

Case Studies in Hypertension

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Hypertension Complicating Cancer Chemotherapy

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Case 1: A 64-year-old woman presented with Rectal carcinoma in November 1998 and underwent a low anterior resection revealing five positive lymph nodes. A computed tomography (CT)-guided biopsy of one of two liver lesions showed metastatic disease. Initial chemotherapy with two courses of a 5-fluorouracil/leucovorin regimen resulted in resolution of the liver lesions. In February 2001, new hepatic lesions appeared on CT scan and the patient underwent 5-fluorouracil/leucovorin/cisplatin therapy and two radiofrequency ablations. Oxaliplatin and high-dose capecitabine were initiated in May 2003 with some improvement in the liver masses as well as resolution of several <1 cm irregular densities that had appeared in both upper lobes of the lungs. The patient underwent laparotomy with intraoperative radiofrequency ablation of two new liver lesions in September 2003.

Enlargement of a liver lesion led to initiation of capecitabine/bevacizumab in April 2004 and the new development of hypertension in May 2004. Over the prior year, blood pressure (BP) had been 132–146/80–90 mm Hg, and May to December 2004 BPs were 181/88 mm Hg, 161/86 mm Hg, 174/91 mm Hg, 189/85 mm Hg, and 186/113 mm Hg. The patient did not like the “weakness” attributed to lisinopril/hydrochlorothiazide 10/12.5 mg, and stopped the combination drug, with a follow-up BP of 182/94 mm Hg. Discontinuation of bevacizumab led to BPs of 138/84 mm Hg and 142/86 mm Hg. She underwent additional radiofrequency ablations of her hepatic metastases and had good functional status in March 2006.

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Case 2: A 60-year-old woman was diagnosed with stage T2 N1, estrogen receptor positive, human epidermal growth factor receptor 2 negative, right breast cancer in September 1998. She had a modified mastectomy and four cycles of doxorubicin/cyclophosphamide/tamoxifen. In January 2002, metastases to the right axillary and right supraclavicular lymph nodes were treated with radiation therapy followed by anastrozole/docetaxel/capecitabine. Six courses were completed in September 2002; however, a CT study revealed the new development of four hepatic lesions, all of which were <1 cm, and a right pleural effusion. Docetaxel and capecitabine were restarted, but neutropenia led to cessation of the docetaxel; the capecitabine dose was increased to 1750 mg/m². The pleural effusion resolved, but the hepatic lesions increased slightly, leading to the addition of vinorelbine to capecitabine 1750 mg/m².

Five bilateral small lung nodules appeared, and the hepatic lesions increased in size to a maximum of 1.8 cm in the left lobe. Chemotherapy was changed to doxorubicin at 40 mg/m² and decreased to 30 mg/m² due to grade 3 mucositis. Cancer progression was evidenced by a right pleural effusion and new hepatic lesions. Exemestane was initiated in June 2004, but because of progression in the liver lesions, this was discontinued and docetaxel/gemcitabine therapy was initiated. Multiple liver lesions stabilized, but an allergic reaction led to discontinuation of docetaxel.

Bevacizumab/paclitaxel chemotherapy was then initiated in January 2006. BPs, which had been 118–132/68–78 mm Hg, increased to 220/110 mm Hg and 180/110 mm Hg 2 weeks later, and the patient reported “not feeling well” when her BP was elevated. Atenolol 25 mg q.d. was started but stopped because of cough requiring an albuterol inhaler. Bevacizumab was discontinued, and a follow-up BP a month later was 113/72 mm Hg. In March 2006, the patient was feeling well on capecitabine alone.



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DISCUSSION

These cases illustrate the array of chemotherapeutic agents and the possibility of prolonged survival for patients with metastatic cancer. The patient in case 1 presented here is an 8-year survivor of metastatic rectal carcinoma. These prolonged survivals indicate that oncologists, as well as the primary care physicians who follow middle-aged and elderly cancer patients, should be alert to preventing cardiovascular diseases such as hypertension. Hypertension is the most frequent comorbid condition found in cancer registry patients.¹

Of interest is the recent discovery that certain chemotherapy agents, particularly monoclonal antibodies that target and inhibit vascular endothelial growth factor (VEGF), are associated with drug-induced hypertension. Antiangiogenesis agents have attracted attention because tumor-induced angiogenesis is associated with tumor growth, invasion, and metastasis.² VEGF is a heparin-binding glycoprotein with high affinity for endothelial cells and a prime regulator of angiogenesis, with increased expression in tumor cells. Its up-regulation has been shown to be a poor prognostic indicator in the majority of human tumors.³ Stimulants of VEGF production in tumor cells include hypoxia, hypoglycemia, and oncogenes such as ras, or inactivation of tumor suppressor genes such as p53 and the von Hippel-Lindau gene.² For the most part, VEGF production is controlled by hypoxia-inducible factor, and production increases significantly in an environment with low oxygen tension.⁴ VEGF also has an antiapoptotic role for endothelial cells in newly formed blood vessels. Vasculature supporting tumor growth is irregular and chaotic, limiting the delivery of chemotherapeutic agents. Anti-VEGF drugs help to remodel this chaotic vasculature and improve the delivery of other chemotherapeutic agents.⁵ For this reason, there is an enhanced antitumor effect with coadministration of anti-VEGF monoclonal antibodies and chemotherapy compared with these agents given independently.² In February 2004, bevacizumab, with biologic activity against all of the VEGF isoforms, was the first monoclonal antibody angiogenesis inhibitor approved by the US Food and Drug Administration.

Both cases presented here involve new-onset hypertension closely associated with the initiation of bevacizumab; this resolved when the drug was discontinued. Other angiogenesis inhibitors associated with hypertension include VEGF-TrapR1R2 and sunitinib malate, as well as sorafenib, erlotinib, and vatalanib.^{6,7} An increased incidence

Table I. Common Terminology for Adverse Events (v 2.0) Grading of Hypertension in Cancer Trials⁸

GRADE	HYPERTENSIVE ADVERSE EVENT
0	None
1	Asymptomatic, transient (≤ 24 h) increase by >20 mm Hg (diastolic) or to $>150/100$ mm Hg if previously within normal limits; not requiring treatment
2	Recurrent, persistent, or symptomatic increase by >20 mm Hg (diastolic) or to $>150/100$ mm Hg if previously within normal limits; monotherapy may be indicated
3	Requiring therapy or more intensive therapy than previously
4	Hypertensive crisis

of hypertension (see Table I for classification) has been noted in phase 2 and 3 bevacizumab trials in the treatment of metastatic colorectal, metastatic breast, metastatic renal carcinoma, and non-small-cell lung cancers.

At the usually recommended bevacizumab dose of 10 mg/kg, the need for antihypertensive drug therapy occurs in 10%–20% of patients. Table II lists the frequency of hypertension reported in bevacizumab trials that had control groups. The level of hypertension is primarily grade 3, which, according to the National Cancer Institute (NCI) adverse event reporting nomenclature (Table I) indicates the use of antihypertensive drugs. There have been no reported occurrences of grade 4 hypertension (hypertensive crisis). Kabbivar et al.⁹ noted that almost half of the patients developing hypertension on bevacizumab had a history of elevated BP, and that the incidence of hypertension was dose related. At 5 mg/kg, hypertension occurred in 11% of patients, increasing to 28% at a dose of 10 mg/kg.⁹ According to the Avastin package insert (2004, Genentech, Inc., South San Francisco, CA), the incidence of hypertension using bevacizumab with 5-fluorouracil regimens ranges from 60% to 67%, compared with 43% in control groups receiving 5-fluorouracil regimens without bevacizumab.¹⁰ The patient presented in case 1 herein probably had stage 1 hypertension before developing a sustained hypertensive response to bevacizumab.

The mechanism of action by which bevacizumab causes hypertension is uncertain. However, VEGF is a stimulator of NO, and the inhibition of VEGF may cause increased systemic vascular resistance.^{11,12} VEGF may also have an effect on receptors associated with angiotensin I and angiotensin II.¹² The mechanism of hypertension caused by the antiangiogenesis factor BAY 43–9006 was investigated in patients who sustained a systolic BP elevation of

Table II. Incidence of Hypertension With Bevacizumab in Trials With a Control Group

TRIAL	Dx	N	REGIMEN	HYPERTENSION (%)	
				ALL GRADES	GRADE 3
Hurwitz ⁵	MCRC	397	Control	8.3	2.3
		393	Control + B 5	22.4	8.3
Kabbinavar ⁹	MCRC	36	Control	3	0
		35	Control + B 5	11	3
		33	Control + B 10	28	8
Yang ¹⁶	MRC	40	Control	2.5	0
		37	Control + B 3	2.7	0
		39	Control + B 10	35.9	20.5
Johnson ¹⁷	NSCL	32	Control	3.1	3.1
		32	Control + B 7.5	15.6	0
		34	Control + B 15	17.6	5.9
Hurwitz ²⁰	MCRC	98	Control	14.3	3.1
		109	Control + B 5	33.9	18.3
Kabbinavar ²¹	MCRC	105	Control	4.8	2.9
		104	Control + B 5	32	16
Miller ²²	MBC	215	Control	2.4	0.5
		229	Control + B 15	33.5	17.9

Dx=diagnosis; MCRC=metastatic colorectal cancer; B=bevacizumab (mg/kg); MRC=metastatic renal carcinoma; NSCL=non-small-cell lung cancer, locally advanced or metastatic; MBC=metastatic breast cancer

≥20 mm Hg 3 weeks after factor initiation. Pulse wave velocities and aortic augmentation indices were increased, indicating increased vascular stiffness.¹³ Infusions of recombinant VEGF in humans and animals have a hypotensive effect.¹² Proteinuria is another adverse effect of the VEGF inhibitors. The incidence of proteinuria in the bevacizumab trials for colorectal cancer has been reported as 22.8%–38%, compared with an incidence of 11.4%–21.7% in control groups treated with chemotherapy alone.¹¹ Regular dipstick urinalyses should be done and urinary protein quantitated if positive. It is recommended that bevacizumab be interrupted if proteinuria (≥2 g/24 h) occurs, and discontinued in the rare occurrence of nephrotic syndrome.¹¹ A study suggesting that preeclampsia, characterized by the development of hypertension and proteinuria in pregnancy, results from placental production of a soluble VEGF isoform led George and Kaelin¹⁴ to hypothesize that hypertension and proteinuria might be surrogate markers for VEGF inhibition and, therefore, drug activity. The largest bevacizumab trial to date reported hypertension and proteinuria as the most common adverse events.⁵

Drug-induced hypertension related to bevacizumab is responsive to standard antihypertensive drug therapy. Hurwitz et al.⁵ reported that all of the hypertension occurring in the phase 1 and 2 trials in metastatic colorectal cancer patients was readily

responsive to standard oral antihypertensive agents including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers. There were no hypertensive crises, deaths, or bevacizumab discontinuations. Another angiogenesis inhibitor drug study reported successful hypertension treatment using diuretics and/or β blockers.¹⁵ The two patients whose cases are presented here had their bevacizumab therapy stopped because of intolerance to the antihypertensive drugs that were attempted, with resolution of hypertension.

Drug-related hypertension can occur with drug initiation and within the first year of treatment. Yang et al.¹⁶ reported that the median interval from the first dose of bevacizumab to the onset of hypertension was 131 days, with a range of 7–316 days. Johnson et al.¹⁷ reported that the greatest increases in systolic pressure ranged 7–14 mm Hg on Day 42, and that seven out of 12 patients who had a significant systolic pressure increase had pre-existing hypertension.

Bevacizumab is administered by IV infusion at 14-day intervals. BP monitoring is recommended at least every 2–3 weeks, and for as long as 3 months following completion of therapy¹⁰ because of its long half-life of approximately 20 days (range, 11–50 days). Bevacizumab should not be initiated in the setting of uncontrolled hypertension.¹¹ If a patient with hypertension on bevacizumab has sustained proteinuria >300 mg/24 h, current

recommendations are to use an ACE inhibitor or an angiotensin receptor blocker.¹⁸ In these cases, multi-drug antihypertensive therapy will almost always be necessary to achieve the goal BP, <130/80 mm Hg.

Prolonged cancer survivals for patients with metastatic cancer are becoming more common, and there is an increasing role for newer monoclonal antibody treatments, including the VEGF inhibitors. We should not neglect the detection and treatment of hypertension in patients receiving ongoing chemotherapy. The National Health and Nutrition Examination Survey (NHANES) showed that more than 50% of individuals in the United States over age 55 have hypertension.¹⁹ Therefore, hypertension seen in cancer patients will predominantly be essential in etiology, rather than being solely related to VEGF inhibitors.

These drugs are very expensive. One gram of bevacizumab, a single 15-mg/kg dose for a 70-kg individual, given once every 14 days costs approximately \$6800. Antihypertensive therapy, which can cost as little as \$70/yr for a generic combination drug, will help to prevent a stroke or cardiovascular event in many longer-surviving cancer patients.

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