Risk of Intracranial Hemorrhage and Cerebrovascular Accidents in Non-small Cell Lung Cancer Brain Metastasis Patients

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Background: Brain metastases confer significant morbidity and a poorer survival in non-small cell lung cancer (NSCLC). Vascular endothelial growth factor-targeted antiangiogenic therapies (AAT) have demonstrated benefit for patients with metastatic NSCLC and are expected to directly inhibit the pathophysiology and morbidity of brain metastases, yet patients with brain metastases have been excluded from most clinical trials of AAT for fear of intracranial hemorrhage (ICH). The underlying risk of ICH from NSCLC brain metastases is low, but needs to be quantitated to plan clinical trials of AAT for NSCLC brain metastases.

Methods: Data from MD Anderson Cancer Center Tumor Registry and electronic medical records from January 1998 to March 2006 was interrogated. Two thousand one hundred forty-three patients with metastatic NSCLC registering from January 1998 to September 2005 were followed till March 2006. Seven hundred seventy-six patients with and 1367 patients without brain metastases were followed till death, date of ICH, or last date of study, whichever occurred first.

Results: The incidence of ICH seemed to be higher in those with brain metastasis compared with those without brain metastases, in whom they occurred as result of cerebrovascular accidents. However, the rates of symptomatic ICH were not significantly different. All ICH patients with brain metastasis had received radiation therapy for them and had been free of anticoagulation. Most of the brain metastasis-associated ICH's were asymptomatic, detected during increased radiologic surveillance. The rates of symptomatic ICH, or other cerebrovascular accidents in general were similar and not significantly different between the two groups.

Conclusions: In metastatic NSCLC patients, the incidence of spontaneous ICH appeared to be higher in those with brain metastases compared with those without, but was very low in both groups without a statistically significant difference. These data suggest a minimal risk of clinically significant ICH for NSCLC brain metastasis patients and proposes having more well designed prospective trail to see the role of AAT in this patient population.

Key Words: Bevacizumab, Intracranial hemorrhage, Brain metastases, Non-small cell lung cancer.

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Brain metastases occur in approximately 30% of patients with metastatic non-small cell lung cancer (NSCLC) and confers significant morbidity and a poorer survival in these patients.[1–6] Ten percent of metastatic NSCLC patients have brain metastases identified at the time of diagnosis of their lung cancer, and an additional 14 to 19% of metastatic NSCLC patients develop brain metastases later during the course of their disease. As survival from metastatic NSCLC improves, these latent brain metastases will become clinically relevant problems requiring treatment.

Brain metastases are a poor prognostic sign in patients with metastatic NSCLC with median survival of 6 months despite the effectiveness of radiotherapy,[7–9] Standard of care radiotherapy can also cause delayed injury and neuron-cognitive decline.[10–15] Many patients also develop multiple new brain metastases or recurrences after maximal radiotherapy, leading to untreatable progressive neurologic morbidity and death.[16] These limitations of standard radiotherapy options demand the development of newer systemic therapies for brain metastases.

One of the most promising new approaches to the therapy for advanced lung cancer has been the addition of antiangiogenic therapies (AAT), a class of targeted biologic agents that have substantially improved the therapy for multiple cancer types, including metastatic NSCLC. The first and most widely used FDA-approved antiangiogenic agent is Bevacizumab, a monoclonal antibody that binds and neutralizes vascular endothelial growth factor, the principle mediator of angiogenesis in growing malignancies.[17–24] Bevacizumab added to standard frontline chemotherapy for NSCLC has shown to improve response rates, time to progression, and

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overall survival compared with chemotherapy alone.[22,25] Antiangiogenic agents like Bevacizumab also are expected to ameliorate directly the morbidity of brain metastases by reducing peritumoral vasogenic edema, mediated by vascular endothelial growth factor[26–28] which is required for progressive growth of brain metastases[29] and represents and important target for treatment of brain metastases.[30]

Unfortunately, patients with brain metastases have not had access to AAT for fear of tumor-related intracranial hemorrhage (ICH) from a choriocarcinoma brain metastasis in the first phase I clinical trial of bevacizumab.[18] It is known although the most common tumor type to undergo brain metastasis hemorrhage is lung cancer, or bronchogenic carcinoma, this is because such a large fraction of patients with brain metastasis have bronchogenic carcinomas.[33–38] However, cumulative historical and anecdotal experience with lung cancer patients suggests that the incidence of spontaneous NSCLC brain metastasis hemorrhage appears to be very low.[31,32,35,36]

We hypothesized that the rates of spontaneous ICH among advanced NSCLC patients with brain metastasis is not significantly higher than patients with advanced NSCLC and no brain metastasis.

METHODS

Study Design

The deidentified data reviewed includes individuals with diagnosis of advanced NSCLC presenting to UTMDACC from January 1998 to September 2005. The subjects had been followed through March 2006. The diagnosis of brain metastasis in these patients was based on results of radiologic imaging reivew, radiologic reports, and physician notes. Only very small (<2 mm), indeterminate, and very slowly growing brain metastases might have been missed. The outcome of interest was ICH—any epidural, subarachnoid, intraventricular, or intraparenchymal hemorrhage anywhere within the central nervous system. ICH was confirmed by review of radiologic imaging, radiologic reports, and physician notes. Any obvious traumatic or iatrogenic hemorrhages were excluded.

Because ICH in patients without brain metastases would most likely be related to cerebrovascular accidents (CVA), we also compared as a control measure the incidence of cerebrovascular occlusive episodes between patients with or without brain metastases. These episodes included both thrombotic and embolic events, ranging from transient ischemia to cerebral infarcts.

Sample Size

The type I error level (alpha) was set at 0.05 and type II error at 0.20 (power 0.80). The baseline prevalence of intratumor bleed in metastatic brain tumors has been reported to be around 2.9%.[31] A sample size of 1052 (526 per group) was calculated to detect a twofold or greater increase in rate of ICH in the brain metastasis patients as compared with the no brain metastasis patients. We had a sample size of 2143 (776 exposed and 1367 unexposed) and with a baseline incidence in no brain metastasis patients of 3.2 events per 1000 person-years and the difference of 12.3 events per 1000 person-years, the power of the study was 0.70.

Person-time of follow-up for brain metastasis and no brain metastasis patients was calculated. All patients were followed from the date of registration till either (1) the date of death (2) the last day of contact, or (3) the day of occurrence of the outcome of interest, whichever occurred first. However, if during the follow up a patient developed brain metastasis his person-time was included under exposed from when the brain metastasis was first recognized.

Hemorrhagic stroke (symptomatic ICH): subjects who were symptomatic and had neurologic symptoms attributable to the ICH were classified as those with hemorrhagic stroke. Most patients with ICH do have symptoms. However, as all patients with advanced NSCLC undergo routine brain imaging, it was expected that asymptomatic ICH would be detected in some patients during imaging.

Potential confounders included age and sex of the patients.[39] Based on available literature, it was hypothesized that these factors could potentially be related to both risk of brain metastasis as well as ICH. Based on previous studies, age was categorized as less than 65 years or 65 years or more.[40–42] Information was also available on whether the brain metatasis patients received any radiotherapy to the brain lesions, used anticoagulants or hormonal therapy, or had a history of hypertension as these factors may influence the risk of intracranial bleeding.[43–46]

Data Management

The data was collected with the approval of the institution's IRB and was maintained in a confidential manner. All patient identifiers had been removed from the data set and no personal information on any subject or medical care provider could be obtained. All the information available in the data set was strictly used for the purpose of this study and not shared.

RESULTS

There were a total of 2143 patients with advanced NSCLC in the study. Out of these, 776 (36%) individuals had brain metastasis at the time of registration. The total time of follow-up for the brain metastasis and no brain metastasis groups were 6961 person-months (580 person-years) and 14, 837 person-months (1236 person-years of follow-up), respectively. None of the patients without brain metastases developed brain metastasis on follow-up.

Selected characteristics of the subjects depending on brain metastasis status are shown in Table 1. There were more males in the study as compared with females (58.2 versus 41.8%). There were a total of 1272 (59.3%) patients who were less than 65 years of age. Within both groups with or without brain metastases the predominant population was white (81.6 and 81.8%, respectively) followed by blacks (9.0 and 9.2%) and Hispanics (6.3 and 5.0%). Within both groups most patients were known to be stage IV at presentation (94.7% among those with brain metastases and 86.2% among those without).

The prevalence of ICH among those with brain metastases was 1.17% as compared with 0.30% among those without (Table 2), a statistically significant 3.96 fold greater risk (95% confidence interval [CI] 1.22–12.83; $p = 0.013$).

The prevalence of thromboembolic CVA among those with brain metastases was 1.68% as compared with 2.05% among those without (Table 2), a 0.82 fold lower risk that was not statistically significant (95% CI 0.43–1.57; $p = 0.56$).

The nine events of ICH within the brain metastasis group occurred over 580 person-years of follow-up and the four within the no brain metastasis group occurred over 1236 person-years. The incidence among those with brain metastases was significantly higher as compared with those without (15.5 events/1000 person-years versus 3.2 events/1000 person-years; $p = 0.0076$), a 4.79 fold greater risk (95% CI = 1.34–21.31) as shown in Table 3.

The incidences of symptomatic ICH, however, were not significantly different between the brain metastasis or no brain metastasis groups (6.9 events/1000 person-years versus 3.2 events/1000 person-years; $p = 0.30$) as shown in Table 4. ICH's were symptomatic in only 4 of the 9 events within the brain metastasis group, but in all of the four events in the no brain metastasis group. This discrepancy in symptomatic ICH between the two groups can be explained as follows. The asymptomatic ICH cases were identified during surveillance scans for patients with known brain metastases, which can contain clinically insignificant punctuate foci of hemorrhage. In patients without brain metastases on prior screening brain scans, surveillance imaging was performed less frequently, and ICH was identified only after symptomatic CVA's.

No alternative explanations for our results could be identified, and the Mantel Haenszel test was used to confirm that sex and age are not potential effect modifiers or confounders (Tables 5 and 6). Among the 776 patients who had brain metastasis only four patients had not received radiation

TABLE 1. Baseline Characteristics of the Study Population

	No. of Patients (%)[a]	
	Exposed ($n = 776$)	**Unexposed ($n = 1367$)**
Gender		
Male	430 (55.4)	816 (59.7)
Female	346 (44.6)	551 (40.3)
Age		
<65 yr	526 (67.8)	746 (54.6)
≥65 yr	250 (32.2)	621 (45.4)
Race		
White	633 (81.6)	1118 (81.8)
Black	70 (9.0)	126 (9.2)
Hispanic	49 (6.3)	69 (5.0)
Other	24 (3.1)	54 (4.0)
Stage		
IIIA	13 (1.7)	40 (2.9)
IIIB	28 (3.6)	148 (10.9)
IV	735 (94.7)	1179 (86.2)

[a] Percentages are of the total; percentages are rounded of to the nearest 10th decimal.

TABLE 3. Incidence Rate and Ratio of Brain Metastasis and ICH

	Brain Metastases	**No Brain Metastases**
ICH	9	4
Person time (person-years)	580	1,236
Incidence rate (per 1000 person-years)	15.5	3.2

Crude incidence rate ratio = 4.79 (95% CI = 1.34–21.31); $p = 0.0076$.

TABLE 4. Incidence Rate and Incidence Rate Ratio of Brain Metastasis and Symptomatic ICH

	Brain metastases	**No brain metastases**
Symptomatic ICH	4	4
Person time (person-years)	580	1236
Incidence rate (per 1000 person-years)	6.9	3.2

Crude incidence rate ratio = 2.13 (95% CI = 0.40–11.44); $p = 0.31$.

TABLE 5. Determining Confounding and Effect Modification by Sex

Sex	**RR (95% CI)**
Females	6.37 (0.71–56.76)
Males	3.16 (0 .76–13.17)
Crude	3.96 (1.22–12.82)
M–H combined (adjusted)	4.03 (1.23–13.19)

Test of homogeneity (M–H) χ^2 (1) = 0.279 Pr > χ^2 = 0.5972.

TABLE 6. Determining Confounding and Effect Modification by Age Group

Sex	**RR (95% CI)**
<65 yr	8.51 (1.03–70.47)
≥65 yr	2.48 (0.50–12.22)
Crude	3.96 (1.22–12.83)
M–H combined (adjusted)	4.44 (1.28–15.42)

Test of homogeneity (M–H) χ^2 (1) = 0.874 Pr > χ^2 = 0.3499.

TABLE 2. Risk and Risk Ratio of Brain Metastasis and CVA, Both ICH or Thromboembolic

	No CVA (% incidence)	**Thromboembolic CVA (% risk)**	**Intracranial Hemorrhage (% risk)**	**Symptomatic Intracranial Hemorrhage (% risk)**
Brain mets ($N = 776$)	754 (97.2%)	13 (1.68%)	9 (1.17%)	4 (0.53%)
No brain mets ($N = 1367$)	1334 (97.6%)	28 (2.05%)	4 (0.30%)	4 (0.30%)
Risk ratio (95% CI)		0.82 (0.43–1.57)	3.96 (1.22–12.22)	1.76 (0.44–7.02)
p		0.56	0.013	0.42

therapy for the brain lesions. Only one patient with brain metastases who developed ICH had not received radiation therapy. None of the subjects in either group were on any known anticoagulants. There was one patient with ICH and a history of hypertension among those with brain metastasis, and one among those without, but their hypertension was under control at the time of ICH. None of the patients who developed ICH were receiving hormonal therapy.

DISCUSSION

The data presented here suggests that the risk of developing ICH in those with brain metastasis is more than in those without brain metastases in a patient population comprised of advanced NSCLC patients; however, this increased risk is very small. The rates of clinically symptomatic ICH were not significantly higher among those with brain metastasis as compared with those without brain metastasis.

In this study, the incidence of ICH was found to be 15.5 events/1000 person-years in those with brain metastasis and 3.2 events/1000 person-years among those without; thus, detecting the increase is more than 2-fold in those with brain metastasis. The incidence of symptomatic ICH in patients with brain metastasis was only 6.9 events/1000 person-years.

To our knowledge, this is the first study with a large sample size to determine the rates of ICH in NSCLC patients with and without brain metastasis. The rate of ICH in brain metastases has been reported to be 2.9% previously[31]; however, these studies included metastasis from many different sites and histologies, some of which form very vascular tumors. We speculate that our low rates of ICH for NSCLC brain metastases might be further attributable to the radiation therapy that almost all of our patients received, because radiotherapy seems to blunt angiogenesis, normalizing tumor vasculature and decreasing the risk of tumor hemorrhage.[47,48] Our detection of asymptomatic ICH in patients with brain metastases may at least in part be related to the practice of more frequent surveillance imaging in these patients.

Our patient groups were designated based on the presence or absence of brain metastases known at the time of death or the last clinic encounter. Although it is possible that some patients in the no brain metastasis group could have developed them by the time of death, none of these patients had visible brain metastases at the time of ICH or ischemic CVA. Conversely, although it is possible that patients in the brain metastasis group could have developed the metastases after the reported CVA, all of these patients had visible brain metastases at the time of ICH or ischemic CVA. Our prevalence of detectable brain metastases in patients with metastatic NSCLC was 36%, consistent with reported rates between 30 and 40%.[2–5] Prior studies have reported decreased survival and increased risk of ICH with large metastatic brain tumors in patients with advanced NSCLC.[49] It is notable that in the present study the four patients who developed clinically symptomatic ICH had tumors ≥2 cm in size, whereas hemorrhage in smaller lesions were likely to remain asymptomatic. However, data on tumor sizes was not available for all cases, and we can only conjecture that tumor size correlates with symptomatic ICH.

Three major limitations must be considered when reviewing these results. Patients evaluated were from a tertiary level referral center, which may produce several selection biases. The patient populations considered may have more advanced disease. An unusual hetereogeneity of socioeconomic groups from indigent to affluent with a broad range in access to health care may also influence the extent of disease upon presentation. The majority of the patients in our study were White so it may not be possible to extrapolate our results to other ethnicities. Another limitation is that with the limited sample size and low rates of symptomatic ICH in the two groups, the study's statistical power was inadequate to comment on the statistical significance of the association. Finally, we did not have data on the RPA classification data on the patients as per the RTOG prognostication categorization. Thus, we were unable to adjust the data for patient's RPA classification status.

The notable strengths of this study include the following. This is one of the largest studied cohorts of patients with advanced NSCLC with or without brain metastases. The data were abstracted from radiologic images, reports, and clinic physician dictations allowing greater accuracy. Data on the exact person-time of follow-up from each patient was available. Finally, chances of differential misclassification were reduced since the exposure was measured before the outcome.

A low incidence of ICH was observed, and the rates of clinically symptomatic ICH in patients with brain metastasis were even lower. This study suggests that in patients with advanced NSCLC and brain metastasis who have stable disease, a history of radiation therapy, and small tumor size, it may be reasonable to include them in trials testing role of AAT, without a significant a priori risk of ICH. However, prospective well designed trials are needed to specifically answer that question. A clinical trial of Bevacizumab with chemotherapy in NSCLC patients is currently underway to assess the safety of this form of antiangiogenic therapy after radiation or surgery for brain metastases.

CONCLUSIONS

In metastatic NSCLC patients, the rates of spontaneous ICH appeared to be higher in those with brain metastases compared with those without, but were very low in both groups. Most of the brain metastasis-associated ICH were not symptomatic, detected during increased radiologic surveillance. The rates of symptomatic ICH were not significantly different between the two groups.

Patients with stable disease and history of radiation therapy to the brain lesion may be reasonable candidates for inclusion in antiangiogenic therapy trials. However, more data from animal studies and well designed prospective trials is still required to answer that question.

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