Retrospective Evaluation of the Clinical and Radiographic Risk Factors Associated With Severe Pulmonary Hemorrhage in First-Line Advanced, Unresectable Non–Small-Cell Lung Cancer Treated With Carboplatin and Paclitaxel Plus Bevacizumab

Alan B. Sandler, Joan H. Schiller, Robert Gray, Isaiah Dimery, Julie Brahmer, Meghna Samant, Lisa I. Wang, and David H. Johnson

From Vanderbilt University, Nashville, TN; University of Texas Southwestern, Dallas, TX; Dana-Farber Cancer Institute, Boston, MA; Genentech Inc, South San Francisco, CA; and Johns Hopkins University, Baltimore, MD.

Submitted January 16, 2008; accepted October 21, 2008; published online ahead of print at www.jco.org on February 17, 2009.

Supported by Genentech Inc, South San Francisco, CA.

Presented in part in abstract format at the 42nd Annual Meeting of the American Society of Clinical Oncology, June 2-6, 2006, Atlanta, GA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Alan B. Sandler, MD, Vanderbilt-Ingram Cancer Center, 2220 Pierce Ave, Nashville, TN 37232; e-mail: asandler@vanderbilt.edu.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

© 2009 by American Society of Clinical Oncology

0732-183X/09/2709-1405/\$20.00

DOI: 10.1200/JCO.2008.16.2412

ABSTRACT

Purpose

Severe (grade ≥ 3) pulmonary hemorrhage (PH) in advanced non–small-cell lung cancer was observed in two prospective, randomized, phase II (N = 99) and phase III (N = 878) trials of bevacizumab plus carboplatin and paclitaxel. Retrospective case-control and cohort analyses were conducted to identify associated radiographic and clinical risk factors for PH.

Patients and Methods

Six patients with PH from the phase II trial, 15 potential PH patients with hemorrhage at any site from the phase III trial, and their matched controls were evaluated with review of baseline and on-treatment radiographs by an independent radiology facility, blinded to patient/control status. Patients with severe (grade ≥ 3) PH from each trial were matched with up to three controls based on sex, age group, histology (phase II), or sex and age group (phase III).

Results

Seven PH patients in the phase III trial were identified as severe PH. Six of the patients were early onset (occurred < 150 days of initiating bevacizumab) and one was late onset. Baseline tumor cavitation, not tumor location, was identified as the only potential risk factor for patients with early onset. Combined analysis of severe PH patients from the phase II and phase III trials (n = 13), compared with their pooled matched controls (n = 42), did not identify any additional baseline radiographic or clinical variables associated with PH.

Conclusion

PH was an uncommon event. Based on these analyses, baseline tumor cavitation may be a potential risk factor for PH. No other baseline clinical variables were predictive for PH although the number of events was small.

J Clin Oncol 27:1405-1412. © 2009 by American Society of Clinical Oncology

INTRODUCTION

In a randomized phase II trial, bevacizumab (BV), a monoclonal antibody against vascular endothelial growth factor (VEGF), combined with carboplatin/paclitaxel (CP) in chemotherapy-naïve, locally advanced, recurrent or metastatic non–small-cell lung cancer (NSCLC), demonstrated significant improvement in median time to disease progression, along with a numerically higher rate of tumor response and improved survival.¹ Severe and life-threatening (grade ≥ 3) pulmonary hemorrhage (PH), however, was observed in 9.1% of BV-treated patients (six of 66).¹ An association of possible risk factors (including squamous cell histology [SCC],

concomitant medications, prior therapy, BV therapy, atherosclerosis, tumor location, and cavitation) were evaluated for the six patients with life-threatening bleeding, compared with 24 controls (matched for age, sex, Eastern Cooperative Oncology Group [ECOG] performance status [PS]) and with the entire study population.² SCC ($P = .105$, matched controls; $P = .004$, study population) and BV therapy ($P = .104$, $P = .082$), respectively, appeared to have the closest association with PH.²

Based on these results, a subsequent ECOG phase III trial in non-SCC patients demonstrated a significant benefit in overall survival (OS) and progression-free survival.³ In the phase III trial, the incidence of severe PH was much lower than in the

phase II trial, in which hemoptysis and SCC were not exclusion criteria (2.3% patients *v* 9.1% of BV-treated patients, respectively).^{1,3} Severe or fatal PH has also been seen in trials with other VEGF pathway-directed agents, such as sorafenib and sunitinib, but risk factors associated with PH in these patients are not completely understood.⁴⁻⁶ Few studies have systematically evaluated the contribution of specific clinical and/or tumor characteristics to developing hemoptysis, especially severe PH, before the introduction of BV. Based on limited retrospective studies, risk factors suggested to be associated with developing hemoptysis include tumor cavitation, SCC, and central tumor location.⁷⁻⁹

We attempted to define potential risk factors associated with PH in the setting of BV therapy by systematically evaluating clinical and/or radiographically defined tumor characteristics chosen a priori that could predict PH. Data were obtained from the phase II and phase III trials described above, and this evaluation was conducted in collaboration with the ECOG. Retrospective case-control and cohort evaluations of BV-treated patients in the phase III trial and combined with those in the phase II trial is presented.

PATIENTS AND METHODS

Study Outcomes

In this analysis, a primary event of early-onset severe PH was the primary outcome of interest and was defined as occurring fewer than 150 days of initiation of BV therapy in patients from the phase III trial. A secondary outcome, the combination of both early- and late-onset severe PH events (≥ 150 days) was also evaluated in BV-treated patients from the phase II and III trials.

Study Population

Phase II study. Ninety-nine patients were randomly assigned to CP ($n = 33$) or CP plus either 7.5 mg/kg or 15 mg/kg of BV ($n = 66$) between May 1998 to September 1999.¹ Major inclusion criteria included stage IIIb (with pleural effusion), recurrent or metastatic NSCLC. Patients with mixed NSCLC/small cell histology or CNS metastases were excluded. Location of the primary tumor lesion was not an eligibility criterion. Analysis included six

patients with life-threatening PH from the phase II trial.² The onset of PH events ranged from 13 to more than 200 days after initiating treatment. For the six patients, up to three controls from the BV-treated arms were matched based on histology (predominantly SCC or excluding predominantly SCC), sex, and age group (< 65 or ≥ 65 years). The cohort analysis population comprised all safety-assessable BV-treated patients in the phase II trial. All patients identified for the patient-control analysis were considered in the cohort analysis; non-patient cases comprised all BV-treated patients who were not identified as patient cases.

Phase III study. Between July 2001 and April 2004, patients received CP ($n = 444$) or CP plus 15 mg/kg BV ($n = 434$).³ The eligibility criteria differed from the phase II in that patients with SCC, or a history of hemoptysis defined as $\geq 1/2$ teaspoons of blood were excluded. Location of primary tumor lesion was not defined for eligibility. The onset of PH events ranged from 13 to more than 400 days after treatment initiation. Based on the clinical record review, patients with severe (grade ≥ 3) early-onset or late-onset PH were identified and adjudicated by an expert panel. Patients with hemorrhage potentially due to an additional complicating factor (ie, lung infection, coagulopathy or hematologic impairment, or disease progression) were excluded. For each patient with a PH event identified as a patient case for this analysis, up to three controls from among the BV-treated patients were matched based on sex and age group (< 65 , ≥ 65 years). Consistent with the phase II trial, the cohort analysis population comprised all safety-assessable BV-treated patients in the phase III trial.

Radiographic Tumor Characteristics

Computed tomography chest scans from all PH patients and matched controls were assessed by an independent review facility (IRF), blinded to the clinical history and patient/control status.

Baseline tumor characteristics. The primary analysis of potentially relevant baseline tumor characteristics consisted of tumor location ([central-defined as within 2 cm of bronchus] *v* [peripheral-defined as tumor epicenter within 2 cm of a pleural surface] *v* [other location-defined as any lesion that was not considered a central or peripheral lesion]); presence and size of cavitation; and longest diameter of largest nodal or tumor mass. Cavitation size was dichotomized by the cumulative size of longest dimension of tumor cavitation in the study population and defined as minor (< 75 th percentile) versus major (≥ 75 th percentile). For patients with multiple cavitory lesions, the size of the largest cavity was recorded. Additional radiographic characteristics evaluated included vascular involvement, tracheobronchial involvement, and total number of measurable intrathoracic lesions.

Fig 1. Overview of pulmonary hemorrhage (PH) patient cases, matched controls, and non-patient cases.¹⁻³ Note: The cohort analysis population comprised all safety-evaluable bevacizumab-treated patients in the phase II study. All patients identified for the case-control analysis were considered patient cases for the purposes of the cohort analysis; non-patient cases comprised all patients who were not identified as potential patient cases. (*) Controls from the bevacizumab-treatment arm were matched based on sex, age group (< 65 , or ≥ 65 years), and histology (predominantly squamous or excluding predominantly squamous). (†) Controls from the bevacizumab-treatment arm were matched based on sex and age group (< 65 , or ≥ 65 years). (‡) Patients included in retrospective case-control analysis. (§) Patients included in retrospective cohort analysis.

Postbaseline tumor characteristics and reproducibility/reliability. Presence of cavitation and maximum size of cavitation that developed in tumor lesions postbaseline, was assessed in any pre-existing or new lesion. Lesions with a change in cavitation size from baseline were included in this analysis. Lesion hypodensity preceding development of cavitation was also evaluated.

All baseline and postbaseline radiographic measurements were independently assessed by two radiologists blinded to the clinical data and measured for concordance.

Clinical/Patient Characteristics

Clinical and demographic variables evaluated at baseline included: sex, age (< 65, ≥ 65 years), race (white, nonwhite), ECOG PS (0, 1), prior treatment with radiation therapy, and prior thoracic surgery. Rapid response to treatment was defined as an unconfirmed partial response (PR; a > 30% decrease in sum of the longest lesion diameter) at first assessment (6 weeks) by Response Evaluation Criteria in Solid Tumors.¹⁰

Statistical Methods

Patient-control analysis. A patient-control design was employed to evaluate radiographic risk factors because this design allowed for the efficient use of an existing study population, did not involve performing any new interventions, and allowed for retrospective collection and review of radiographic images in all PH patients requiring only a sample of the non-patient cases (as opposed to all non-patient cases) as controls. It is a scientifically efficient

approach for studying rare events, and estimates of the odds ratio (OR) obtained from a well-conducted patient-control analysis is generally considered a good proxy measure of relative risk for the target event.¹¹ A patient-control analysis was performed on the early-onset patient cases and matched controls identified from the phase III trial and another was performed on patients and matched controls pooled from the phase II and III trials.

The statistical association between baseline radiographic variables and patient/control status was assessed separately for each variable and frequencies were calculated. Differences between patients and controls for nominal categorical variables were evaluated using *P* values from a stratified Cochran-Mantel-Haenszel test of general association (with an asymptotic χ^2 distribution), in which each patient case and matched control(s) made up a stratum. The magnitude of association was assessed using the stratified Mantel-Haenszel (MH) estimate of the common OR¹² and the corresponding 95% CI calculated from a variance estimate of the log OR as specified by Robins et al.¹³ Continuous variables were discretized at the sample median or the 75th percentile for all patients and controls and then analyzed as a nominal categorical variable.

Cohort analysis. Statistical associations between clinical factors and risk of PH were evaluated using the entire BV-treated study population since the data were readily available in the phase II/III study databases. The *P* value was calculated from the Cochran MH (CMH) χ^2 test; the CIs for

Table 1. Patient Demographics and Clinical Characteristics at Study Entry (phase II and III studies)

Characteristic	Phase III				Phase II			
	PH (n = 7)*		No PH (n = 412)†		PH (n = 6)‡		No PH (n = 60)§	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median		61.0		63.0		65.0		61.5
Range		35-79		27-88		55-75		34-80
< 65	4	57.1	238	57.8	3	50.0	35	58.3
≥ 65	3	42.9	174	42.2	3	50.0	25	41.7
Sex								
Female	4	57.1	205	49.8	1	16.7	30	50.0
Male	3	42.9	207	50.2	5	83.3	30	50.0
Race								
White	7	100	345	83.7	5	83.3	34	56.7
Non-white	0		67	16.3	1	16.7	26	43.3
ECOG PS								
0	2	28.6	167	40.7	0	0	34	56.7
≥ 1	5	71.4	243	59.3	6	100.0	26	43.3
Disease stage								
IIlb	3	42.9	47	11.4	0	0	9	15.0
IV	4	57.1	309	75.0	4	66.7	42	70.0
IV, recurrent	—	—	56	13.6	0		1	1.7
Histologic type								
Squamous cell	0		1	0.2	4	66.7	9	15.0
Adenocarcinoma	5	71.4	288	69.9	2	33.3	41	68.3
Large cell anaplastic carcinoma	0	0	0	0	0	0	5	8.3
Large cell undifferentiated	1	14.3	16	3.9	0	0	0	0
Bronchoalveolar	0		10	2.4	0	0	0	0
NSCLC, NOS	1	14.3	75	18.2	0	0	0	0
Other	0		22	5.3	0	0	5	8.3

NOTE. Column totals for individual variables may not equal the overall total due to the presence of missing values. The entire study population presented in Table 1 was bevacizumab-treated patients.

Abbreviations: PH, pulmonary hemorrhage; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified.

*Patients adjudicated as having experienced a primary event of grade ≥ 3 pulmonary hemorrhage (includes six with early onset and one with late onset).

†Total number of bevacizumab-treated patients in E4599 (n = 427) less the number of potential patient cases sent for adjudication (n = 15).

‡Patients with pulmonary hemorrhage identified in the original phase II study by Novotny et al.²

§Total number of bevacizumab-treated patients in study AVF0757g (7.5 mg/kg and 15 mg/kg arms; n = 66) less the number of patient cases identified (n = 6).

||Non-white race includes a patient or institutional refusal, other, and unknown.

the CMH estimate were calculated using the variance estimate as specified by Robins et al.¹³

Patients with missing data for clinical or radiographic variables were excluded from the corresponding analysis.

RESULTS

Patients, Matched Controls, and Non-Patient Cases

Of the six phase II study patient cases identified with severe PH,² three were early onset; overall, 11 controls were matched to these patients based on sex, age group (< 65, or > 65 years), and histology (predominately SCC, or excluding predominately SCC).

Fifteen patients among the BV-treated patients who participated in the phase III study were identified as experiencing hemorrhage at any site. The adjudication panel confirmed that 10 of 15 patients had pulmonary hemorrhages, seven of which had a primary PH event. Three were excluded after concluding that the event of hemorrhage was due to sepsis (n = 1) or disease progression (n = 2). Six developed PH and were deemed early onset. For the patient-control analysis, 31 controls were matched to the seven patients and 29 controls were matched to the six early-onset patients. An overview of the patients, matched controls, and non-patient cases is presented in Figure 1.

Phase II and III Patient Demographics (patients and non-patient cases)

Patient demographics and disease characteristics were similar across both studies with an overall predominant histology of adeno-

carcinoma (Table 1). However, the populations differed by sex—the phase III study had a greater proportion of females experiencing PH. In addition, a higher percentage of phase II patients had SCC (66.7%), compared with non-patient cases (15%) in the same study.

Characteristics of Patients With Pulmonary Hemorrhage

Selected clinical and radiographic characteristics of PH patients in the phase II study and phase III study are presented in Tables 2 and 3, respectively. One of the patients in the phase II study had a history of prior hemoptysis at baseline and there were no patients who experienced both cavitation at baseline and developed cavitation postbaseline (Table 2). Of the three patients in the phase III study that developed cavitation on treatment, one had a cavitory lesion at baseline and two had a history of hemoptysis (Table 3). Five of the six patients in the phase III study had a fatal PH.

Patient-Control Analysis

Phase III. Results of the phase III matched patient-control analysis are presented in Table 4. In this population, lesion location, size, and severe PH were not associated. There appeared to be an association between intrathoracic tumor cavitation and severe PH (two of six patients, one of 29 controls). The risk of developing early-onset severe PH was higher with cavitation at baseline (OR, 9.6; 95% CI, 0.86 to 107.64; *P* = .034), compared with patients without evidence of tumor cavitation at baseline.

Table 2. Demographics and Clinical Characteristics of Early-Onset and Late-Onset Patients With Grade $\geq$ 3 Primary Event of Pulmonary Hemorrhage (phase II study)

Patient No.	Age (years)	Sex	ECOG PS	Histology	Location of Tumor	Baseline Hemoptysis	Baseline Cavitation	Post-Baseline Cavitation*	Hemoptysis Event†	Days to Event Since First BV Infusion
1	66	Female	1	Squamous	Pretracheal LLL, R post mid-lung, L flank mass; central lesion: LD 60 mm; central lesion: LD 20 mm	No	Yes	No	Grade 5	13
2	75	Male	1	Squamous	L hilar mass, mediastinal and subcarinal nodes, pleural mass. L pleural mass; central lesion 3: LD 40 mm, 20 mm, 35 mm; other lesion: LD 36 mm	No	No	Yes	Grade 3	12
3	60	Male	1	Adenocarcinoma	R paratracheal, RLL sulcus, RML/UL mass, mult pulm lesions, mediastinal nodes; central: LD 27 mm 39 mm; peripheral: LD 48 mm; other: LD 24 mm	No	No	Yes	Grade 5	93
4	72	Male	2	Squamous	LLL mass, RLL mass, L&R adrenal mass; other: LD 59 mm; central: LD 93 mm	No	Yes	No	Grade 3	247
5	64	Male	1	Squamous	LLL mass, AP window nodes, R paratracheal nodes, L paratracheal nodes; other: LD 48 mm	No	No	No	Grade 5	202
6	55	Male	1	Adenocarcinoma	R pleural nodule, L large mass; central: LD 37 mm; central: LD 40 mm	No	No	No	Grade 5	282

NOTE. Three patients had early-onset pulmonary hemorrhage, and three patients had late-onset pulmonary hemorrhage.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; BV, bevacizumab; LLL, left lower lobe (lung); R, right; LD, longest dimension; L, left; RLL, right lower lobe (lung); UL, upper lobe (lung); mult, multiple; pulm, pulmonary; RML, right middle lobe; AP, aorto-pulmonic.

*Defined as development of cavitation post-baseline in a non-cavitory lesion present at baseline, and presence of new cavitory lesions.

†While on study.

Table 3. Clinical Characteristics of Patients With Early-Onset Grade ≥ 3 Primary Event of Pulmonary Hemorrhage (phase III study)

Patient No.	Age (years)	Sex	ECOG PS	Histology	Location of Tumor	Baseline Hemoptysis	Baseline Cavitation	Post-Baseline Cavitation*	Hemoptysis Event†	Days to Event Since First BV Infusion
1	60	Female	1	Adenocarcinoma	Central: hilar mass (7 cm); mediastinal adenopathy	No	No	Yes	Grade 3	51
2	35	Male	0	PD large cell cancer	Central: L hilar mass; (5.4 4.5 cm) with central necrosis	No	Yes	Unknown	Grade 5	8
3	79	Female	1	PD carcinoma	Central: RUL (6 cm) w/ obstruction; mass protruding into R bronchus, abut SVC, and encases azygous	No	No	Unknown	Grade 5	14
4	77	Male	0	Adenocarcinoma	Other: right infrahilar (5.2 cm), subcarinal node (4.3 cm), precarinal node (3.7 cm)	Yes	No	Unknown	Grade 5	17
5	58	Female	1	Adenocarcinoma	Other: LUL (1.8 cm); Central: mediastinal node, LUL (1.8 cm); peripheral	Yes	Yes	Yes	Grade 5	54
6	61	Female	1	Adenocarcinoma	RUL (10 cm) involving mainstem and UL bronchus	Yes	No	Yes	Grade 5	43

*Defined as development of cavitation post baseline in a non-cavitary lesion present at baseline, and presence of new cavitary lesions.

†While on study.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; BV, bevacizumab; PD, progressive disease; L, left; RUL, right upper lobe (lung); R, right; SVC, subclavian vein compression; LUL, left upper lobe (lung); UL, upper lobe.

Analysis of additional baseline and postbaseline radiographic factors and their matched controls in the phase III study is shown (Table 5). Postbaseline cavitation in any intrathoracic lesion, and endobronchial involvement (at baseline) were associated with the development of PH. Cavitation size was ≥ 49 mm (≥ 75 th percentile) in two patients and smaller than 49 mm (< 75 th percentile) in one patient. Cavitary lesions in all five controls were smaller than 49 mm in longest diameter. A higher proportion of severe PH patients were associated with massive cavitation, while minor cavitation occurred in a higher proportion of controls. Of the three patients that developed cavitation on treatment, the tumor lesions were hypodense at baseline in two, compared with one of five in controls. Tracheobronchial involvement occurred to a greater extent in the patients than in controls.

Combined phase II and III. Consistent with findings in the phase III population alone, baseline intrathoracic cavitation appeared to be associated with severe PH in the combined phase II/III population (four of 13 patients *v* two of 36 controls; Table 4). Based on the combined results, baseline cavitation was associated with an increased risk (OR, 4.5; 95% CI, 0.73 to 28.33), although not significant ($P = .063$; Table 4). A computed tomography scan of one patient with severe PH who had baseline hemoptysis and tumor cavitation is shown in Appendix Figure A1 (online only).

In this combined analysis, tumors located centrally were present in 34 (62%) of 55 patients. Among patients assessed for response at 6 weeks, the rate of PH was 1.9% in patients with response versus 0% in those without ($P =$ not significant). This assessment was limited, however, because of a large proportion of missing values in patients (four of six; 66%) with three patients dying before the first assessment at 6 weeks and one discontinuing due to toxicity. Among the non-

patient cases, the primary reasons for discontinuation before the first assessment were disease progression, toxicity, or death.

Cohort Analysis

For the phase III cohort or the combined phase II/III cohort, there was no statistically significant association with developing severe PH and baseline clinical risk factors (sex, age group [≥ 65 years], ECOG PS [0, 1], prior treatment with radiation therapy, and prior thoracic surgery, data not shown). A slightly higher percentage of patients in the combined phase II/III population had an ECOG PS ≥ 1 , compared with ECOG PS = 0 (3.9% *v* 1.0%, data not shown).

DISCUSSION

BV was the first antiangiogenic agent to increase efficacy of a platinum doublet in a phase II trial of NSCLC.¹ However, of the 66 patients who received BV, life-threatening pulmonary hemorrhage occurred in six, including four fatal events. Serious hemorrhagic events appeared to be more common among patients with predominantly SCC. These preliminary results prompted the confirmatory phase III study, E4599, comparing CP with or without BV in patients with nonsquamous NSCLC.³ Results of this trial demonstrated that BV combined with CP extended the median OS from 10.3 to 12.3 months (hazard ratio = 0.79; $P = .003$) and led to eventual US Food and Drug Administration approval in this population. The exclusion of patients with SCC and/or evidence of baseline gross hemoptysis in the phase III trial resulted in a lower incidence of PH in patients receiving BV³ (incidence of severe PH in phase III was 2.3% [10 of 427]).

Our goal in this study was to identify key clinical and radiographic factors that allow us to identify patients at risk for severe

Table 4. Potential Baseline Radiographic Risk Factors for Severe Pulmonary Hemorrhage (patients and matched controls from bevacizumab-treatment arms)

Risk Factor	Phase III (early onset)									Phase II + Phase III (early and late onset)								
	PH Patients (n = 6)			Matched Controls (n = 29)		Odds Ratio	95% CI	P	PH Patients (n = 13)			Matched Controls (n = 42)		Odds Ratio	95% CI	P*		
	No.	No.	%	No.	%				No.	No.	%	No.	%					
Lesion location																		
Presence of centrally located tumor																		
Yes	16	3	50.0	13	44.8	1.2	0.22 to 615	.856	26	8	61.5	18	42.9	2.3	0.64 to 7.96	.204		
No	19	3	50.0	16	55.2	1.0 (ref)			29	5	38.5	24	57.1	1.0 (ref)				
Only peripheral tumor lesion(s)																		
Yes	4	1	16.7	3	10.3	1.7	0.17 to 16.63	.637	6	2	15.4	4	9.5	1.6	0.26 to 9.96	.612		
No	31	5	83.3	26	89.7	1.0 (ref)			49	11	84.6	38	90.5	1.0 (ref)				
Presence of centrally located node																		
Yes	23	5	83.3	18	62.1	4.4	0.33 to 58.87	.281	34	9	69.2	25	59.5	2.1	0.41 to 11.02	.390		
No	12	1	16.7	11	37.9	1.0 (ref)			21	4	30.8	17	40.5	1.0 (ref)				
Cavitation																		
Presence in intra-thoracic lesion																		
Yes	3	2	33.3	1	4.0	9.6	0.86 to 107.64	.034	6	4	30.8	2	5.6	4.5	0.73 to 28.33	.063		
No	28	4	66.7	24	96.0	1.0 (ref)			43	9	69.2	34	94.4	1.0 (ref)				
Cavitation size†																		
≥ 75th percentile	1	0	0.0	1	100.0	—		—	2	1	25.0	1	50.0	—		—		
< 75th percentile	2	2	100.0	0	0.0				4	3	75.0	1	50.0					
Size of the longest dimension																		
Largest central tumor‡§																		
≥ median	8	1	50.0	7	53.8	1.00	0.06 to 15.59	1.000	17	6	66.7	11	44.0	2.2	0.46 to 11.0	.279		
< median	7	1	50.0	6	46.2	1.0 (ref)			17	3	33.3	14	56.0	1.0 (ref)				
Largest central node‡																		
≥ median	12	4	80.0	8	44.4	3.28	0.44 to 24.51	.191	13	3	42.9	11	55.6	0.4	0.46 to 11.0	.439		
< median	11	1	20.0	10	55.6	1.0 (ref)			12	4	57.1	7	44.4	1.0 (ref)				

NOTE. Column totals for individual variables may not equal the overall total due to the presence of missing values. Definitions for radiographic variables include: central lesion was defined as a tumor within 2 cm of the trachea, main and lobar bronchi; a peripheral lesion was defined as any non-central lesion, the epicenter of which was within 2 cm of the costal or diaphragmatic pleura based on each affected lobe of the lung. Any lesion that was not considered a central or peripheral lesion was classified as "other." The size of a pulmonary lesion(s) was characterized according to the longest dimension of the largest central tumor, and longest dimension of the largest central node (defined similarly to that of pulmonary lesions). Each of these variables were further sub-categorized for central tumors that were either < or ≥ 5 cm or central node < or ≥ 3 cm. Odds ratio of 1.0 indicates ref category for odds ratio comparison.

Abbreviations: PH, pulmonary hemorrhage; ref, reference.

*P values were calculated using stratified Cochran-Mantel-Haenszel tests, with sex and age group as stratification factors.

†[minimum, maximum] in (mm) is [4, 43] for phase III analysis and [4, 83] for combined analysis; 75th percentile for phase III study is 43 mm, for combined analysis is 49 mm.

‡Total number conditional on presence of node or tumor under Lesion Location; cut-off based on median value of the analysis population.

§[minimum, maximum] in (mm) is [21, 109] for both phase III and combined analyses; median for phase III analysis is 55 mm, for combined analysis is 54 mm.

||[minimum, maximum] in (mm) is [14, 78] for both phase III study and combined analysis; median for phase III analysis is 32 mm, for combined analysis is 31 mm.

hemorrhage. The findings from the phase II study,² and our combined analysis from the phase II and III studies identified baseline cavitation as a potential risk factor for severe PH regardless of histology or location.

The pathogenesis of tumor cavitation and the impact of systemic chemo-, or antiangiogenic therapy on its development have not been reported. One suggested mechanism for development of cavitation is that rapid growth of the tumor exceeding the tumor blood supply, and/or inhibition of tumor-associated vasculature may lead to cavity formation and growth pattern of squamous histology and contribute to the development of PH. For example, the classic presentation of squamous histology is an endobronchial lesion arising in the proximal segmental bronchus, whereas adenocarcinomas generally occur more peripherally. SCC is the most common histologic type to develop a cavitating primary lesion;

however, adenocarcinomas also cavitate.¹⁴ Cavitation occurs in 2% to 16% of primary lesions.^{7,9,15-17}

In our analysis, development of severe PH for the majority of patients, regardless of histology, was in close temporal relation to the initiation of BV treatment (administered every 3 weeks). Severe PH occurred within 100 days in three of six patients from the phase II trial, and in six of seven patients from the phase III trial. In the other three patients from the phase II trial, and the one in the phase III, severe PH occurred beyond 200 days. Late-onset PH events may be more likely influenced by risk factors other than those present at baseline, including mechanisms related to either disease progression or development of comorbid conditions, such as obstructive pneumonia, and were excluded from the primary analysis. Even with the inclusion of these late-onset events the overall results for risk factors at baseline were unchanged.

Table 5. Potential Post-Baseline and Additional Baseline Radiographic Risk Factors for Early-Onset Severe Pulmonary Hemorrhage in Phase III (patients and matched controls from bevacizumab-treatment arms)

Risk Factor	No.	Patients (n = 6)		Matched Controls (n = 29)		Odds Ratio	95% CI	P
		No.	%	No.	%			
Additional baseline factors								
Vascular involvement by highest involvement								
No contact	2	0		2	8.0	1.0 (ref)		.118
Contiguous	21	3	50.0	18	72.0	—		
Constricted	8	3	50.0	5	20.0	—		
Suspicion of endobronchial involvement								
Yes	6	3	50.0	3	10.3	12.8	1.02 to 160.7	.024
No	29	3	50.0	26	89.7	1.0 (ref)		
Tracheobronchial involvement								
Yes	27	6	100.0	21	72.4	—		.147
No	8	0		8	27.6	1.0 (ref)		
Extent of tracheobronchial involvement								
No involvement	8	0		8	27.6	1.0 (ref)		.075
Possible involvement	4	0		4	13.8	—		—
Definite involvement	23	6	100.0	17	58.6	—		
Total No. of measurable intrathoracic lesions*								
≥ 4	18	3	50.0	15	51.7	0.9	0.16 to 5.25	.935
< 4	17	3	50.0	14	48.3	1.0 (ref)		
Post-baseline factors								
Cavitation								
Presence in intra-thoracic lesion								
Yes	8	3	100.0	5	21.7	—		.020
No	18	0	0.0	18	78.3	1.0 (ref)		
Cavitation size [4, 83]†								
≥ 49 mm	2	2	66.7	0	0.0	—		—
< 49 mm	6	1	33.3	5	100.0	1.0 (ref)		

NOTE. Column totals for individual variables may not equal the overall total because of missing values. Vascular involvement of the tumor (classified as: no contact between tumor and vessel; tumor and vessel are contiguous; vessel is constricted, occluded, or ends in a cavitory lesion). Tracheobronchial involvement was defined as a dichotomous variable indicating the presence/absence (yes/no) of tracheobronchial involvement and as a trichotomous ordinal variable (no, possible, yes) indicating differential levels (extent) of tracheobronchial involvement. The following criteria were defined to evaluate bronchial involvement, while allowing the radiologists to remain blinded to case-control status: Category 1—the tumor does not contact the margin of the tracheobronchial tree; Category 2—the tumor does contact the margin of the tracheobronchial tree without encasement or narrowing; Category 3—the tumor either partly or entirely encases the tracheobronchial tree; Category 4—the tumor either partly or entirely encases the tracheobronchial tree, with tracheobronchial narrowing; Category 5—the tracheobronchial tree ends in a mass with or without consolidation; Category 6—there is localized intraluminal soft tissue density. Odds ratio of 1.0 (ref) = ref category for odds ratio comparison.

Abbreviation: ref, reference.

*Variable is dichotomized at the median value.

†[minimum, maximum] in millimeters (mm). Variable is dichotomized at the 75th percentile.

While central tumor location was common, there was no correlation between this and the risk of PH. Exclusion of patients with active hemoptysis may be one way to reduce risk of PH since hemoptysis was present in all of the patients with baseline cavitation. In our analysis, none of the other potential clinical risk factors, or radiographic variables such as tumor proximity to vascular structures were independent risk factors for severe PH.

Exclusion of patients with SCC to mitigate against PH is supported by the observation of PH with other anti-VEGF therapies.^{18,19} In previously treated, recurrent NSCLC patients with squamous cell histology treated with sunitinib, three fatal hemorrhagic events (two treatment related) were reported, with one patient developing cavitation and grade 5 hemorrhage after treatment with sorafenib. Of note, the anatomic location (presence of a centrally located tumor) did not appear to predispose other patients in these studies with nonsquamous cell histology to a risk of hemorrhage.

In conclusion, the a priori identification of risk factors associated with severe PH is the optimal approach to manage patients treated with BV. Our study is the first to evaluate risk factors for severe PH in patients with NSCLC treated with BV across studies; we determined that baseline cavitation was the main risk factor in the predominately non-SCC population of the phase III study and combined analysis of the phase II and phase III studies also identified baseline tumor cavitation as a potential risk factor. From the phase II experience, which included patients with predominant squamous histology, it was hypothesized that central tumor location may be an increased risk factor for PH when treating NSCLC patients with bevacizumab (Avastin; Genentech Inc, South San Francisco, CA). However, in E4599, when patients with predominant squamous histology were excluded from the trial, central location did not appear to be predictive of risk for PH. Based on these data, NSCLC patients with nonsquamous tumors should not be excluded from BV treatment based solely on central tumor location.

The small number of events of severe PH in these populations limited the ability to fully assess the role of SCC, cavitation, and other possible risk factors for PH. In addition, the largest study, E4599, did not capture less serious degree of PH (ie, grade 2) which might have proven useful. It is hoped that with continued surveillance in ongoing and future clinical trials in advanced or metastatic NSCLC will provide additional information.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Isaiah Dimery, Genentech (C); Meghna Samant, Genentech (C); Lisa I. Wang, Genentech (C)
Consultant or Advisory Role: Alan B. Sandler, AstraZeneca (C),

Genentech (C); Joan H. Schiller, AstraZeneca (C), Genentech (C), Pfizer (C); Robert Gray, Genentech (U); Julie Brahmer, Cephalon (C), Eli Lilly & Co (C), Genentech (C); David H. Johnson, Genentech (U) **Stock Ownership:** Isaiah Dimery, Genentech; Meghna Samant, Genentech; Lisa I. Wang, Genentech **Honoraria:** Alan B. Sandler, Genentech **Research Funding:** Alan B. Sandler, Genentech; Joan H. Schiller, AstraZeneca, Genentech, Merck & Co, Pfizer; Robert Gray, Genentech; Julie Brahmer, AstraZeneca, Medarex, Pfizer, Wyeth **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Alan B. Sandler, Isaiah Dimery, Lisa I. Wang, David H. Johnson

Provision of study materials or patients: Joan H. Schiller, Julie Brahmer

Collection and assembly of data: Robert Gray

Data analysis and interpretation: Alan B. Sandler, Joan H. Schiller, Isaiah Dimery, Meghna Samant, Lisa I. Wang, David H. Johnson

Manuscript writing: Alan B. Sandler, Isaiah Dimery, Lisa I. Wang, David H. Johnson

Final approval of manuscript: Alan B. Sandler, Joan H. Schiller, Robert Gray, Isaiah Dimery, Julie Brahmer, Meghna Samant, Lisa I. Wang, David H. Johnson

REFERENCES

- Johnson DH, Fehrenbacher L, Novotny WF, et al: Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 22:2184-2191, 2004
- Novotny WF, Holmgren E, Griffing S, et al: Identification of squamous cell histology and central, cavitary tumors as possible risk factors for pulmonary hemorrhage (PH) in patients with advanced NSCLC receiving bevacizumab (BV). *Proc Am Soc Clin Oncol* 20:330a, 2001 (abstr 1318)
- Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355:2542-2550, 2006
- Socinski MA, Novello S, Sanchez JM, et al: Efficacy and safety of sunitinib in previously treated, advanced non-small cell lung cancer (NSCLC): Preliminary results of a multicenter phase II trial. *J Clin Oncol* 24:49s, 2006 (suppl; abstr 7001)
- Adjei AA, Molina JR, Hillman SL, et al: A front-line window of opportunity phase II study of sorafenib in patients with advanced non-small cell lung cancer: A North Central Cancer Treatment Group study. *J Clin Oncol* 25:396s, 2007 (suppl; abstr 7547)
- Gauler TC, Besse B, Meric JB, et al: Phase II open-label study to investigate efficacy and safety of PTK787/ZK 222584 (PTK/ZK) orally administered once daily or twice daily at 1,250 mg as second-line monotherapy in patients (pts) with stage IIIB/IV non-small cell lung cancer (NSCLC). *J Clin Oncol* 25:394s, 2007 (suppl; abstr 7541)
- Miller RR, McGregor DH: Hemorrhage from carcinoma of the lung. *Cancer* 46:200-205, 1980
- Salajka F: Occurrence of haemoptysis in patients with newly diagnosed lung malignancy. *Schweiz Med Wochenschr* 129:1487-1491, 1999
- Pentheroudakis G, Kostadima L, Fountzilas G, et al: Cavitating squamous cell lung carcinoma—distinct entity or not? Analysis of radiologic, histologic, and clinical features. *Lung Cancer* 45:349-355, 2004
- Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
- Rothman KJ, Greenland S: *Modern epidemiology* (ed 2). Philadelphia, PA, Lippincott Williams and Wilkins, 1998
- Agresti A: *Categorical Data Analysis*. New York, NY, John Wiley & Sons, 1990
- Robins J, Breslow N, Greenland S: Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* 42:311-323, 1986
- Seo JB, Im JG, Goo JM, et al: Atypical pulmonary metastases: Spectrum of radiologic findings. *Radiographics* 21:403-417, 2001
- Mouroux J, Padovani B, Elkaim D, et al: Should cavitated bronchopulmonary cancers be considered a separate entity? *Ann Thorac Surg* 61:530-532, 1996
- Chaudhuri MR: Primary pulmonary cavitating carcinomas. *Thorax* 28:354-366, 1973
- Kolodziejewski LS, Dyczek S, Duda K, et al: Cavitated tumor as a clinical subentity in squamous cell lung cancer patients. *Neoplasma* 50:66-73, 2003
- Socinski MA, Novello S, Brahmer JR, et al: Phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol* 26:650-656, 2008
- Gatzemeier U, Blumenschein G, Fosella F, et al: A phase II trial of single-agent sorafenib in patients with advanced non-small cell lung carcinoma. *J Clin Oncol* 24:364s, 2006 (suppl; abstr 7002)

Acknowledgment

We thank Genentech Inc for their assistance in the preparation of this manuscript.