endothelial proliferation	Endostatin
	Inhibits endothelial proliferation	2-ME (2-methoxyestradiol) CC-5013 (Thalidomide analog)
	Apoptosis in proliferating endothelium	Combretastatin A4 phosphate
	Protein kinase C-beta inhibitor	LY 317615 (Enzastaurin)
	Unknown	Thalidomide
Non-specific	Induces IFN-gamma and IP-10	Interleukin-12
	Inhibitor of calcium influx	CAI

Source: National Cancer Institute Database. Angiogenesis foundation clinical trials database (http://www.angio.org).

years (range=33-84 years). BV was given in combination with 5-fluorouracil, oxaliplatin and leucovorin (FOLFOX) (n=38), 5-fluorouracil, irinotecan and leucovorin (FOLFIRI) (n=5), gemcitabine and capecitabine (n=8) or interferon (n=4). The median dose of BV was 10 mg/kg (range=5-15 mg/kg). Eleven developed new-onset hypertension, 44 experienced exacerbation of pre-existing hypertension. Hypertension occurred after a median of 11 weeks following BV therapy (range=3-33 weeks). Patients with history of hypertension (n=44) were normotensive at pre-study screening. Grade 1 hypertension was observed in 1 patient; grade 2 in 29 patients; and grade 3 in 22 patients. BV was discontinued in 3 others due to hypertensive complications: one patient each suffered from tightness in chest, transient ischemic attack (TIA) and accelerated hypertension. Hypertension was controlled [blood pressure (BP) ≤140/90)] in 47 (85%) and uncontrolled (BP >140/90) in 8 patients. Anti-hypertensive agents used were ACE-I, beta-blockers, calcium channel blockers, ACE II receptor antagonists and diuretics (Table II). Quinapril was the most commonly used ACE-I either alone or in combination at a median dose of 20 mg daily (range 5-40 mg). Metoprolol was the most frequently used beta-blocker at a range of 25 mg-400 mg daily. Renal function abnormalities occurred in 13 patients (creatinine 1.3-3.3) and proteinuria occurred in seven patients. Quinapril was an effective agent in this review (Table II). Due to the limited sample size, statistical evaluation was not possible.

Table II. *Management of BV-induced hypertension: retrospective review.*

Anti-hypertensive agents	No. of patients	Hypertension controlled	Hypertension uncontrolled
ACE-I	16	16	0
β-Blocker	3	3	0
Ca^{++} channel blocker	6	6	0
Diuretics	1	1	0
ACE-I + β-Blocker	6	4	2
ACE-I + Ca^{++} channel blocker	5	5	0
ACE-I + Diuretics	4	4	0
Angiotensin II receptor antagonists in combinations	5	2	3
Other combinations	5	2	3
No anti-hypertensive agent	4	4	-
Total	55	47 (85%)	08 (15%)

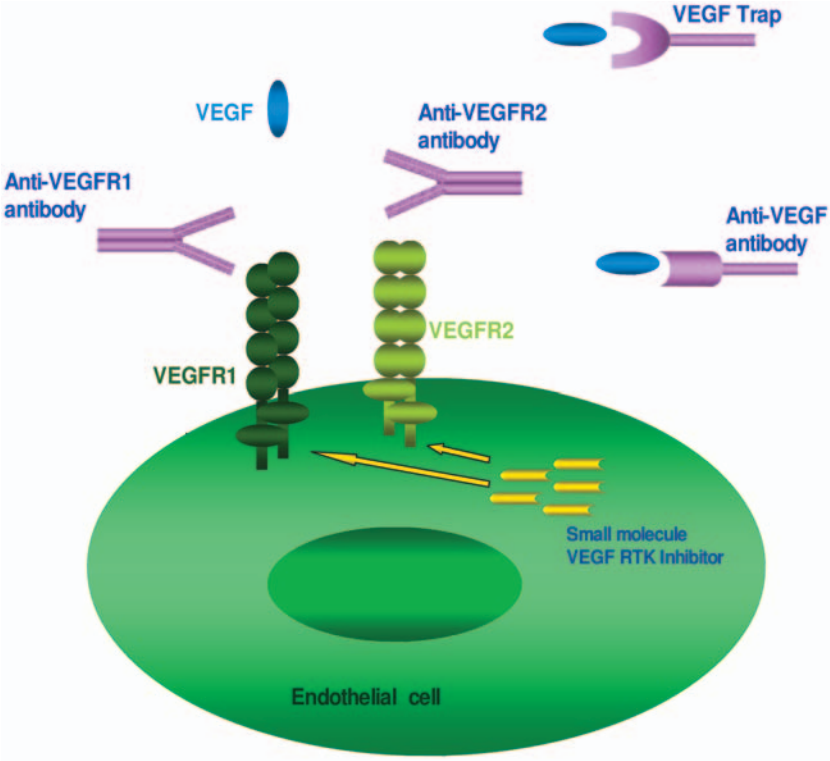

Figure 1. *An anti-VEGF monoclonal antibody binds to VEGF and prevents its interaction with VEGFR-1 (Flt-1) and VEGFR-2 (KDR/flk-1) on the endothelial cell surface and inhibits downstream signaling events. Anti-VEGFR1 and -R2 antibodies interfere with receptor-ligand binding and signaling. VEGF-Trap, extracellular domains of VEGFR1 and VEGFR2 fused to Fc portion of human IgG, binds to the VEGF and neutralizes it.*

Discussion

The mechanism of anti-angiogenic therapy-related hypertension is not fully understood but is believed to be nitric oxide (NO)-mediated (3). Pre-clinical *in vivo* studies have demonstrated that VEGF increases endothelial NO synthase (eNOS) expression by activation of the KDR receptor tyrosine kinase and protein kinase C signaling pathway (4). It is hypothesized that inhibition of VEGF decreases eNOS expression and the consequent decrease in NO leads to an increase in mean arterial pressure (Figure 2). NO produced in the vasculature by eNOS plays a vital role in controlling mean arterial pressure through the following mechanisms: i) inhibition of platelet and leukocyte aggregation, ii) inhibition of vascular smooth muscle cell proliferation and reduced vascular resistance iii) vasodilatation by diffusion across the endothelium into neighboring smooth muscle and iv) increased urinary sodium excretion (5). Thus NO is critical for maintaining plasma volume and blood pressure. Anti-angiogenic therapy induced hypertension may also be the consequence of increased microvascular resistance and vascular regression resulting from endothelial cell apoptosis (6). Patients with metastatic colorectal cancer, renal cell carcinoma, breast and lung cancer treated with BV at dose levels of 5-15 mg/kg in clinical trials reported an incidence of 11 to 20% of Grade III-IV hypertension (Table III). AG-013736, SU11248 (Sunitinib), BAY 43-9006 (Sorafenib), PTK787/ZK 222584 (Vatalinib) and ZD6474 (Zactima) are other anti-angiogenic agents studied in clinical trials that have shown promising results. Hypertension was observed as a consistent side-effect of these agents (Table IV).

In our retrospective study, 35% patients experienced hypertension secondary to BV therapy. Similar figures have been quoted by Yang *et al.* (7). Higher doses of single agent or the addition of more than one antihypertensive agent were required to normalize the blood pressure. Etiology of BV-induced hypertension is multifactorial therefore a combination of therapies may be necessary. Our findings were consistent with other reports in the literature. In our study, ACE-I (quinapril) was the most frequently used and effective antihypertensive agent. However, calcium-channel blockers, ACE-I and diuretics were the oral antihypertensive agents used in the colon cancer (8) and carcinoid studies (9) while diuretics or beta-blockers were used in the sorafenib and vatalinib studies (10, 11). *In vivo* studies have shown that ACE-I has the potential to reverse the microcirculatory changes (6). In

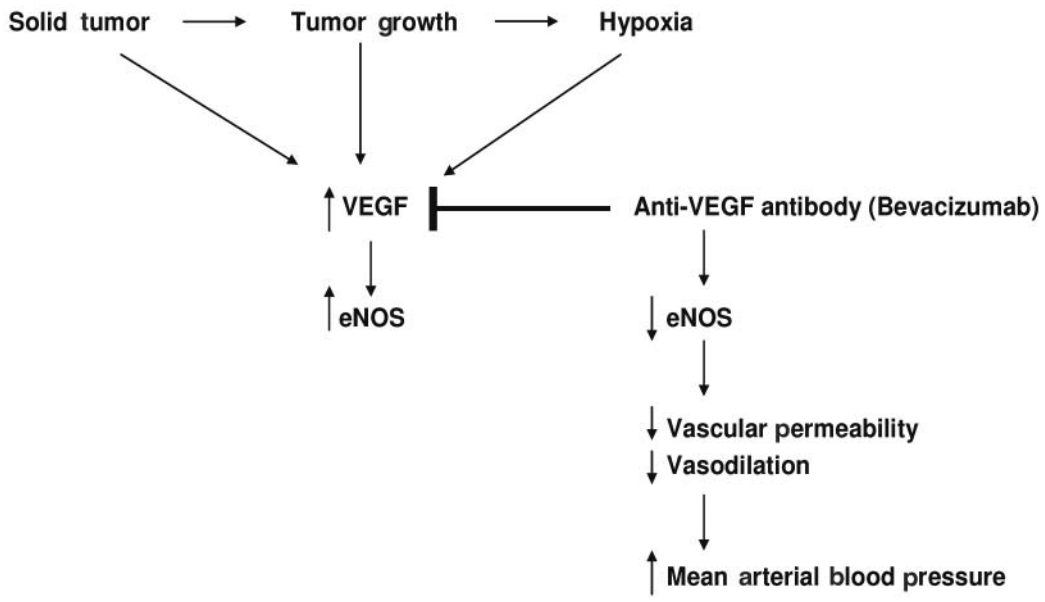

Figure 2. *Mechanisms of hypertension secondary to anti-angiogenic therapy.*

Table III. *Incidence of bevacizumab induced hypertension: clinical studies.*

No.	Pathological disease	Dose of drug	Incidence of hypertension, grade III/IV	Reference
1	Metastatic colorectal cancer - BV/FU/LV	5 mg/kg	16%	Kabbinavar *et al.* (13;14)
2	Metastatic colorectal cancer - BV/Irinotecan/FU/LV	5 mg/kg	11%	Hurwitz H *et al.* (8)
3	Metastatic colorectal cancer - BV/FOLFIRI	5 mg/kg	15%	Hoff PM *et al.* (15)
4	Advanced pancreatic cancer -BV/Capecitabine/Gemcitabine	15 mg/kg	11.7%	Javle MM *et al.* (16)
5	Metastatic pancreatic cancer - BV/Gemcitabine	10 mg/kg	19%	Friberg G *et al.* (3)
6	Metastatic renal cell carcinoma - BV	10 mg/kg	20.5%	Yang JC *et al.* (7)
7	Metastatic non small cell lung cancer - BV/Carboplatin/Paclitaxel	15 mg/kg	5.7%	Johnson DH *et al.* (17)
8	Metastatic breast cancer - BV/Capecitabine	15 mg/kg	17.9%	Miller KD *et al.* (18)

Abbreviations: FU= 5-fluorouracil; LV= leucovorin; FOLFIRI= 5-FU, LV and irinotecan.

Table IV. *Hypertension associated with small molecule tyrosine kinase inhibitors of VEGFR.*

No.	Diseases	Anti-angiogenic agent	Incidence of hypertension, grade III/IV	Reference
1	Advanced solid tumors	AG-013736	30%	Rugo HS *et al.* (19)
2	Metastatic renal cell carcinoma	AG-013736	12%	Rini B *et al.* (20)
3	GIST	SU-011248 (Sunitinib)	7%	George *et al.* (21)
4	Metastatic renal cell carcinoma	SU-011248 (Sunitinib)	5%	Motzer RJ *et al.* (22)
5	Metastatic breast cancer	SU-011248 (Sunitinib)	14%	Miller *et al.* (23)
6	Acute myeloid leukemia	SU-011248 (Sunitinib)	6.25%	Fiedler W *et al.* (24)
7	Advanced renal cell carcinoma	BAY 43-9006 (Sorafenib)	11%	Escudier B *et al.* (25)
8	Advanced cancers	PTK787/ZK222584	9.3%	Thomas AL *et al.* (11)
9	Medullary thyroid cancer	ZD6474	12%	Wells S (26)
10	Metastatic colorectal cancer	SU5416 (Semaxinib)	16.66%	Lockhart AC *et al.* (27)

addition, ACE-I decrease the catabolism of bradykinin and increases release of vasodilator NO from the endothelium. A majority of the patients treated with ACE-II receptor antagonists, either as a single agent or in combination with other antihypertensive agents, did not become normotensive in our study. ACE-II increases blood pressure directly by vasoconstriction or through an aldosterone effect. The ACE-II receptor antagonist used was losartan which, unlike ACE-I lacks the vasodilator effect of NO (12). In our retrospective analysis, we noted that HT as a complication of BV therapy was most likely to occur in patients with pre-existing HT; this finding was also reported in the carcinoid study. Therefore, patients with pre-existing HT require close monitoring while on therapy. Hurwitz *et al.* (8) and Mares *et al.* (9) noted that control of hypertension occurred in most cases with routine, oral, anti-hypertensive agents. In our study, the doses of anti-hypertensive agents, ACE-I in particular, were quite high (median dose=20 mg of quinapril). Higher starting doses are required to manage hypertension in this situation, as a starting dose of 5 mg was ineffective. In summary, hypertension associated with anti-angiogenic therapy is a manageable toxicity that can be controlled with ACE-I.

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