Outcomes Associated with Brain Metastases in a Three-Arm Phase III Trial of Gemcitabine-Containing Regimens Versus Paclitaxel Plus Carboplatin for Advanced Non-small Cell Lung Cancer

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Background: Brain metastases (BMs) are a common complication of non-small cell lung cancer (NSCLC). Because of historical data indicating a poor prognosis for patients with BM, few randomized phase III studies of advanced NSCLC have included patients with BM at presentation. Because the potential benefits of systemic therapy in patients with BM are uncertain, we analyzed data from a recent phase III study.

Methods: One thousand one hundred thirty-five chemonaïve patients with stage IIIB/IV NSCLC were randomized to receive gemcitabine/carboplatin, gemcitabine/paclitaxel, or paclitaxel/carboplatin. Stratification was based on presence or absence of BM, stage, and baseline weight loss. Patients with BM were required to be clinically stable after treatment with radiotherapy or surgery before entry. Results were retrospectively analyzed by presence or absence of BM at study entry.

Results: Rate of BM was 17.1% overall. The response rate was 28.9% for patients with BM ($n = 194$) versus 29.1% without BM ($n = 941$). Time to progression was 4.3 months with BM and 4.6 months without BM ($p = 0.03$). Median survival was 7.7 months (95% confidence interval: 6.7–9.3) among patients with BM ($n = 194$) and 8.6 months (95% confidence interval: 7.9–9.5) for patients without BM ($n = 941$), $p = 0.09$. Rates of hematologic adverse events were not different among patients with and without BM.

Conclusions: There were no significant differences in response, survival, or hematologic toxicity for patients with or without BM; however, patients with BM had a small but significantly shorter time to progression. Nonprogressing patients with treated BM are appropriate candidates for systemic therapy and entry into clinical trials.

Key Words: NSCLC, Phase III, Brain metastases, Nonplatinum doublets.

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The estimated incidence of non-small cell lung cancer (NSCLC) in the United States is approximately 174,000 new cases each year.[1] At the time of diagnosis, most patients (>80%) have locally advanced or metastatic disease, and the 5-year survival is less than 10% in this patient population.[2,3] Chemotherapy has become standard treatment for patients with advanced NSCLC, with platinum-based or nonplatinum doublets producing a modest survival benefit and improvement in quality of life compared with best supportive care alone.[4–9]

Brain metastasis (BM) is a common and serious complication of NSCLC disease that is associated with significant morbidity and poor survival.[10] Estimates of BM among patients with NSCLC during the course of disease range from 30 to 50%, and lung cancer represents the most common malignancy of the central nervous system.[11–13] Analyses of patients with lung cancer from the 1970s to 1980s indicated that the incidence of BM among newly diagnosed patients was approximately 10%.[14,15]

During that era, median survival associated with BM in advanced or metastatic NSCLC was <3 months.[16–19] Because of the poor prognosis, patients with BM have often been treated with palliative measures such as steroids and whole brain radiation therapy (WBRT).[20,21] As a result of poor prognosis and a concern that chemotherapy may have a limited ability to cross the blood-brain barrier, few randomized phase III studies of advanced or metastatic NSCLC have included patients with BM.[22] However, the past 30 years have

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witnessed major technological advances in the ability to diagnose asymptomatic BM. The routine adoption of computed tomography and magnetic resonance imaging (particularly with contrast enhancement) at diagnosis have markedly increased the ability to detect disease.[23] In addition to improved detection, there is considerable evidence that these patients experience an improved overall prognosis.[24,25] There is also growing recognition that metastases of the central nervous system are responsive to chemotherapy[26,27]; consequently, it is important to reexamine the actual prognosis of these patients and their suitability for routine entry onto clinical trials.

Patients with stable BM were included in the phase III trial described in the current report comparing a reference regimen of paclitaxel/carboplatin to either gemcitabine/carboplatin or gemcitabine/paclitaxel. The overall clinical results have been reported previously.[28] The current analysis focuses on patient outcomes from the trial stratified by presence or absence of BM.

PATIENTS AND METHODS

Patient Selection/Study Design

Detailed information with respect to patient selection and study design of this trial is included in a separate publication.[29] Briefly, patients with a histologically confirmed diagnosis of stage IIIB (with pleural or pericardial effusion), stage IV, or recurrent NSCLC were enrolled in this study.[30] Stage IV patients with BM were eligible provided that, in the opinion of the site investigator, the BM were clinically stable after treatment with surgery or WBRT.

Mixed tumors were categorized by the predominant cell type unless small-cell anaplastic elements were present in which case the patient was ineligible. All patients were required to be ≥18 years of age and have measurable or evaluable disease (according to Eastern Cooperative Oncology Group solid tumor criteria); an Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate bone marrow reserve (neutrophils $>1500/mm^3$, platelets $>100{,}000/mm^3$), adequate hepatic function (aspartate transaminase ≤5 times institutional upper limit of normal and serum bilirubin ≤1.5 mg/dl times institutional ULN), and adequate renal function (creatinine clearance ≥40 ml/min or serum creatinine ≤1.5 mg/dl).

Patients who met all eligibility criteria were randomly allocated to receive one of the following three treatment regimens: arm A: gemcitabine 1000 mg/m^2 infused over 30 minutes on days 1 and 8 plus carboplatin area under the curve 5.5 over 15 to 30 minutes on day 1; arm B: gemcitabine 1000 mg/m^2 infused over 30 minutes on days 1 and 8 plus paclitaxel 200 mg/m^2 infused over 3 hours on day 1; or arm C: paclitaxel 225 mg/m^2 infused over 3 hours on day 1 plus carboplatin area under the curve 6.0 >15 to 30 minutes on day 1. Treatment cycles for all three treatment arms were repeated every 21 days for six cycles or until unacceptable toxicity or disease progression. Appropriate antiemetic and supportive measures were used. At randomization, patients were stratified by baseline weight loss, stage of disease, and presence or absence of BM. Patients who developed BM as the only evidence of progressive disease were able to be treated with whole brain radiation and corticosteroids for BM and remained on study. Chemotherapy was resumed 2 weeks after the completion of brain irradiation. However, if the patient failed to meet entry criteria after radiation therapy, the patient was removed from the study.

This study was reviewed and approved by an ethical review board at each participating institution, and it was conducted in accordance with the precepts established by the Declaration of Helsinki. Patients who were eligible for participation provided written informed consent consistent with all applicable governing regulations before undergoing any study procedure or receiving any study drug.

Statistical Analysis

The sample size for this study was 1134 patients. The large number of patients accrued in this study allowed for statistical analyses of outcomes by specific patient subgroups. Overall survival (OS), response rates (RRs), time to progression (TTP), and safety results were stratified by presence or absence of BM. Survival and TTP were assessed using the intention-to-treat population and calculated from the date of randomization to the date of death or documented progression. The Kaplan-Meier product-limit method was used to construct survival and TTP curves and calculate unadjusted

TABLE 1. Rate of Brain Metastases by Patient Subgroup

Characteristic	No. of Patients in Subgroup	Rate of Brain Metastases in Subgroup (%)	*p* for Comparison within Subgroup
All patients	1135	17.1	—
Age (yr)			
<70	797	21.3	<0.0001
≥70	338	7.1	
Gender			
Male	688	15.7	0.12
Female	447	19.2	
Ethnicity			
White	972	16.7	0.75
African-American	138	18.8	
Hispanic	9	22.2	
Histology			
Adenocarcinoma	537	19.0	0.001
Adenosquamous	23	17.4	
Large cell	45	13.3	
Squamous	202	6.9	
Bronchioloalveolar	18	5.6	
Performance status			
0	427	12.9	0.008
1	699	19.7	
2	4	0.0	
Weight loss, *n* (%)			
<5	710	18.3	0.16
≥5	425	15.2	
Disease stage IV or recurrent disease	1019	19.0	—

medians.[31] TTP was defined as the time from randomization to the first date of disease progression. For patients who did not have documented disease progression and did not receive any other antitumor therapy, TTP was censored at the date of death or date of last visit. TTP was also censored for patients who received other antitumor therapy before disease progression. Response Evaluation Criteria in Solid Tumors was used for response evaluation.[32] RRs were calculated by summing the number of patients with complete responses and partial responses, and clinical benefit rates were calculated by summing the number of patients with complete responses, partial responses, and stable disease. Safety was assessed by calculating the percentage of patients experiencing grade 3 or 4 toxicities using National Cancer Institute common toxicity criteria version 2.0.[33] All tests were two sided.[34]

To further compare outcomes by ethnicity and test for potential treatment-by-BM interaction, Cox proportional hazard models[35] and a logistic regression model were created. The reported multivariate models were cofactor adjusted for weight loss, sex, performance status, ethnicity, and disease stage and included main effects terms for treatment and BM status. The treatment-by-metastases status interaction was tested separately by adjusting for those factors.

TABLE 2. Patient Characteristics by Brain Metastases Status

Characteristic	Brain Metastases Present (N = 194)	Brain Metastases Absent (N = 941)
Age		
Median, yr (range)	60 (37–78)	65 (33–91)
<70 yr, *n* (%)	170 (87.6)	627 (66.6)
≥70 yr, *n* (%)	24 (12.4)	314 (33.4)
Gender, *n* (%)		
Male	108 (55.7)	580 (61.6)
Female	86 (44.3)	361 (38.4)
Ethnicity, *n* (%)		
White	162 (83.5)	810 (86.1)
African American	26 (13.4)	112 (11.9)
Hispanic	2 (1.0)	7 (0.7)
Histology, *n* (%)		
Adenocarcinoma	102 (52.6)	435 (46.2)
Adenosquamous	4 (2.1)	19 (2.0)
Large cell	6 (3.1)	39 (4.1)
Squamous	14 (7.2)	188 (20.0)
Bronchioloalveolar	1 (0.5)	17 (1.8)
Performance status, *n* (%)		
0	55 (28.4)	372 (39.5)
1	138 (71.1)	561 (59.6)
2	0 (0.0)	4 (0.4)
Weight loss, *n* (%)		
<5	130 (67.0)	580 (61.6)
≥5	64 (33.0)	361 (38.4)
Disease stage, *n* (%)		
IIIB with effusion	0 (0.0)	116 (12.3)
IV or recurrent disease	194 (100.0)	825 (87.7)
Assignment to treatment, *n* (%)		
Gemcitabine-carboplatin	66 (34.0)	313 (33.3)
Gemcitabine-paclitaxel	64 (33.0)	313 (33.3)
Paclitaxel-carboplatin	64 (33.0)	315 (33.4)

N, number of patients; *n*, number in group.

RESULTS

Patient Characteristics

Between July 2000 and November 2005, 1135 patients were screened for eligibility/entry into this trial at 105 investigative sites in the United States. Of these, 194 (17.1%) had BM. Table 1 summarizes the rate of BM by patient subgroup. The rate of BM was greater among patients aged <70 years compared with ≥70 years (21.3% versus 7.1%, $p < 0.0001$) and was greater among patients with nonsquamous histology compared with squamous histology (19.3 versus 6.9%, $p < 0.0001$).

Table 2 compares the baseline characteristics of patients with BM to patients without BM. The BM group included a higher percentage of women (44.3%) compared with the non-BM group (38.4%). The rate of BM was uniform across treatment therapies.

Dose Administration

Study therapy was administered to 1077 patients (94.9%) of the 1135 who were randomized. This included 183 of 194 patients (94.3%) with BM and 894 of 941 (95.0%) without BM. Mean number of cycles administered was 3.7 (SD = 1.9) for patients with BM and 3.8 (SD = 1.9) for patients without BM. The protocol-defined maximum of six

TABLE 3. Main Efficacy Parameters

Variable	Brain Metastases Present (N = 194)	Brain Metastases Absent (N = 941)
Best overall response, *n* (%)		
Complete response	1 (0.5)	12 (1.3)
Partial response	55 (28.4)	262 (27.8)
Stable disease	56 (28.9)	328 (34.9)
Progressive disease	43 (22.2)	186 (19.8)
Unknown/not done	39 (20.1)	153 (16.3)
Response rate (CR + PR), *n* (%) (95% CI)	56 (28.9) (22.6–35.8)	274 (29.1) (26.2–32.1)
Clinical benefit rate (CR + PR + SD), *n* (%) (95% CI)	112 (57.7) (50.4–64.8)	602 (64.0) (60.8–67.0)
Overall survival		
Events, *n* (%)	182 (93.8)	852 (90.5)
Censored, *n* (%)	12 (6.2)	89 (9.5)
Median, mo (95% CI)	7.7 (6.7–9.3)	8.6 (7.9–9.5)
1 yr, % (95% CI)	30.6 (24.1–37.2)	36.1 (33.0–39.2)
2 yr, % (95% CI)	11.2 (6.7–15.8)	13.2 (10.9–15.5)
3 yr, % (95% CI)	4.2 (1.0–7.3)	6.6 (4.8–8.4)
Time to progression		
Events, *n* (%)	183 (94.3)	871 (92.6)
Censored, *n* (%)	11 (5.7)	70 (7.4)
Median, mo, (95% CI)	4.3 (3.4–5.6)	4.6 (4.2–5.1)

CR, complete response; PR, partial response; *N,* number of patients; *n,* number in group; CI, confidence interval.

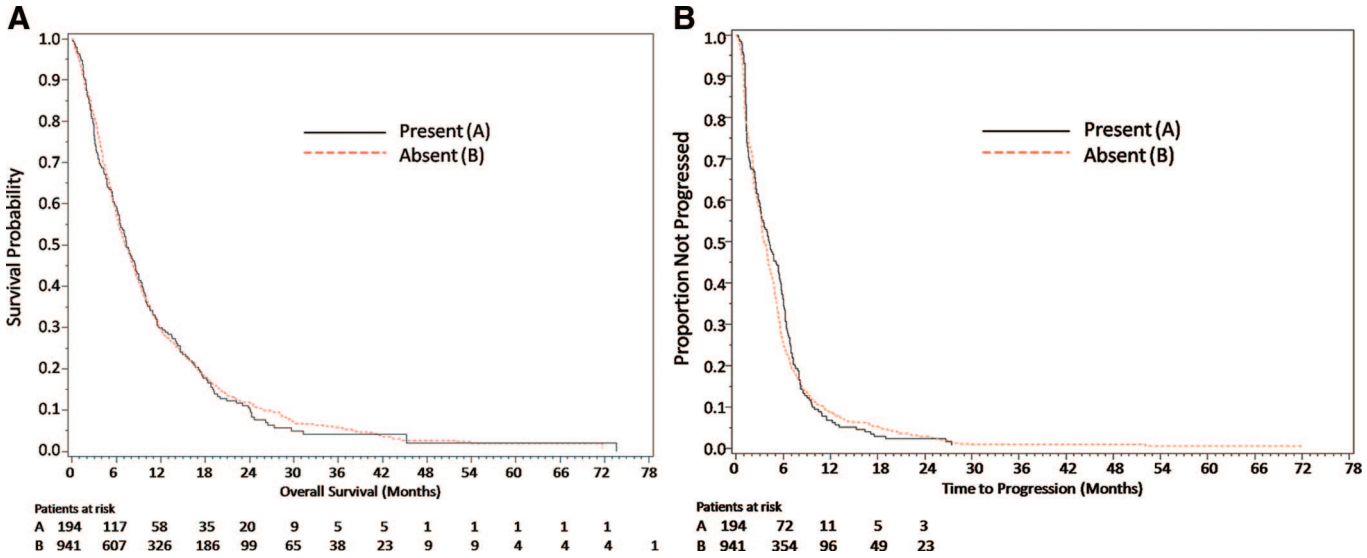

FIGURE 1. Kaplan-Meier estimates of overall survival (*A*) and time to disease progression (*B*) by brain metastases status of present versus absent.

TABLE 4. Regression Analyses with Treatment by Brain Metastases Interaction Effect

Metastases Subgroup	*n*	Response Rate, % (95% CI)	Cofactor Adjusted OR (95% CI)	*p* for OR	Treatment by Metastases Interaction *p*
Present					
Gemcitabine/carboplatin	66	28.8 (18.3–41.3)	1.30 (0.59–2.85)	0.52	0.18 comparing gemcitabine/carboplatin and paclitaxel/carboplatin
Gemcitabine/paclitaxel	64	34.4 (23.0–47.3)	1.68 (0.77–3.66)	0.19	
Paclitaxel/carboplatin	64	23.4 (13.8–35.7)	1.0 (reference)	Reference	
Absent					
Gemcitabine/carboplatin	313	24.6 (19.9–29.8)	0.72 (0.51–1.03)	0.07	0.26 comparing gemcitabine/paclitaxel and paclitaxel/carboplatin
Gemcitabine/paclitaxel	313	31.6 (26.5–37.1)	1.01 (0.72–1.42)	0.94	
Paclitaxel/carboplatin	315	31.1 (26.0–36.5)	1.0 (reference)	Reference	
Metastases Subgroup	***n***	**Median Survival, mo (95% CI)**	**Cofactor Adjusted HR (95% CI)**	***p* for HR**	**Treatment by Metastases Interaction *p***
Present					
Gemcitabine/carboplatin	66	7.6 (6.3–10.1)	0.97 (0.68–1.40)	0.89	0.79 comparing gemcitabine/carboplatin and paclitaxel/carboplatin
Gemcitabine/paclitaxel	64	8.2 (4.6–10.5)	0.94 (0.65–1.36)	0.74	
Paclitaxel/carboplatin	64	7.7 (6.1–10.2)	1.0 (reference)	Reference	
Absent					
Gemcitabine/carboplatin	313	8.1 (7.1–9.3)	1.04 (0.88–1.22)	0.66	0.80 comparing gemcitabine/paclitaxel and paclitaxel/carboplatin
Gemcitabine/paclitaxel	313	9.2 (7.7–10.2)	1.00 (0.85–1.18)	0.96	
Paclitaxel/carboplatin	315	9.0 (7.8–10.3)	1.0 (reference)	Reference	
Metastases Subgroup	***n***	**Median TTP, mo (95% CI)**	**Cofactor Adjusted HR (95% CI)**	***p* for HR**	**Treatment by Metastases Interaction *p***
Present					
Gemcitabine/carboplatin	66	4.6 (3.2–6.3)	0.92 (0.64–1.33)	0.67	0.74 comparing gemcitabine/carboplatin and paclitaxel/carboplatin
Gemcitabine/paclitaxel	64	3.9 (2.6–6.0)	1.06 (0.74–1.54)	0.74	
Paclitaxel/carboplatin	64	5.0 (3.0–6.0)	1.0 (reference)	Reference	
Absent					
Gemcitabine/carboplatin	313	4.3 (4.1–5.1)	1.0 (0.85–1.17)	0.98	0.57 comparing gemcitabine/paclitaxel and paclitaxel/carboplatin
Gemcitabine/paclitaxel	313	4.8 (4.1–5.6)	0.97 (0.82–1.14)	0.71	
Paclitaxel/carboplatin	315	4.6 (4.2–5.5)	1.0 (reference)	Reference	

Models were cofactor adjusted without interaction term.
HR, hazard ratio; *n,* number in group; OR, odds ratio; TTP, time to progression; CI, confidence interval.

cycles was administered to 31.1% ($n = 57$) of patients with BM and 34.7% ($n = 310$) of patients without BM. Relative dose intensities (% of planned dose that was administered) of gemcitabine (88.5% versus 87.6%), carboplatin (90.1% versus 91.0%), and paclitaxel (99.4% versus 98.8%) were similar in patients with and without BM. The median time from diagnosis to randomization was 58.4 days for the BM present group and 41.0 days for the BM absent group.

The median time from diagnosis to the start of treatment was 50.0 days for the BM present group and 29.0 days for the BM absent group.

Efficacy

The primary results of this study demonstrated that all three regimens produced similar efficacy in terms of OS, RR, and TTP.[28,29] Table 3 summarizes the main efficacy parameters in the trial by presence or absence of BM. Although median survival was longer for patients without BM compared with patients with BM (8.6 versus 7.7 months), differences in OS were not statistically significant (log-rank $p = 0.09$). At 3 years, 4.2% of patients with BM and 6.6% of patients without BM were alive. RRs were 28.9% (95% confidence intervals [CI] = 22.6–35.8) for patients with BM and 29.1% (95% CI = 26.2–32.1) for patients without BM. Median TTP measured from the date of randomization was 4.3 months for patients with BM (95% CI = 3.4–5.6) and 4.6 months for patients without BM (95% CI = 4.2–5.1). Differences in TTP from the date of randomization were statistically significant (log-rank $p = 0.03$). However, median TTP measured from the date of diagnosis was not statistically significant between groups (6.5 months for the BM present group [95% CI:5.1–7.3] and 5.8 months for the BM absent group [95% CI = 5.4–6.3]; $p = 0.58$). Kaplan-Meier curves from randomization for OS and TTP by BM status are shown in Figure 1.

Table 4 summarizes a logistic regression model with response as the outcome variable and two Cox regression models with OS and TTP as the outcome variables, respectively. Among patients with BM, RRs, OS, and TTP were similar across treatment groups. In the BM group, median survival ranged from 7.6 months (95% CI = 6.3–10.1) in the gemcitabine-carboplatin group to 8.2 months (95% CI = 4.6–10.5) in the gemcitabine-paclitaxel group. None of the comparisons across treatment groups in any of the regression models achieved statistical significance.

Toxicity

Chemotherapy safety is summarized for patients with and without BM in Table 5. Rates of grade 3 or 4 hematologic toxicities and rates of transfusions were similar between patients with and without BM. Rates of grade 3 or 4 nonhematologic toxicities were also similar by BM status. However, the rate of grade 3 or 4 nausea was greater among patients with BM (10.9 versus 5.1%, $p = 0.006$), as were other grade 1 to 4 nonhematologic toxicities. These included fatigue (78.7% versus 70.5%, $p = 0.02$), anorexia (52.5%

TABLE 5. Toxicity According to Treatment Group (Safety Population)

	Brain Metastases Present ($N = 183$)		Brain Metastases Absent ($N = 894$)		p-value for Overall Comparison
Type of Toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	
Hematologic events, n (%)					
Neutropenia	32 (17.5)	23 (12.6)	146 (16.3)	136 (15.2)	0.73
Febrile neutropenia	6 (3.3)	0 (0.0)	22 (2.5)	7 (0.8)	1.0
Thrombocytopenia	37 (20.2)	11 (6.0)	197 (22.0)	246 (27.5)	0.79
Platelet transfusion	7 (3.8)		23 (2.6)		0.33
Anemia	27 (14.8)	0 (0.0)	90 (10.1)	3 (0.3)	0.09
Red blood cell transfusion	0 (0.0)		5 (0.6)		0.60
Transfusion	7 (3.8)		38 (4.3)		1.0
Nonhematologic events, n (%)					
Arthralgia (Grade 3 or 4)	5 (2.7)		18 (2.0)		0.57
Alopecia (Grade 2)	85 (46.4)		343 (38.4)		0.17
Diarrhea (Grade 1 to Grade 4)	52 (28.4)		199 (22.3)		0.08
Nausea (Grade 3 or Grade 4)	20 (10.9)		46 (5.1)		0.006
Vomiting (Grade 1 to Grade 4)	64 (35.0)		249 (27.9)		0.06
Fatigue (Grade 1 to Grade 4)	144 (78.7)		630 (70.5)		0.02
Anorexia (Grade 1 to Grade 4)	96 (52.5)		329 (36.8)		<0.001
Any nervous system disorder (Grade 1 to Grade 4)	114 (62.3)		530 (59.3)		0.46
Cerebrovascular accident (Grade 4)	0 (0.0)		3 (0.3)		1.0
Dizziness (Grade 1 to Grade 4)	26 (14.2)		65 (7.3)		0.003
Headache (Grade 1 to Grade 4)	24 (13.1)		50 (5.6)		<0.001
Tremor (Grade 1 to Grade 4)	4 (2.2)		4 (0.4)		0.03

N, number of patients; *n,* number in group.

versus 36.8%, $p < 0.001$), dizziness (14.2% versus 7.3%, $p = 0.003$), headache (13.1% versus 5.6%, $p < 0.001$), and tremor (2.2% versus 0.4%, $p = 0.03$). No cerebrovascular accidents occurred among patients with BM.

DISCUSSION

The brain is a common site of metastatic spread in advanced NSCLC. It is likely that the incidence of BM is on the rise with the increasing numbers of patients with adenocarcinoma histology.[36] Consequently, it is important to develop evidence-based guidelines for their overall management. Historically, patients with BM have been excluded from clinical trials because of poor prognosis. However, data from the current report indicate that patients with or without BM may experience similar outcomes when enrolled in clinical trials of systemic therapy. OS was not significantly different between patients with BM and without BM. Median survival (8.6 months versus 7.7 months) and 1-year, 2-year, and 3-year survival rates for patients with BM and without BM mirrored each other, with a slight trend favoring patients without BM. Patients without BM enjoyed a minimally superior TTP compared with those without BM. Differences in TTP between groups were possibly related to the longer time from diagnosis to randomization and treatment for patients with BM due to the administration of WBRT in patients with BM. Three-year survival among patients with BM was 4.2% (95% CI = 1.0–7.3), which is encouraging. Regression models showed that OS, RR, and TTP outcomes did not vary by BM status across the three treatment groups in this trial, suggesting that there may not be a preferred chemotherapeutic regimen by BM status.

Reluctance to administer systemic chemotherapy to patients with BM has been related to concerns of adequacy of delivery across the blood-brain barrier. However, Ott et al.[37] demonstrated that the blood-brain barrier in patients with BM may in fact be permeable during treatment. Others have demonstrated that it is possible to achieve therapeutic levels of chemotherapy such as platinum agents within the spinal fluid.[38] Robinet et al.[27] reported a trial in which patients ($n = 167$) received either early (at diagnosis) or delayed (after at least two cycles of chemotherapy) WBRT. Patients received chemotherapy (cisplatin/vinorelbine) concurrent with WBRT in both arms. Chemotherapy alone produced an intracranial RR of 27%, and there was no difference in median or 6-month survival between the two arms. Cotto et al. and Minotti et al.[39,40] reported 16% and 35% RR, respectively, with 4 and 5.3 months of medium survival with evidence of intracranial response. Lee et al.[41] described an experience with 30 patients treated at MD Anderson who were treated with carboplatin and paclitaxel. They noted a higher RR in the brain (33%) than in extracranial sites (23%). This response was often accompanied by an increase in edema.

There were no significant differences by BM status with respect to grade 3 or 4 hematologic toxicities. Patients with BM were more likely to experience grade 1 to grade 4 fatigue, gastrointestinal symptoms, and nervous system disorders when compared with patients without BM. Grades 1 to 4 nervous system disorders that had elevated rates among patients with BM included dizziness, headache, and tremor.

One concern with respect to the incorporation of targeted therapies such as vascular endothelial growth inhibitors into the treatment of patients with BM is the risk of intracranial hemorrhage or cerebrovascular events among patients with BM. A recent analysis suggests that the rate of these events is low and not different between patients with BM compared with patients without BM.[42] In this study, no cerebrovascular accidents occurred among patients with BM, compared with a 0.3% rate among patients without BM.

Accrual of patients with BM to trials of systemic treatment for first-line advanced NSCLC has started to gain acceptance. A review of 28 ongoing phase III trials registered to the clinicaltrials.gov website indicates that as many as 70% are open to enrolling patients with BM.[43] The current analysis suggests that this change in attitude is appropriate as the outcomes among patients with BM seem to be similar to those without BM.

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