Bevacizumab Safety in Patients with Central Nervous System Metastases

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Abstract

Purpose: Patients with central nervous system (CNS) metastases were excluded from bevacizumab trials following a case of fatal cerebral hemorrhage in a patient with hepatocellular carcinoma in 1997. Safety information for bevacizumab-treated patients with CNS metastases was reviewed to determine whether general exclusion of these patients from bevacizumab treatment is still justified.

Experimental Design: A retrospective exploratory analysis was conducted using datasets from 13 randomized controlled phase II/III trials (dataset A), two open-label single-arm safety trials (dataset B), and two prospective studies including patients with treated CNS metastases (dataset C). In datasets A and B, known CNS metastasis was an exclusion criterion; patients with CNS metastasis had unrecognized CNS metastases at study entry or developed them during the trial. All reported cerebral hemorrhage grades in patients with CNS metastases were quantified.

Results: In dataset A, occult brain metastases were identified in 187 of 8,443 patients (91 in bevacizumab arms and 96 in non-bevacizumab arms). Three bevacizumab-treated patients (3.3%) developed grade 4 cerebral hemorrhage, whereas one control-arm patient (1.0%) developed grade 5 cerebral hemorrhage. In dataset B, 321 of 4,382 patients had initially occult CNS metastases, in whom two control-arm patients (0.6%) developed grade 5 cerebral hemorrhage. In 131 patients with treated CNS metastases in dataset C, one bevacizumab-treated patient (0.8%) developed grade 2 cerebral hemorrhage.

Conclusions: In this selected population, patients with CNS metastases are at similar risk of developing cerebral hemorrhage, independent of bevacizumab therapy. Consequently, such patients with CNS metastases from advanced/metastatic breast cancer, non–small cell lung carcinoma, and renal and colorectal cancer should not be generally excluded from bevacizumab therapy or clinical trials. Clin Cancer Res; 16(1); 269–78. ©2010 AACR.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biological activity of human vascular endothelial growth factor (VEGF; refs. 1, 2), thus reducing tumor vascularization and inhibiting tumor growth (3). Bevacizumab has shown efficacy in combination with chemotherapy in metastatic breast, colorectal, and non–small cell lung carcinoma (NSCLC), and in combination with interferon in renal cell carcinoma (4–8).

Patients with central nervous system (CNS) metastases have until recently been routinely excluded from bevacizumab trials, following a single case in 1997 of a 29-year-old patient with hepatocellular carcinoma (HCC) who experienced a fatal cerebral hemorrhage from a previously undiagnosed brain metastasis in a phase I study of bevacizumab (9). However, CNS metastases from HCC have an inherent tendency to bleed because patients with HCC are likely to have coagulopathy due to impaired liver function, resulting in cerebral hemorrhage incidences of up to 87.5%, independent of the type of therapy received (10–13).

Since the single case of CNS hemorrhage in 1997 through to February 2009, >577,000 patients have been exposed to bevacizumab. More safety data have thus become available, particularly in patients with occult CNS metastases at study entry and in those developing CNS metastases due to disease progression. Independent reports have concluded that there is no increased risk of cerebral hemorrhage in bevacizumab-treated patients with CNS metastases (14–17). In patients with NSCLC and CNS metastases who were treated with bevacizumab, the risk of tumor-associated CNS hemorrhage was reported to be similar to rates in control patients with metastases who did not receive bevacizumab (14–17). Furthermore, recent phase II data supporting the use of bevacizumab in the treatment of high-grade gliomas (18–20) have called into question the exclusion of patients with CNS metastases from bevacizumab clinical trials.
To assess the risk of cerebral hemorrhage in patients with CNS metastases treated with bevacizumab and to revisit the exclusion of these patients from trials, we conducted a retrospective exploratory analysis of safety data from 13 phase II/III randomized controlled trials (RCTs; refs. 4–8, 21–28), two open-label single-arm safety studies (29, 30), and two recent prospective studies that included patients with treated CNS metastases (14, 31).

**Patients and Methods**

Three datasets were analyzed for the purpose of this safety review using the National Cancer Institute Common Terminology Criteria for Adverse Events; all reported adverse events of cerebral hemorrhage in patients with CNS metastases were included. The datasets were as follows: 13 RCTs (4–8, 21–28); 2 open-label single-arm safety studies: SAIL (Safety of Avastin in Lung; MO19390) and ATHENA (Avastin Therapy for Advanced Breast Cancer; MO19391; refs. 29, 30); and 2 prospective studies including patients with treated CNS metastases: ATLAS (AVF3671g) and PASSPORT (AVF3752g; refs. 14, 31).

**Randomized controlled trials.** The analysis was based on safety data from 13 completed bevacizumab RCTs conducted by the Eastern Cooperative Oncology Group (ECOG), Roche, and Genentech, which included a total of 8,443 patients (Table 1). The cutoff date for the analysis was March 31, 2008. Patients in the Roche and Genentech studies were included in the analysis if they had received at least one dose of study drug (chemotherapy, bevacizumab, or placebo). Patients who were randomized to the control arm of a study but received at least one dose of bevacizumab during the study treatment phase were also included in the bevacizumab-treated population. For ECOG trials, the safety population as defined in the study protocol was used.

Initially, the patient database was searched for patients with CNS metastases using the following search terms: brain; malignant neoplasm of spinal cord; central nervous system, neoplasm; cerebellar tumor; meningeal neoplasm; nervous system, neoplasm; spinal cord neoplasm; neoplasm of uncertain behavior of meninges; and neoplasm of uncertain behavior of brain and spinal cord. With the primary aim of identifying cases of cerebral hemorrhage, the following two-step analysis was done. First, experienced medical professionals (medical doctors and oncologists employed by Roche) identified CNS metastases through a detailed review of individual patient files. As the presence of CNS metastases at enrollment was an exclusion criterion for all RCTs, patients identified during this medical review either had occult (undiagnosed/unrecognized) CNS metastases at baseline or developed CNS metastases during the trials. Second, the patients with CNS metastases identified by this procedure were analyzed for reports of cerebral hemorrhage (all grades were included), applying the Medical Dictionary for Regulatory Activities (version 10.1) term "intracranial hemorrhage."

In 10 of the 13 studies, related hemorrhage events were collected until at least 21 d after the last study drug administration. In AVF2119g, hemorrhage events were collected up to 7 d after the last study dose in the control arm and 21 d in the bevacizumab arm. In AVF2107g and AVF2192g, bleeding events were collected for 14 d after the last dose.

In 11 of the 13 studies, chronic daily treatment with aspirin ≥325 mg/d was an exclusion criterion. Use of aspirin was not allowed in studies AVF0780g and AVF0757g. BO17708 was the only study not to have therapeutic oral or parenteral anticoagulation as an exclusion criterion. In all studies except BO17705 and BO17708, corticosteroid use was generally permitted.

**Large open-label single-arm safety studies.** The occurrence of cerebral hemorrhage in patients with CNS metastases was analyzed in two ongoing, fully recruited, single-arm, open-label studies (data cutoff date March 10, 2009, for SAIL and March 16, 2009, for ATHENA; refs. 29, 30). The analysis included a total of 4,382 patients (2,166 in SAIL; 2,216 in ATHENA).

SAIL is an open-label study of bevacizumab in combination with platinum-containing chemotherapy as first-line treatment for patients with advanced or recurrent nonsquamous NSCLC. Similarly, ATHENA is an open-label study of bevacizumab plus taxane-based therapy for the first-line treatment of patients with locally recurrent or metastatic breast cancer. The primary objective of both
studies was to assess the safety profile of bevacizumab when used as first-line treatment in a broader population. Evidence of CNS metastases at study commencement (even if previously treated) was an exclusion criterion for both studies, hence the specific safety of bevacizumab was assessed in patients who either developed CNS metastases during treatment or had occult CNS metastases at study entry.

In ATHENA and SAiL, bleeding events had to be reported up to 6 mo after the last bevacizumab infusion, irrespective of severity and causal relationship. Prophylactic anticoagulation was allowed, but aspirin (>325 mg/d) or therapeutic anticoagulation (oral or parenteral) within 10 d of the first bevacizumab dose was an exclusion criterion. Concomitant use of steroids was allowed during the trials at the physicians’ discretion.

### Prospective studies including patients with treated CNS metastases

Patients with a history of treated CNS metastases were included in these two prospective trials that combined bevacizumab with chemotherapy in patients with NSCLC (14, 31). The fully recruited PASSPORT study specifically included patients with treated CNS metastases; 115 patients were analyzed (data cutoff date was June 23, 2008). ATLAS included 26 patients with CNS metastases out of a total of 730 enrolled (data cutoff date was October 12, 2007).

PASSPORT is an open-label single-arm phase II trial of bevacizumab in combination with first- or second-line therapy in patients with treated CNS metastases from nonsquamous NSCLC. First- and second-line therapy consisted of either chemotherapy or erlotinib with bevacizumab, according to institutional standards. The primary objective was to assess the rate of symptomatic CNS hemorrhage grade ≥2 during bevacizumab therapy. Patients with CNS metastases were allowed to enter the trial after previous treatment with whole CNS radiation therapy and/or neurosurgery. After treatment of CNS metastases, the absence of progression or CNS hemorrhage had to be confirmed clinically and by magnetic resonance imaging or computed tomography.

ATLAS is a randomized, double-blind, placebo-controlled phase IIIb trial comparing bevacizumab therapy with or without erlotinib after completion of chemotherapy with bevacizumab for the first-line treatment of metastatic breast cancer (31). The study included 26 patients with CNS metastases out of a total of 730 enrolled (data cutoff date was October 12, 2007).
locally advanced, recurrent, or metastatic NSCLC. Patients were initially treated with four cycles of bevacizumab in combination with the investigators' choice of platinum-based chemotherapy regimens. Patients who did not experience disease progression and did not have significant toxicity were randomized to receive maintenance therapy with bevacizumab plus erlotinib or bevacizumab plus placebo until disease progression. Patients with a history of CNS metastases were eligible for enrollment if they had received treatment with whole brain radiation therapy and/or neurosurgery.

In ATLAS and PASSPORT, patients were followed for adverse events for 30 and 60 d, respectively, after discontinuation of study treatment. PASSPORT permitted concomitant treatment including low-dose aspirin, therapeutic heparin/warfarin, and corticosteroids. ATLAS excluded patients with an ongoing requirement at screening for dexamethasone treatment or chronic therapeutic warfarin. Low-dose aspirin and therapeutic heparin were allowed.

### Results

**Randomized controlled clinical trials.** Thirteen RCTs across various indications (locally advanced, unresectable, or metastatic NSCLC; renal, pancreatic, breast, and colorectal cancer) were included in the analysis (Table 1). Overall, 8,443 patients were enrolled, of whom 4,760 received bevacizumab. A total of 187 patients (2.2%) were identified as having CNS metastases: 91 (1.9%) in the bevacizumab-treated group and 96 (2.6%) in the control group (i.e., non–bevacizumab-treated patients). Demographic characteristics, performance status (ECOG, Karnofsky), and study indications were similar in both groups (Table 2).

Median duration of study treatment in patients with CNS metastases was longer in the bevacizumab-treated group compared with the control group: 168 days (range, 1–658 days) versus 106 days (range, 1–493 days). Median time from first treatment to diagnosis of CNS metastases was 190 days (range, –23 (i.e., 23 days before treatment.

| Table 2. Demographic characteristics of patients identified with CNS metastasis in each dataset |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Patients with CNS metastases   | Randomized controlled trials    | Large open-label single-arm safety studies | Studies including patients with treated CNS metastases |
| ---                            | Bev (n = 91) | Non-Bev (n = 96) | ATHENA (n = 140) | SAIL (n = 181) | ATLAS (n = 26) | PASSPORT (n = 115) |
| Sex, n (%)                     |                   |                   |                   |                   |                   |                   |
| Male                           | 34 (37.4)        | 44 (45.8)        | 0 (0)            | 100 (55.2)       | 17 (65.4)        | 62 (53.9)         |
| Female                         | 57 (62.6)        | 52 (54.2)        | 140 (100)        | 81 (44.8)        | 9 (34.6)         | 53 (46.1)         |
| Age, y                         | 58 (23-81)       | 58 (33-81)       | 52 (26-81)       | 56 (29-78)       | 61 (39-75)       | 60 (23-90)        |
| ECOG PS at baseline, n (%)     |                   |                   |                   |                   |                   |                   |
| 0                              | 30 (42.9)*       | 29 (39.7)†       | 74 (52.9)        | 81 (44.8)        | 8 (30.8)         | 44 (38.3)         |
| 1                              | 40 (57.1)*       | 44 (60.3)†       | 57 (40.7)        | 86 (47.5)        | 17 (65.4)        | 71 (61.7)         |
| 2                              | —                | —                | 9 (6.4)          | 14 (7.7)         | 1 (3.8)          | —                |
| Karnofsky score at baseline, n (%) |                   |                   |                   |                   |                   |                   |
| 100-91%                        | 4 (36.4)‡        | 6 (46.2)§        |                   |                   |                   |                   |
| 90-81%                         | 2 (18.2)‡        | 7 (53.8)§        |                   |                   |                   |                   |
| 80-71%                         | 5 (45.5)‡        | —                |                   |                   |                   |                   |
| Study indication, n (%)        |                   |                   |                   |                   |                   |                   |
| CRC                            | 16 (17.6)        | 18 (18.8)        | —                | —                | —                | —                |
| NSCLC                          | 36 (39.6)        | 43 (44.8)        | —                | 181 (100)        | 26 (100)         | 115 (100)         |
| Breast                         | 28 (30.8)        | 22 (22.9)        | 140 (100)        | —                | —                | —                |
| Other                          | 11 (12.1)        | 13 (13.5)        | —                | —                | —                | —                |

NOTE: Karnofsky score was only collected in the AVOREN and AVITA studies; all other studies reported ECOG PS.

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

* n = 70.
† n = 73.
‡ n = 11.
§ n = 13.
In the bevacizumab-treated group, 14 of 91 patients (15.4%) were on study treatment at diagnosis or after being diagnosed with CNS metastases compared with 16 of 96 patients (16.7%) in the control arm. The median number of days between the end of treatment and diagnosis of CNS metastases was 18 days [range, −6 (i.e., 6 days before treatment started) to 787 days] and 14 days (range, 1–662 days) in SAiL and ATHENA, respectively. In the 321 patients with CNS metastases, six were treated with bevacizumab after diagnosis of CNS metastasis, none of whom developed cerebral hemorrhage. The median time between the end of bevacizumab treatment and diagnosis of CNS metastasis was 61 days [range, −162 (i.e., diagnosis of CNS metastases was 162 days before the last dose of bevacizumab) to 448 days] and 83 days (range, −236 to 437 days) in SAiL and ATHENA, respectively.

A search through all reported adverse events identified three cases (0.9%) of cerebral hemorrhage up to 183 days after the last bevacizumab dose (Table 3) in the 321 patients with CNS metastases. Of the three patients from the SAIL trial, two developed a grade 1 cerebral hemorrhage 15 and 151 days after the last dose of bevacizumab, and the third had a grade 3 cerebral hemorrhage 8 days after the last bevacizumab dose while receiving concomitant anticoagulation therapy. The cause of death was progressive disease for two patients and unknown for one patient who died 131 days after the occurrence of cerebral hemorrhage (Table 4).

**Prospective studies including patients with treated CNS metastases: ATLAS and PASSPORT.** This analysis included 131 patients from these studies. The fully recruited PASSPORT phase II trial enrolled 115 patients with NSCLC and treated CNS metastases; 106 were evaluable for safety. In the ongoing ATLAS trial, 26 of 730 enrolled patients (3.6%) had treated CNS metastases, of whom 25 were evaluable for safety. In the 321 patients with CNS metastases, six were treated with bevacizumab after diagnosis of CNS metastasis, none of whom developed cerebral hemorrhage. The median time between the end of bevacizumab treatment and diagnosis of CNS metastasis was 61 days [range, −162 (i.e., diagnosis of CNS metastases was 162 days before the last dose of bevacizumab) to 448 days] and 83 days (range, −236 to 437 days) in SAIL and ATHENA, respectively.

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Table 4. Details of patients who experienced cerebral hemorrhage

| Treatment group | Study, indication | Demographics | Total treatment cycles | Last treatment day | Day of CNS metastasis diagnosis | Day of cerebral hemorrhage | Day of death | Additional information from case narratives (excluding cerebral hemorrhage) |
|-----------------|------------------|--------------|------------------------|-------------------|-------------------------------|--------------------------|-------------|-------------------------------------------------------------------------|
| Randomized controlled trials | | | | | | | | |
| Bev ECOG 3200, CRC | 59 y, male | 5 | 59 | 83 | 71 | 268 | Severe AEs during study: grade 4 hypertension; grade 3 seizure on day of cerebral hemorrhage |
| | | | | | | | | Cause of death: not stated |
| Bev ECOG 3200, CRC | 75 y, male | 3 | 29 | 39 | 39 | 114 | Severe AE during study: grade 3 seizure on day of cerebral hemorrhage |
| | | | | | | | | Cause of death: CRC progression |
| Bev ECOG 4599, NSCLC | 68 y, male | 13 | 267 | 289 | 288 | 306 | Severe AE during study: grade 3 pancreatitis with INR of 1.6 one day before diagnosis of cerebral hemorrhage |
| | | | | | | | | Cause of death: NSCLC progression |
| Non-Bev BO17705, RCC | 66 y, female | NA | 405 | 407 | 407 | 409 | Patient collapsed on day 407 and was diagnosed with BM and cerebral hemorrhage |
| | | | | | | | | Cause of death: cerebral hemorrhage |
| Large open-label single-arm safety studies | | | | | | | | |
| Bev SAiL, NSCLC | 44 y, male | 7 | 168 | 319 | 319 | 450 | Newly diagnosed CTC grade 1 hypertension 7 mo before diagnosis of CNS metastasis |
| | | | | | | | | No concomitant anticoagulant treatment at diagnosis of CNS metastasis |
| | | | | | | | | Cause of death: unknown |
| Bev SAiL, NSCLC | 59 y, female | 13 | 265 | 273 | 273 | 313 | Heparin treatment started for PE 7 mo before diagnosis of CNS metastasis |
| | | | | | | | | During study: newly diagnosed PE 7 mo before diagnosis of CNS metastasis |
| | | | | | | | | Cause of death: progression of disease |

(Continued on the following page)
the patient died 93 days after the occurrence of cerebral hemorrhage (Table 4).

**Discussion**

This analysis addressed whether patients with CNS metastases are at increased risk of cerebral hemorrhage when treated with bevacizumab. The retrospective exploratory safety review of RCTs identified that 2.2% of patients had CNS metastases. The rate of cerebral hemorrhage in the bevacizumab-treated group was 3.3%, compared with 1.0% in the non-bevacizumab group. This difference in rates in the few patients with CNS metastases and cerebral hemorrhage does not seem disproportionately high. Mortality rates were similar between the bevacizumab and control arms.

In SAiL and ATHENA, 3 cases of cerebral hemorrhage in 321 patients (0.9%) with occult CNS metastases were reported, whereas in two prospective NSCLC trials including patients with treated CNS metastases, a single patient developed a grade 2 cerebral hemorrhage (0.8%). Consequently, there seemed to be no difference in the rate of cerebral hemorrhage in patients with treated and untreated CNS metastases. The reported incidences of cerebral hemorrhage in retrospective studies of patients with CNS metastases from peripheral tumors not exposed to bevacizumab range from 5% to 29% (33–37). Comparing these background rates with those presented here, there is no apparent increased risk of cerebral hemorrhage in bevacizumab-treated patients with CNS metastases. A potential reason for the lower rates of cerebral hemorrhage in this analysis might be the selected patient population included in the trials (e.g., most had an ECOG performance status of 0 or 1), which potentially does not reflect the real-life cancer population with clinically symptomatic CNS metastases.

Several investigators have independently provided arguments for including patients with CNS metastases in clinical trials of VEGF inhibitors (17, 38). A database search of clinical trials examined the cerebral hemorrhage risk with anti-VEGF therapy, such as bevacizumab, sorafenib, and sunitinib, in the presence or absence of CNS metastases. Fifty-seven studies were identified, totaling 10,598 patients, and a low rate of <1% was reported for cerebral hemorrhage. Four trials specifically examined anti-VEGF therapy in patients with CNS metastases—each reported no cases of cerebral hemorrhage (38). The authors concluded that there was no evidence that anti-VEGF therapy confers an increased risk of cerebral hemorrhage, regardless of the presence of CNS metastases.

Recent case reports addressing treatment of CNS metastases with bevacizumab include four cases of patients with treated CNS metastases from breast cancer (39) and a treatment-naive patient with CNS metastases from colorectal cancer (40). None of these cases reported tumor-associated cerebral hemorrhage. Similarly, preliminary data of bevacizumab use in patients with CNS metastases from
malignant melanoma do not suggest an increased risk of cerebral hemorrhage (41). Data are available from bevacizumab trials in primary malignant brain tumors. Although these tumors are different from CNS metastases of primary tumors, highly vascularized high-grade malignant gliomas are interesting in this context, as any potential propensity of bevacizumab to precipitate cerebral hemorrhage might be evident in these patients. Bevacizumab, as a single agent and in combination with irinotecan, has been shown to be well tolerated and to induce significant responses in patients with recurrent malignant glioblastoma multiforme. In a phase II trial of bevacizumab alone and in combination with irinotecan that was done in 167 highly pretreated patients with recurrent glioblastoma multiforme, two patients in the bevacizumab arm (2.4%) experienced grade 1 cerebral hemorrhage, whereas three patients in the bevacizumab/irinotecan arm (3.8%) experienced grade 1, 2, and 4 cerebral hemorrhage (42). Another phase II trial using bevacizumab and irinotecan in 33 patients with recurrent malignant glioma reported one patient with cerebral hemorrhage, which occurred after the ninth cycle; the patient made a full recovery (19). A comparison of these data with retrospective data from patients with primary brain tumors, of whom 5% to 10% experienced cerebral hemorrhage without bevacizumab treatment, does not indicate an apparent increase in the risk of cerebral hemorrhage with bevacizumab (43).

The limitations of this analysis are self-evident: Retrospective exploratory analyses cannot serve as a replacement for prospective trials. Furthermore, this analysis compares selected patient populations across trials and indications with different pretreatments/treatments and follow-up times. Unreported or missing data might have biased results. Only a randomized prospective study for each tumor type could systematically address this question, and although such trials are difficult to conduct, an ongoing trial is evaluating the efficacy and safety of bevacizumab in NSCLC patients with untreated and asymptomatic CNS metastases (NCT00800202). Another limitation is that computed tomography scans were not routinely performed and therefore only symptomatic cerebral hemorrhages were identified.

Despite these limitations, the available data indicate that the risk of cerebral hemorrhage in bevacizumab-treated patients with CNS metastases does not seem disproportionately high compared with those who did not receive bevacizumab. Moreover, exclusion of patients with CNS metastases from bevacizumab treatment was based on a single patient with occult CNS metastasis from HCC, a cancer that has a high incidence of cerebral hemorrhage, independent of the treatment received. Consequently, patients with CNS metastases in advanced/metastatic breast cancer, NSCLC, and renal and colorectal cancer should not be generally excluded from bevacizumab therapy or from trials. For other indications, no data thus far exist regarding the effect of bevacizumab on patients with brain metastases and further studies are warranted. The findings presented in this article are limited to bevacizumab and cannot be extrapolated to other inhibitors of VEGF signaling.

In conclusion, in this selected patient population, patients with CNS metastases are at a similar risk of developing a cerebral hemorrhage, independent of bevacizumab therapy. Results from ongoing studies will provide further guidance regarding the use of bevacizumab in patients with brain metastases. Final results from the ATLAS study, which included patients with brain metastases, will be of particular interest. Treatment decisions should be driven by the benefit/risk assessment made by physicians for individual patients.
Disclosure of Potential Conflicts of Interest

B. Besse received an honorarium in 2007 for speaking on behalf of Roche; U.-P. Rohr, S.F. Lasserre, and S. Augustus are employed by Roche; P. Compton and J. Huang are employed by Genentech.

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