

Intracranial Hemorrhage in Patients Treated with Bevacizumab and Low-Molecular Weight Heparin

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Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody that targets the vascular endothelial growth factor (VEGF) receptor. Bevacizumab is approved for the treatment of metastatic colorectal cancer and metastatic non-small cell lung cancer, but has also demonstrated efficacy in breast, renal, and pancreatic cancers when used in combination with other agents.¹⁻⁵ Although minor bleeding is a known complication of bevacizumab therapy, serious hemorrhage (grade 3 and 4) occurs in only 3% of patients.⁵ Patients with brain metastases were excluded from early clinical trials due to concern for intracranial hemorrhage (ICH). This risk remains theoretical, as increased ICH was not observed in a recent study of bevacizumab and irinotecan for malignant gliomas.⁶ A recent report suggests that concomitant administration of bevacizumab and full-dose anticoagulation does not significantly increase the risk of serious hemorrhage in patients being treated for thromboembolic disease.⁷ The patients in the report were treated with warfarin and the risk associated with full-dose low-molecular weight heparin (LMWH) is unknown.

We report two cases of symptomatic, life-threatening ICH in patients treated with bevacizumab and full-dose LMWH. Neither patient had any known brain lesion prior to treatment with bevacizumab. The first patient is a 72-year-old woman with fallopian carcinoma who had progressed through initial chemotherapy and focal radiation. Prior to presentation she was treated with bevacizumab and gemcitabine (Gemzar, Eli Lilly) for 6 months and tinzaparin (Innohep, Pharmion) 9,000 U daily for 2 months for an upper-extremity venous thrombosis. The patient reported 2 weeks of insidious-onset dysarthria, ataxia, and difficulty with her handwriting. On examination she had mild dysarthria, hemiparesis, and gait

instability, which improved over the following month. Computed tomography (CT) and gadolinium-enhanced magnetic resonance imaging (MRI) revealed an acute pontine hemorrhage without any clear underlying lesion. A cavernous angioma was considered; however, there was no evidence of chronic hemorrhage on gradient echo sequence as typically seen with cavernous malformations. Her admission blood pressure was 163/78 mm Hg, previously normotensive. Her international normalized ratio (INR) was 0.88 and her platelet count was 246,000/mL.

The second patient is a 59-year-old woman with a history of refractory primary peritoneal cancer. Bevacizumab was added to cisplatin and irinotecan, 5 months prior to presentation. She had been receiving enoxaparin (Lovenox, Sanofi-Aventis) 70 mg twice daily for 6 days for pulmonary emboli before complaining of sudden-onset severe headache with a normal neurologic examination and no history of head trauma. CT scan, MRI with MR angiography, and CT angiography revealed a subarachnoid hemorrhage (SAH) without any underlying aneurysm. The fluid-attenuated inversion recovery (FLAIR) sequence had areas of signal intensity suggestive of acute hypertensive vasculopathy. This patient had an INR of 1.01, a platelet count of 83,000/mL, and a blood pressure of 185/115 mm Hg documented several days prior to her event.

Hypertension is a known complication of bevacizumab therapy and can affect up to 32% of patients.⁸ The first patient described herein likely had elevated blood pressure as a reaction to ICH, but the second patient may have had bevacizumab-induced hypertension with subsequent SAH. In both cases, anticoagulation and bevacizumab were held without further progression of neurologic symptoms (Figure 1). These cases suggest that full-dose anticoagulation in patients treated with bevacizumab and LMWH may increase the risk of ICH, regardless of whether a patient has an underlying parenchymal or vascular intracranial lesion. Additional studies are needed to adequately define the risk of anticoagulation

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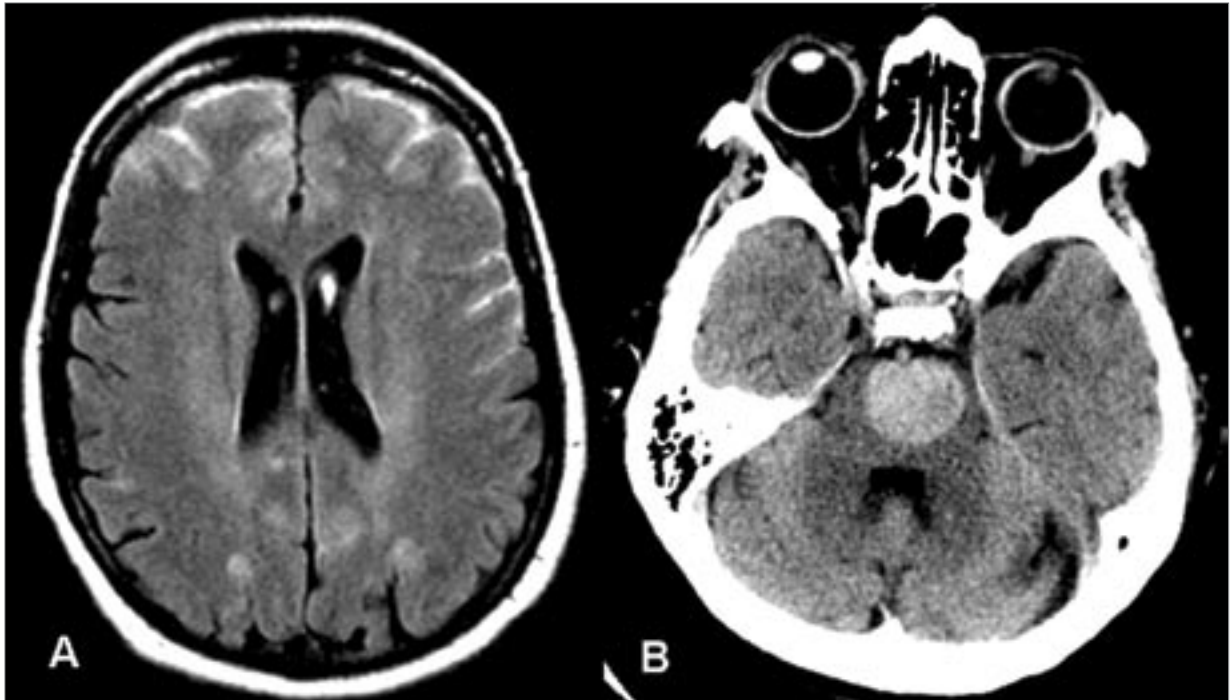


Figure 1. Two patients treated with bevacizumab and low-molecular weight heparin: (A) fluid-attenuated inversion recovery magnetic resonance imagery of subarachnoid hemorrhage in the setting of hypertension; (B) noncontrast computed tomography of pontine hemorrhage without underlying lesion.

in patients treated with bevacizumab with and without known thromboembolic disease. Studies should also account for potentially different risks in patients treated with LMWH versus warfarin. Until such data are available, we recommend cautious use of full-dose LMWH with bevacizumab, particularly in the setting of hypertension. Patients who develop any neurologic symptoms merit an urgent and thorough evaluation.

Disclosure

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Review

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Bevacizumab is a recombinant, humanized, monoclonal antibody that inhibits VEGF, thus inhibiting angiogenesis. Bevacizumab is the first antiangiogenic agent clinically proven to extend survival and is approved by the US Food and Drug Administration (FDA) in combination with 5-fluorouracil-based chemotherapy for the first- or second-line treatment of metastatic colorectal cancer.¹ In addition, the FDA recently approved bevacizumab in metastatic non-small cell cancer. Bevacizumab does not have any overlapping hematologic or gastrointestinal (GI) toxicities with chemotherapeutic agents. Major toxicities encountered in phase III/IV trials of bevacizumab in colorectal cancer include hypertension (grade 3/4, 1–18%), proteinuria (grade 3, 0–2%), wound healing complications (1%), bleeding (grade 3/4, <1–6%), arterial thromboembolism (ATE; <1–2%), and GI perforation (0–2%). The incidence of bevacizumab-related toxicities was similar in clinical trials and in community-based registry studies (BRiTE and First BEAT).¹ It is also important to note that these toxicities are a class effect for all anti-VEGF therapies. As the clinical use of bevacizumab continues to increase in the treatment of colorectal cancer and other malignancies, it is prudent to understand the toxicities that can arise and know how to manage them.

Nguyen and Abrey describe two cases of symptomatic, life-threatening central nervous system (CNS) hemorrhage in patients (without known brain metastasis) who were treated with bevacizumab and full-dose LMWH.² Grade 3 hypertension, defined as hypertension requiring the addition or modification of antihypertensive agents, is the most common toxicity associated with bevacizumab treatment. The overall rate of grade 3 hypertension in phase III/IV studies is 1–18%.³ Hypertension can occur at any time during the course of treatment. Preexisting hypertension does not predispose patients to grade 2/3 hypertension. No deaths from hypertension have been reported. More than 1% of patients have discontinued therapy because of hypertension. Blood pressure is typi-

cally controlled with a single antihypertensive agent. Neurologic insults in the form of stroke, transient ischemic attack, and SAH have been reported following the administration of bevacizumab. A pooled analysis was conducted from five randomized trials that included 1,745 patients: AVF0757g (lung cancer), AVF2119g (breast cancer), and AVF2192g, AVF0780g, and AVF2107g (3 studies of colorectal cancer).⁴ Search terms for the analysis that were indicative of arterial events included events that were CNS-related, including stroke, transient ischemic attack, and SAH; cardiovascular-related (myocardial infarction, angina, ischemia, atherosclerosis); and other (peripheral vascular disease). The rate of ATEs in the chemotherapy-only group was 1.9%, whereas the rate in the bevacizumab-plus-chemotherapy group was 4.4%. Fatal events with chemotherapy alone were 0.4% (3/782) versus 0.7% (7/963) with chemotherapy plus bevacizumab. Hemorrhage is also associated with bevacizumab.¹ Epistaxis is the most common bleeding event associated with bevacizumab: 46% in patients on the 5-mg/kg dose versus 53% on the 10-mg/kg dose.¹ However, in phase III trials with a dose of 5 mg/kg, there was no significant increase in risk with bevacizumab.³ Similarly, the incidence of serious bleeding events was only 1.3% in the First BEAT study: 8 deaths due to bleeding (3 of these also had GI perforation).⁵ In the Eastern Cooperative Oncology Group E3200 study, which used the higher 10-mg/kg dose of bevacizumab, there was only a marginal increase of bleeding of 1%, compared with less than 1% with the lower dose.⁶ The BRiTE data registered a 2.2% rate of serious bleeding events.⁵

Nguyen and Abrey suggested that bevacizumab-associated hypertension led to SAH in the second patient. SAH comprises 1–7% of all strokes.⁷ Smoking, hypertension, nonwhite ethnicity, and excessive alcohol intake have statistically significant and consistent associations with an increased risk of SAH in case-control and longitudinal studies.^{8,9} As mentioned earlier, grade 3 hypertension was observed in 1–18% of patients treated in the phase III/IV studies.³ No deaths from hypertension have been reported. Grade 4 hypertension, defined as hypertension leading to life-threatening consequences (eg, hypertensive crisis) is rare; only a single case in a phase II breast cancer study has been observed.¹⁰ Although hypertension is a known risk factor for SAH, other factors may be involved in CNS bleeding in the second patient, such as ATE and bleeding associated with the agent. VEGF is a major regulator of endothelial renewal; antagonizing VEGF might decrease the renewal capacity of the endothelium in response to trauma, increasing the tendency to bleed.¹

A multivariate risk analysis by Skillings and associates from the five randomized trials identified two risk

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factors associated with ATE. These factors were previous ATE (stroke, heart attack) and age greater than 65 years.⁴ Nguyen and Abrey did not comment on the previous history of ATE in the two cases. The first patient was over 65 years of age (72 years) and the second was only 59 years old. Other risk factors might include hypertension and smoking.

Neither of the two patients in the cases reported here had known CNS metastases. The risk of CNS bleeding in the presence of CNS metastasis is not known at present because patients with CNS metastases were excluded from the pivotal company-sponsored studies of bevacizumab. This exclusion was based on the finding of severe CNS hemorrhage in 1 patient with CNS metastasis in an initial phase I study.¹ However, a recent phase II study conducted by Vredenburgh and colleagues in patients with recurrent malignant glioma showed no CNS hemorrhage.¹¹ Patients received bevacizumab and irinotecan intravenously every 2 weeks of a 6-week cycle. Bevacizumab was administered at 10 mg/kg. Patients with evidence of CNS hemorrhage on initial brain MRI were excluded. Among 32 patients treated, no CNS hemorrhages occurred, but 3 patients developed deep venous thromboses or pulmonary emboli, and 1 patient had an arterial ischemic stroke. Although this study makes the risk of CNS bleeding theoretical, caution should be taken. Future studies will further confirm the safety of bevacizumab in this population.

Experience with bevacizumab in phase II studies, particularly in non-small cell lung cancer, recognized bleeding as a safety signal. Therefore, patients receiving full-dose anticoagulation were excluded from the pivotal phase III study by Hurwitz and colleagues.³ Hambleton and associates performed an analysis to assess the outcomes of patients with metastatic colorectal cancer who had a thrombotic event while receiving study treatment (bevacizumab or placebo) and remained on the study while receiving full-dose anticoagulation with warfarin.¹² Of those patients with a thrombotic event treated with warfarin, 30 patients (54.5%) in the irinotecan, 5-fluorouracil, and leucovorin (IFL) arm and 53 patients (82.8%) in the IFL/bevacizumab arm continued on the study treatment. Grade 3/4 bleeding in those on warfarin and study drug occurred in 2 (6.7%) IFL-treated patients and 2 (3.8%) IFL/bevacizumab-treated patients. These data suggested that the concomitant use of full-dose anticoagulation therapy with bevacizumab in combination with chemotherapy does not appear to increase the risk of hemorrhagic complications in patients with metastatic colorectal cancer. The two patients reported by Nguyen and Abrey were treated with bevacizumab and full-dose LMWH: tinzaparin (9000 U daily) for 2 months for an upper-extremity venous thrombosis and enoxaparin (70 mg twice daily) for 6 days for pulmonary emboli,

respectively. In a comparison using the combined database of the 2,040 and 818 patients who received enoxaparin and the 2,038 and 821 patients who received unfractionated heparin in ASSENT-3 and ASSENT-3 PLUS, the rates of CNS hemorrhage were similar between treatment groups (1.3% vs 0.9%; $P=.26$); however, an excess of CNS hemorrhage occurred among those administered enoxaparin during the ASSENT-3 PLUS trial (6.7% vs 0.8%; $P=.013$), especially among women over 75 years of age.¹³ Interestingly, both the cases in the present report are women.

Patients receiving bevacizumab should be observed for the development or worsening of hypertension by performing frequent blood pressure measurements. Daily home monitoring is encouraged, when possible. In most cases, a single-agent antihypertensive can control hypertension. If hypertension develops, bevacizumab should be temporarily discontinued; patients may continue bevacizumab when hypertension is controlled to below 150/100 mm Hg. For persistent or symptomatic hypertension or grade 3 hypertension, bevacizumab should be withheld until controlled. Bevacizumab should be permanently discontinued if blood pressure is not controlled. If grade 4 hypertension develops, bevacizumab treatment should be permanently discontinued. Standard antihypertensive therapy, typically angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, or diuretics, can be used to control grade 3 hypertension, and bevacizumab can be continued without a dose modification. ACE inhibitors may be more attractive because they might also decrease proteinuria as well as blood pressure; however, no data to determine the best antihypertensive agent are available. In addition to the mechanistic rationale, diuretics should also be used cautiously to treat bevacizumab-related hypertension due to potential worsening of dehydration secondary to chemotherapy-induced diarrhea.

Data on the safety of concomitant use of LMWH and bevacizumab are not available. While on anticoagulation, bevacizumab may be resumed if the INR is therapeutic (between 2 and 3), the patient does not have a history of severe bleeding on bevacizumab, and there is no evidence of tumor involving major blood vessels. Bevacizumab should be discontinued in patients who experience grade 3 hemorrhage while receiving full-dose anticoagulation (within therapeutic range or increased range). For grade 3 hemorrhage in a patient who is not receiving full-dose anticoagulation, bevacizumab should be held until the bleeding has resolved, there is no coagulation disorder that would increase the risk of subsequent bleeding, and there is no anatomic or pathologic condition that increases the risk of hemorrhage. If the patient experiences a repeat grade 3 or a new grade

4 hemorrhagic event, bevacizumab should be permanently discontinued.

Although patients over 65 years of age have an increased risk of ATE, oncologists must use their own medical judgment in assessing the overall risk/benefit of therapy. In the pivotal bevacizumab trial, there were 271 patients at least 65 years of age. This group of patients continued to have a benefit in progression-free survival (hazard ratio, 0.57) and overall survival (hazard ratio, 0.61), despite the higher risk of ATE. In addition, patients who had a history of previous arterial events and were over 65 years of age also had progression-free and overall survival benefits, with hazard ratios of 0.55 and 0.59, respectively. Albeit important, the data on the benefit of bevacizumab in patients over 65 years of age are present, but interaction of age and previous ATEs must be considered in certain patients, and extra caution should be taken when treating these patients with bevacizumab. Many patients with a prior ATE are routinely treated with low-dose aspirin. When these patients entered clinical trials of bevacizumab, they were able to continue low-dose aspirin therapy without any evidence of increased risk of bleeding.¹⁴ Due to the limited number of patients on aspirin who developed a new ATE during bevacizumab therapy, there are insufficient data at present to determine if low-dose aspirin reduces the risk of future events while on bevacizumab. This is an important topic for future study given the number of patients over 65 years of age who could potentially benefit from bevacizumab therapy. The use of high-dose aspirin cannot be recommended due to the lack of safety data. It is recommended that patients with a severe ATE during bevacizumab treatment discontinue treatment permanently.

As current trials mature, safety data will be clarified further, and specific guidelines for the management of bevacizumab-related toxicities will become more detailed. As the use of bevacizumab increases, more information will be necessary to identify specific factors placing patients at higher risk of complications. The key to administering treatment safely will be thorough education of patients,

nurses, and other healthcare providers. Future studies should aim at discerning the safety of LMWH in patients receiving bevacizumab.

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