

Bevacizumab-related toxicities: association of hypertension and proteinuria

Cynthia L. Martel, MD, PhD,¹ Cary A. Presant, MD, FACP,² Ben Ebrahimi, MD,² Gargi Upadhyaya, MD,² Mayank Vakil, MD,² Christina Yeon, MD,² Linda D. Bosserman, MD, FACP,² and Richard Horns, MD²

¹ City of Hope Medical Group, Pasadena, CA, and ² Wilshire Oncology Medical Group, La Verne, CA

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has demonstrated clinical activity in colorectal, renal, breast, and lung cancers. It has been associated with hypertension, proteinuria, and other unique toxicities. We examined the incidence and management of bevacizumab-related toxicities since the US Food and Drug Administration approved the drug in 2004. Forty consecutive patients receiving bevacizumab were evaluated. New or worsened hypertension developed in 12 patients (30%), and proteinuria occurred in 9 patients (23%), 6 of whom also developed hypertension. Bevacizumab was stopped in two patients due to proteinuria and was temporarily or permanently withheld in four patients due to other toxicities (perforated nasal septum, fissure, gastrointestinal bleeding, and chest pain). The total incidence of toxicity was 47.5%. There was a statistically significant association between hypertension and proteinuria ($P = 0.006$). Fifteen percent of patients developed a syndrome of proteinuria and hypertension, which we have termed BETS (bevacizumab toxicity syndrome). Since hypertension and proteinuria are statistically associated, we suggest that optimal management of BETS should include early intervention with antihypertensive drugs protective against proteinuria and nephropathy, such as angiotensin-converting enzyme inhibitors. Prompt intervention before hypertension or proteinuria becomes severe may allow prolonged therapy with bevacizumab and, therefore, improved clinical outcomes.

Bevacizumab (Avastin) is a humanized recombinant monoclonal antibody directed against vascular endothelial growth factor (VEGF)¹ that inhibits VEGF-induced angiogenesis and tumor growth and may also reduce intratumoral pressure. Bevacizumab was approved by the US Food and Drug Administration (FDA) in 2004 for the first-line treatment of patients with metastatic carcinoma of the colon and rectum, in combination with intravenous fluorouracil (5-FU)-based chemotherapy. In a pivotal phase III trial, bevacizumab was shown to improve response rates and to prolong progression-free and overall survival in patients with metastatic colorectal cancer when added to first-line therapy with irinotecan (Camptosar) and bolus 5-FU with leucovorin.² Bevacizumab has also been shown to have clinical activity in renal cell carcinoma,³ breast carcinoma,⁴ and nonsquamous non-small cell lung carcinoma.⁵

Bevacizumab is generally well tolerated, but its use is associated with some unique toxicities, including an increased incidence of hypertension^{2,3,6,7}; rates of hypertension of up to 36%, with rates of grade 3 hypertension up to 16%, have been reported. Bevacizumab is also associated with proteinuria; an absolute increase in the incidence of proteinuria of 27% over baseline, with a rate of grade 3 proteinuria of 1%, has been reported.^{2,3,6,7} Various other toxicities are rare, including epistaxis and other bleeding events, thrombosis, and gastrointestinal perforation.^{2,3}

Since the frequency of toxicity occurring during clinical use of drugs (in patients who often have many comorbidities) is sometimes higher than that reported in clinical trials, we investigated the incidence and management of hypertension, proteinuria, and other toxicities in a consecutive series of patients treated with bevacizumab since its approval by the FDA through April 2005 in six oncology centers.

Since the frequency of toxicity occurring during clinical use of drugs (in patients who often have many comorbidities) is sometimes higher than that reported in clinical trials, we investigated the incidence and management of hypertension, proteinuria, and other toxicities in a consecutive series of patients treated with bevacizumab since its approval by the FDA through April 2005 in six oncology centers.

Methods

A retrospective multicenter observational study was performed at six community oncology centers in

Manuscript received October 11, 2005; accepted January 4, 2006.

Correspondence to: Cary A. Presant, MD, FACP, Wilshire Oncology Medical Group, 1250 South Sunset, West Covina, CA 91790; telephone: 626-856-5858; fax: 626-856-5853; e-mail: cary.presant@womgi.com.

Commun Oncol 2006;3:90-93 © 2006 Elsevier Inc. All rights reserved.

southern California. Medical records of all patients treated with bevacizumab from its approval by the FDA in 2004 through April 2005 were reviewed. Data collected included the patient's diagnosis dates of therapy with bevacizumab, best response to therapy, comorbidities, and the incidence of hypertension, proteinuria, and other toxicities. Information regarding administration of bevacizumab and chemotherapeutic agents, as well as vital signs, toxicities, and response to chemotherapy, was available through a centralized common electronic medical record utilized by all centers. Additional information on patient characteristics, as well as toxicities and response to therapy, was obtained from chart review and communication with treating physicians.

Toxicities likely to be related to bevacizumab were evaluated. Toxicities known or highly suspected to be due to concomitant chemotherapy (eg, neutropenia) were not analyzed. The incidence of hypertension was assessed by the National Cancer Institute–Common Toxicity Criteria (NCI–CTC) version 3.0. Proteinuria was defined as any elevation of urinary protein measured by dipstick and/or 24-hour urine collection.

Statistical analysis was performed by the Fisher's exact test using the Pearson's chi-square calculation.

Results

A total of 40 patients received bevacizumab. The majority of patients (33) had adenocarcinoma of the colon or rectum, 2 had renal cell carcinoma, 2 had carcinoma likely originating from the appendix, and 1 each had small cell carcinoma of the rectum, adenocarcinoma of the anus, and squamous cell carcinoma of the anus. None of the patients was treated on a clinical trial.

All patients underwent blood pressure measurement prior to the start of therapy with bevacizumab and prior to each administration of the drug. Twelve patients (30%) experienced hypertension of any degree that was new or worsened using NCI–CTC version

3.0 criteria (Table 1). Four of these patients had pre-existing hypertension. In three patients, hypertension was managed with an increased dose of the antihypertensives already being used or the addition of a new antihypertensive. One patient with pre-existing hypertension developed grade 1 hypertension, which was not treated.

Eight patients developed de novo hypertension. One patient with grade 1 de novo hypertension and one patient with grade 2 de novo hypertension were treated with antihypertensives. The remaining six patients all had grade 1 hypertension, which was not treated. The incidence of hypertension was not associated with the duration of bevacizumab therapy. No patient had to discontinue bevacizumab therapy due to hypertension.

The protocol for monitoring of proteinuria varied among physicians. Five patients received no prospective monitoring for proteinuria. Of the remaining patients, most underwent routine monitoring for proteinuria by dipstick before every administration of bevacizumab. If warranted by new or worsening proteinuria as noted on dipstick, some patients underwent a 24-hour urine protein collection at baseline and during therapy. Nine patients (23%) developed proteinuria of any degree by dipstick or 24-hour urine collection (Table 1). Five patients had trace or +1 protein on dipstick; four patients had evidence of proteinuria on 24-hour urine collection (280–2,537 mg/day).

Two patients discontinued bevacizumab due to proteinuria. One patient, who had proteinuria of 268 mg/24 hours at baseline, developed worsening of proteinuria to 2,430 mg/24 hours after 92 days of therapy. This patient had a history of diabetes, hypertension, and coronary artery disease, had undergone nephrectomy, and was being treated for renal cell carcinoma with single-agent bevacizumab. He attained complete remission on therapy. Two months

after bevacizumab was stopped, his proteinuria had decreased to 1,269 mg/24 hours, and therapy with bevacizumab was resumed. However, after two doses, another 24-hour urine collection demonstrated worsening of proteinuria to 1,953 mg, and bevacizumab was again discontinued. In addition, this patient developed grade 3 hypertension during treatment, which was controlled with adjustment of antihypertensives.

Another patient, who had rectal cancer and a history of diabetes and hypertension, had proteinuria of 1,953 mg at baseline. After less than 1 month of bevacizumab therapy, a repeat 24-hour urine collection showed proteinuria of 2,539 mg, and bevacizumab was stopped. Another 24-hour urine collection performed 2 months later still showed proteinuria of 2,537 mg, so bevacizumab was not resumed. This patient did not have worsening of hypertension while on bevacizumab therapy. There was no association between the incidence of proteinuria and the duration of bevacizumab therapy. No patient developed renal insufficiency, as determined by creatinine levels.

Six patients (15%) had an onset of both hypertension and proteinuria while receiving bevacizumab (Table 2). Two patients who developed new or worsened hypertension while on treatment with bevacizumab were not assessed for proteinuria. For the purposes of statistical analysis, they were assumed not to have had proteinuria. There was a statistically significant association between hypertension and proteinuria ($P = 0.006$). The occurrence of proteinuria was observed

TABLE 1
Hypertension and/or proteinuria after bevacizumab therapy

Toxicity	Number of patients	Grade of toxicity		
		0	1	2 or 3
Hypertension	40	28	7	5
Proteinuria	40	31	5	4

TABLE 2

Association of bevacizumab-related hypertension and proteinuria

Proteinuria grade	Hypertension grade	
	1, 2, or 3	0
1, 2, or 3	6	3
0	6	25

TABLE 3

Occurrence of proteinuria by severity of bevacizumab-related hypertension

Hypertension grade	Total number of patients	Number (%) of patients with proteinuria
0	28	3 (11%)
1	7	2 (29%)
2, 3	5	4 (80%)

more often in patients with more severe hypertension (Table 3).

A total of 19 of the 40 patients experienced toxicity attributable to bevacizumab, for an incidence of 47.5%. In addition to hypertension and proteinuria, other toxicities likely caused by bevacizumab were observed. Five patients had epistaxis, which was temporary and did not require intervention. One patient had gastrointestinal bleeding, one patient developed a perforated nasal septum, one patient developed an anal fissure, and one patient had chest pain of an uncertain cause. The latter four patients all stopped bevacizumab therapy. In the patient with the anal fissure, the fissure healed after a treatment break of 2 months, and bevacizumab was resumed with no further toxicity. The patient who developed chest pain was not found to have any evidence of cardiac disease on further evaluation, and no specific cause of the chest pain was found; this patient declined to resume bevacizumab therapy. There were no documented thromboembolic events. Prophylactic anticoagulation was not used.

Discussion

Bevacizumab is generally well tolerated, although its use is associated

with significant rates of hypertension and proteinuria.^{2,3,6,7} The rates of the toxicities observed in this study are similar to those reported in the pivotal study by Hurwitz et al² and in other studies^{3,6,7} demonstrating that bevacizumab can be used safely outside a clinical trial setting.

We observed a significant association between hypertension and proteinuria. This is the first study to identify an overall correlation between those two toxicities regardless of grade. Although a correlation between the degree of these two toxicities has not been previously noted in most of the available published data on bevacizumab, Yang et al³ did note that grade 2 or 3 proteinuria was statistically more likely to occur in patients who developed grade 2 or 3 hypertension than in those with no or only grade 1 hypertension. Our study appears to confirm this correlation between increasing grades of hypertension and proteinuria (Table 3).

A causative relationship between hypertension and proteinuria cannot be established based on these data. Indeed, there was no clear temporal association between hypertension and proteinuria, with half the patients first developing hypertension and the other half first developing proteinuria. However, there is clearly a correlation between hypertension and proteinuria, suggesting a bevacizumab toxicity syndrome (BETS). It is possible that there is a common pathophysiologic mechanism involved in the development of both of these bevacizumab toxicities.

Management recommendations

Thus far, recommendations for management of hypertension and proteinuria related to bevacizumab have been vague. The only guideline from the manufacturer of bevacizumab regarding management of proteinuria is that the drug should be stopped if severe proteinuria develops.⁸ No specific guidelines for the management of

hypertension have been made.

Recommendations for the management of hypertension in the general population have been published by the National High Blood Pressure Education Program Coordinating Committee.⁹ This Committee suggests that hypertension be treated with a goal of achieving a blood pressure below 140/90 mm Hg for most individuals; however, individuals with renal disease, including those with preserved renal function who have proteinuria, should be treated with a goal blood pressure below 130/80 mm Hg. Management of chronic conditions such as hypertension is often afforded decreased importance in individuals with advanced malignancy due to their limited life expectancy. However, as therapies for cancer continue to improve and the role of bevacizumab continues to expand, more patients will receive bevacizumab for longer periods, and the long-term management of toxicities such as hypertension and proteinuria will assume greater importance.

Given the statistically significant association between hypertension and proteinuria, we suggest that management of either of these complications should include agents protective against both conditions, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).⁹ Early intervention for hypertension (eg, blood pressure higher than 130/80 mm Hg) and/or proteinuria (of any degree) may prevent or delay progression of BETS. Monitoring for both hypertension and proteinuria should be performed regularly. Regular quantitation of proteinuria, either with periodic 24-hour urine determinations or measurements of the urine protein/creatinine ratio, may increase the precision of monitoring for this complication of bevacizumab therapy. Initiation of an agent such as an ACE inhibitor or an ARB at the first sign of blood pressure elevation, even if only grade 1, and at the

first sign of proteinuria (even a trace of proteinuria) may allow patients to remain on bevacizumab therapy longer and receive a greater cumulative dosage, which could potentially improve survival while decreasing toxicity. Prospective trials for management of BETS are warranted.

References

1. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 1997;57:4593–4599.
2. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–2342.
3. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–434.
4. Miller KD, Wang M, Gralow J, et al. E2100, a randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Paper presented at the 41st Annual Meeting of the American Society of Clinical Oncology; May 13–17, 2005; Orlando, Fla. Educational Session.
5. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (c) with or without bevacizumab (NSC #704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): an Eastern Cooperative Oncology Group (ECOG) trial—E4599. Paper presented at the 41st Annual Meeting of the American Society of Clinical Oncology; May 13–17, 2005; Orlando, Fla. Abstract LBA4.
6. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005;23:3697–3705.
7. Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005;23:3706–3712.
8. Avastin (bevacizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2004.
9. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Insti-

tute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572.

ABOUT THE AUTHORS

Affiliations: Dr. Martel is currently a medical oncologist at City of Hope Medical Group, Pasadena, CA; Dr. Present, Dr. Ebrahimi, Dr. Upadhyaya, Dr. Vakil, Dr. Yeon, Dr. Bosserman, and Dr. Horns are oncologists at Wilshire Oncology Medical Group, La Verne, CA.

Competing interests: Dr. Present has received honoraria from Genentech, Inc. and has served on a Genentech Advisory Board; Dr. Ebrahimi has received honoraria from Genentech, Inc. and has served on a Genentech Advisory Board; Dr. Vakil has received honoraria from Genentech, Inc. and has served on a Genentech Advisory Board. Wilshire Oncology Medical Group has performed research studies for and received research funding from Genentech, Inc. No financial conflicts reported for Dr. Martel, Dr. Upadhyaya, Dr. Yeon, Dr. Bosserman, and Dr. Horns.