Phase II Study of Sunitinib in Patients with Non-small Cell Lung Cancer and Irradiated Brain Metastases

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Introduction: Brain metastases frequently cause significant morbidity in patients with non-small cell lung cancer (NSCLC). Sunitinib is a multitargeted inhibitor of tyrosine kinase receptors, including vascular endothelial growth factor receptors and platelet-derived growth factor receptors, which has single-agent antitumor activity in refractory NSCLC. This phase II study evaluated the antitumor activity and safety of sunitinib in patients with pretreated NSCLC and irradiated brain metastases.

Methods: Patients received sunitinib 37.5 mg on a continuous daily dosing schedule. The primary end point was progression-free survival. Secondary end points included overall survival, patient-reported outcomes, and safety, including risk of intracranial hemorrhage (ICH) associated with focal neurological deficit.

Results: Sixty-four patients received sunitinib (median age 61 years), most (83%) had received prior systemic therapy, 63% had adenocarcinoma, and 19% had squamous cell carcinoma; most (55%) were never-smokers. Median progression-free survival was 9.4 weeks (90% confidence interval [CI]: 7.5–13.1), and median overall survival was 25.1 weeks (95% CI: 13.4–35.5). The most common treatment-emergent (all-causality) nonhematologic toxicities (any grade) were fatigue (38%) and decreased appetite and constipation (both 25%). The most common grade 3/4 nonhematologic toxicities were dyspnea (9%) and fatigue (8%). Lymphopenia (20%) and neutropenia (13%) were the most common grade 3/4 hematologic abnormalities. Serious neurologic adverse events occurred in six patients (9%), and none were treatment-related. No cases of ICH were reported.

Conclusions: Sunitinib administration on a continuous daily dosing schedule in patients with NSCLC and brain metastases was safe and manageable, with no increased risk of ICH.

Key Words: Non-small cell lung cancer, Sunitinib, Brain metastases, Safety.

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Brain metastases develop in more than 25% of patients with non-small cell lung cancer (NSCLC) at some point during the course of their disease[1,2] and are associated with significant morbidity, mortality, and poor prognosis.[3,4] Therapeutic options include surgery, stereotactic radiosurgery, whole-brain radiotherapy (WBRT), and chemotherapy. While surgery and stereotactic radiosurgery may be considered in highly selected cases, WBRT is commonly used in most patients. WBRT can stabilize or even improve symptoms; however, the median overall survival (OS) of treated patients is approximately 4 months.[5]

The role of cytotoxic chemotherapy in the treatment of brain metastases remains unclear as many clinical trials have excluded patients with brain metastases. Some intracranial responses have been reported with first-line chemotherapy regimens including vinorelbine plus gemcitabine and carboplatin[6] and cisplatin/carboplatin plus gemcitabine,[7,8] and with the addition of WBRT to paclitaxel and cisplatin,[9] and cisplatin and vinorelbine[10]; however, the role of the blood-brain barrier in reducing drug access to brain metastases has always been a concern. Similarly, few clinical trials of targeted agents have been conducted in patients with brain metastases although, in a phase II prospective study, single-agent gefitinib showed some activity in 42 NSCLC patients with brain metastases.[11]

Early reports suggested that patients with brain metastases may be more susceptible to intracranial hemorrhage (ICH).[12,13] The observations led to NSCLC patients with brain metastases being excluded from studies of the anti-

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vascular endothelial growth factor (anti-VEGF) monoclonal antibody, bevacizumab.[14–18] However, the incidence of ICH in studies of antiangiogenic agents including a monoclonal antibody (bevacizumab) and tyrosine kinase inhibitors (sunitinib and sorafenib) remains low (<3.3%).[19–25] Indeed, the incidence of ICH was the focus of an open-label bevacizumab study that evaluated 106 patients with NSCLC and brain metastases where no case of ICH was observed.[20]

Sunitinib malate (SUTENT®; Pfizer Inc., La Jolla, CA) is an oral, multitargeted tyrosine kinase inhibitor of VEGF receptors -1, -2, and -3, platelet-derived growth factor receptors (PDGFRs) -α and -β, stem-cell factor receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R), and glial cell line-derived neurotrophic factor receptor (RET) (Pfizer Inc., data on file, 2008).[26–29] Sunitinib is approved for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant/-intolerant gastrointestinal stromal tumors and has promising single-agent antitumor activity in refractory NSCLC.[22,30] Preclinical data suggest that VEGF signaling is required for the growth of brain metastases, and that sunitinib is able to penetrate the blood-brain barrier rapidly due to its low molecular weight and high lipophilicity.[31,32] A phase II, open-label, single-arm study was designed to assess the antitumor activity and safety of sunitinib in patients with advanced NSCLC and brain metastases. In this study, particular attention was given to the evaluation of neurologic deficit.

METHODS

Study Design

This trial was an open-label, single-arm, phase II study designed to evaluate the intracranial and systemic antitumor activity of single-agent sunitinib in patients with NSCLC and brain metastases who had previously received WBRT and up to two systemic therapies. The primary end point was progression-free survival (PFS), and secondary end points included overall and intracranial time to progression (TTP), time to neurologic progression, objective response rate (ORR), intracranial ORR, OS, 1-year survival, patient-reported outcomes (PRO), and safety.

This study (NCT00372775) was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws. The study was approved by the institutional review board or independent ethics committee of each participating center, and all patients gave written, informed consent.

Study Population

Male or female patients aged 18 years or older with histologically or cytologically proven NSCLC and radiologically confirmed brain metastases ≤4 cm in any linear direction were enrolled. Other inclusion criteria included WBRT ≥2 weeks before study entry; a maximum of two prior systemic therapies; evidence of unidimensionally measurable disease for systemic disease; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate organ function. Patients were to have completed all chemotherapy, immunotherapy, and radiotherapy ≥4 weeks before study entry (WBRT may have occurred ≥2 weeks before study entry). Patients who received WBRT and subsequently developed intracranial recurrence were also enrolled.

Key exclusion criteria included brainstem lesions, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease; candidate for definitive therapy for brain metastases; intracranial or intratumoral hemorrhage; uncontrollable seizure activity; treatment with potent cytochrome P450 3A4 enzyme inhibitors or inducers ≤2 weeks before study entry; National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 hemorrhage less than 4 weeks before starting study treatment; uncontrolled hypertension; oral anticoagulant therapy; history of myocardial infarction, severe or unstable angina, coronary or peripheral artery bypass graft, congestive heart failure, cerebrovascular accident or pulmonary embolism within 12 months before study entry; and major surgery or radiation therapy less than 4 weeks before starting the study treatment.

Treatment Regimen

Patients received sunitinib 37.5 mg on a continuous daily dosing schedule in 4-week cycles for 13 cycles (1 year) or until study withdrawal. Dose reduction to 25 mg/d was permitted for patients experiencing sunitinib-related toxicity. Patients experiencing grade ≤1 nonhematologic or grade ≤2 hematologic toxicity within the first 8 weeks of treatment could be dose-escalated to 50 mg/d. The study would be terminated early if three cases of ICH associated with neurologic deficit were reported after confirmation by an independent radiological review board.

Assessments

Antitumor activity was evaluated by radiologic tumor assessments carried out at screening, on cycle 2 day 1, cycle 3 day 1, and every 8 weeks thereafter. Radiologic assessment was also performed if disease progression was suspected. Intracranial disease was measured using three-dimensional thin-slice magnetic resonance imaging (conducted on day 1 of cycles 2 and 3 and odd cycles thereafter, and at end of the treatment or withdrawal from study), and systemic disease was measured using magnetic resonance imaging or computed tomography scan.

Overall antitumor efficacy was based on objective tumor assessments performed according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0; partial response [PR] = ≥30% decrease in target lesion size; progressive disease [PD] = ≥20% increase in target lesion size).[33] Intracranial response was assessed using World Health Organization criteria as RECIST has not been validated for evaluating brain lesions (PR = ≥50% reduction from baseline in the sum of the products of all enhancing tumors and PD = ≥25% increase from smallest size in the sum of the products of all enhancing tumors or the appearance of any new tumor). However, for overall antitumor efficacy, unidimensional measurements of brain lesions were assessed according to RECIST.

PRO was assessed using the self-administered functional assessment of cancer therapy (FACT)/National Com-

prehensive Cancer Network (NCCN) Lung Symptom Index (FLSI) and the FACT/NCCN Brain Symptom Index (FBrSI), in which patients were asked to score questions based on their impact during the past 7 days. The FLSI comprises six questions measuring common symptoms affecting lung cancer patients, including dyspnea, cough, fatigue, weight loss, and pain. The FBrSI comprises 15 questions measuring common symptoms affecting brain tumor patients, including headaches, seizures, fatigue, nausea, motor dysfunction (weakness in arms/legs, trouble with coordination), communication deficit (difficulty finding words/expressing thoughts), deficiency in physical/role functioning (difficulty bathing, dressing, eating, etc.), and deficiency in emotional functioning. Data were collected on days 1 and 15 of the first two 4-week cycles, on day 1 only in subsequent cycles, at the end of treatment or withdrawal from the study, and on day 28 post-treatment assessment. Patients completed the questionnaire at the clinic before administration of the study drug or other clinical activities.

Safety was assessed by monitoring adverse events (AEs) graded according to NCI CTCAE, version 3.0. Standard laboratory hematologic and blood chemistry parameters were assessed at baseline, on day 1 of cycles 2 to 13, and at the end of treatment. There was an optional assessment point for both on day 1 of cycle 1 and at 28 days post-treatment. Hematologic parameters were measured on day 15 of cycles 2 to 4. Thyroid stimulating hormone and coagulation were assessed at screening and then as clinically indicated thereafter as per standard medical practice.

Statistical Analysis

Data are presented for all patients enrolled in the study who received ≥1 dose of study medication. Based on previous PFS and TTP data from patients with NSCLC with brain metastases, and the expectation that approximately 25% of patients will receive study treatment as first-line systemic therapy after WBRT, it was assumed that a median PFS of 10 weeks would be observed in the study population if treated with standard of care, and a PFS of 14 weeks would be considered clinically relevant with sunitinib therapy. Assuming a type I error rate of 5% (one-sided) and a type II error rate of 20%, a 9-month accrual period, a minimum follow-up period of 12 months, and a 10% dropout rate, it was estimated that 60 patients would need to be enrolled. Time to event end points (PFS, overall and intracranial TTP, and OS) were summarized using Kaplan-Meier estimates. The number and percent of subjects achieving objective response (complete response [CR] or PR) was summarized along with the corresponding exact two-sided 95% confidence interval [CI]. Exploratory analyses of PRO data were conducted using repeated measures mixed models with autoregressive covariance structure to study changes from baseline at each subsequent visit. A change was considered meaningful if the numerical change was more than 5% of the total score (a minimally clinically important difference) and $p < 0.10$.[34] Baseline PRO value was included as a covariate and visit was used as a class variable. No adjustments were made for multiple comparisons. All patients with baseline and at least one postbaseline PRO measurement were included in the analysis. Descriptive statistics were used to summarize AEs and other safety data.

RESULTS

Patient Disposition and Baseline Characteristics

Between March 2007 and December 2009, 66 patients were enrolled and 64 received treatment (61% male; median age, 61 years [range, 35–77]). Two patients were enrolled but not treated (one chose alternative treatment and the other had global deterioration of health status, before receiving study treatment). Patients had an ECOG performance status of 0/1 (98%) or 2 (2%) (Table 1). The majority of patients had adenocarcinoma (63%) or squamous cell carcinoma (19%) and had received prior systemic therapy (83%) and WBRT (98%). Sixty-four patients were evaluable for safety and 61 were evaluable for overall response.

Patients received sunitinib for a median of two cycles (range, 1–13), and the median dose administered was 37.5

TABLE 1. Patient Baseline Characteristics

Characteristic	Patients ($N = 64$)
Gender, *n* (%)	
Male	39 (61)
Female	25 (39)
Age (yr)	
Median	61
Range	35–77
<65, *n* (%)	44 (69)
≥65, *n* (%)	20 (31)
ECOG PS, *n* (%)	
0/1	35 (55)/28 (44)
2[a]	1 (2)
Histology, *n* (%)	
Adenocarcinoma	40 (63)
Squamous cell carcinoma	12 (19)
Large cell carcinoma	2 (3)
Bronchioalveolar carcinoma	1 (2)
Not otherwise specified/other	8 (13)/1 (2)
Smoking status, *n* (%)	
Smoker	9 (14)
Ex-smoker	20 (31)
Never-smoker	35 (55)
Ethnicity, *n* (%)	
Caucasian/other	60 (94)/4 (6)
Prior treatments, *n* (%)	
Whole-brain radiotherapy[b]	63 (98)
Surgery	57 (89)
Systemic therapy	53 (83)
Number of prior systemic regimens, *n* (%)[c]	
1	44 (69)
2	8 (13)
≥3[d]	1 (2)

[a] One patient had an ECOG PS of 2 due to protocol deviation.
[b] One patient did not receive whole-brain radiotherapy due to protocol deviation.
[c] 11 patients did not receive prior systemic therapy.
[d] One patient received ≥3 prior systemic regimen due to protocol deviation.
ECOG PS, Eastern Cooperative Oncology Group performance status.

mg/d (range, 27–40). At least one dose delay was required in 10 patients (16%) and dose reduction to 25 mg/d occurred in 17 patients (27%), primarily due to AEs. Twenty-nine patients (45%) required dose interruption and two patients (3%) had their dose increased to 50 mg/d.

Study discontinuations were primarily due to disease progression or relapse (n = 30, 47%). In addition, eight patients (13%) discontinued due to AEs, four of which were considered related to sunitinib (pulmonary embolism, renal failure, cutaneous rash, and platelets decrease [each n = 1]).

Overall Antitumor Activity

Median PFS was 9.4 weeks (90% CI: 7.5–13.1). Median PFS estimated in a subgroup of patients (n = 9) reporting progressive disease as best response to WBRT was 12.5 weeks (95% CI: 9.8–24.1). Median TTP was 15.1 weeks (95% CI: 8.4–15.8). Sixty-one patients were evaluable for overall response. One patient (1.6%) had a PR and 18 patients (29.5%) had stable disease (SD) ≥8 weeks, giving an ORR of 1.6% (95% CI: 0.0–8.8). Median OS was 25.1 weeks (95% CI: 13.4–35.5). Kaplan-Meier estimates for PFS are shown in Figure 1, and best percentage change in target tumor lesion size is shown in Figure 2. There were 10 best changes from baseline in target lesion size that exceeded the 30% reduction threshold required to achieve a PR by RECIST (Figure 2). However, with the exception of the patient with PR mentioned above, target lesion reductions were not recorded as PRs because reductions in target lesion size were not confirmed (due to disease progression or discontinuation from the study), or because in some cases new lesions were also reported in nontarget lesions and therefore the overall response was PD not PR.

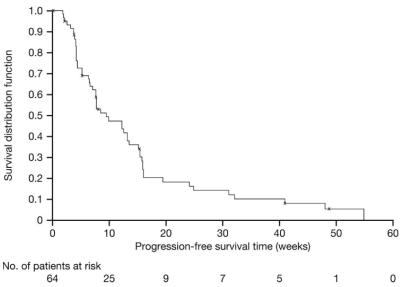

FIGURE 1. Kaplan-Meier estimates for progression-free survival.

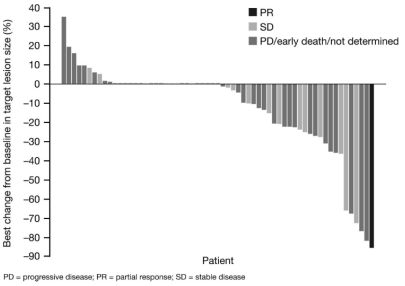

FIGURE 2. Best percentage change from baseline in target tumor lesion size.

Intracranial Antitumor Activity

Median time to intracranial progression was 15.4 weeks (95% CI: 12.1–24.8). Among 23 patients with measurable intracranial disease at baseline, one patient (4.3%) had an intracranial PR (also recorded as an overall response) and seven patients (30.4%) had SD ≥8 weeks. Baseline characteristics of the patients evaluable for overall antitumor activity and the patients evaluable for intracranial antitumor activity were generally similar—with the exception of smoking status (14.1% and 34.8% of patients were smokers, respectively).

Patient-Reported Outcomes

Changes from baseline in FLSI and FBrSI and item scores are presented in Table 2. Both the FBrSI score and FLSI score remained stable and did not change significantly from baseline during the treatment period. Meaningful improvement was reported in three common symptoms of lung cancer (cough, weight loss, and dyspnea) during multiple treatment cycles. In addition, brain symptoms including "headache" and patients' "worry that their condition will get worse" both decreased during multiple treatment cycles. However, patients also reported worsening in certain symptoms in one or more treatment cycles (Table 2).

Safety

All patients who received treatment (N = 64) were evaluable for safety. The most common treatment-emergent (all-causality) nonhematologic AEs of any grade were fatigue (n = 24, 38%) and decreased appetite and constipation (both n = 16, 25%; Table 3). The most common grade 3/4 AEs were dyspnea and fatigue (six patients [9%] and five patients [8%], respectively). Other AEs of interest included hypertension (n = 12 [19%]) and one event of hypothyroidism (grade 2). Treatment-related nonhematologic grade 4 AEs occurred in three patients: oral pain, oropharyngeal pain, and dysphagia (n = 1), hemoptysis (n = 1), and pulmonary embolism (n = 1). Grade 3/4 hematologic laboratory abnormalities are shown in Table 3.

Serious neurologic AEs occurred in six patients (9%): epilepsy (n = 2) and convulsion, cerebral ischemia, intentional self-injury (grade 5), and tremor (each n = 1), and none were judged to be related to sunitinib. No cases of ICH were reported as confirmed by third-party radiologic review (RadPharm Inc., Princeton, NJ).

TABLE 2. Functional Assessment of Cancer Therapy (FACT) Lung and Brain Symptom Assessment: Mean Change from Baseline Scores

	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1
Days after start of treatment	14–22	26–37	40–55	56–72	84–72	113–119
Patients, *n*	36	34	27	23	17	10
FLSI overall index score	0.33	0.38	−0.22	0.62	−0.19	0.12
Items						
I have been short of breath	**−0.22***	**−0.22***	**−0.26***	**−0.36†**	**−0.43†**	0.03
I have a lack of energy	0.10	0.19	0.16	0.10	0.18	*0.53†*
I have pain	0.23	−0.04	0.02	−0.09	0.30	−0.20
I am losing weight	**−0.30†**	**−0.32†**	0.03	−0.04	−0.30	**−0.43***
I have been coughing	**−0.39†**	**−0.25***	−0.14	**−0.60†**	0.02	−0.23
I have certain areas of my body where I experience pain	0.21	0.17	0.23	0.04	0.33	−0.07
FBrSI overall index score	−0.62	−1.19	−0.53	−1.24	−0.45	−1.79
Items						
I get headaches	**−0.24†**	−0.11	**−0.36†**	−0.11	−0.16	0.03
I have had seizures	−0.01	*0.18†*	0.08	0.06	−0.03	0.07
I have weakness in arms or legs	0.11	0.23	0.00	*0.42†*	*0.40**	0.22
I need help caring for myself	0.16	*0.21**	0.11	0.19	0.21	0.32
I have lack of energy	0.15	*0.27**	0.21	0.19	0.26	0.15
I have difficulty expressing thoughts	−0.06	0.03	0.16	0.00	0.01	*0.38**
I have trouble with coordination	0.05	*0.37†*	*0.32†*	0.25	0.21	*0.47†*
I get frustrated that I cannot do things	*0.28**	0.26	0.10	0.09	0.23	−0.05
I have nausea	0.14	0.06	0.32	0.36	−0.24	0.10
I am able to find the right word(s) to say what I mean	0.02	0.22	0.50*	0.41	0.49	0.33
I am losing hope in the fight against my illness	−0.02	−0.06	−0.01	0.01	−0.04	0.06
I have trouble meeting needs of family	0.00	0.14	−0.03	0.08	0.00	0.12
I worry my condition will get worse	−0.18	**−0.28***	**−0.45†**	−0.27	**−0.49†**	−0.32
I am afraid of having a seizure	0.12	0.03	0.08	−0.24	−0.20	−0.01
I am able to enjoy life	−0.22	−0.20	−0.27	−0.23	*−0.48†*	−0.35

Bold scores suggest a meaningful decrease in symptoms while on treatment. Italicized scores suggest a meaningful increase in symptoms while on treatment.
* $p < 0.10$.
† $p < 0.05$.
FLSI, FACT Lung Symptom Index (range 0–24, with higher score indicating better outcome); FBrSI, FACT Brain Symptom Index (range 0–60, with higher score indicating better outcome). All symptom item scores have a range of 0–4, with higher scores indicating more symptom, except for two items "able to find the right words(s) to say what I mean" and "able to enjoy life" in which high scores indicate less symptom. A change was considered meaningful if the numerical change was more than 5% of the total score (a minimally clinically important difference) and $p < 0.10$.[34]

As of March 2010, 54 patients have died: 48 deaths were attributed to systemic disease progression, 3 were attributed to AEs (intentional self-injury [suicide], chronic obstructive pulmonary disease [disease present at screening], and worsening of respiratory function), and the causes of the final 3 deaths were unknown. Six of the 10 patients alive at the end of the study received one regimen containing pemetrexed as follow-up systemic therapy; the other four patients received erlotinib.

DISCUSSION

Brain metastases are a common occurrence in patients with advanced NSCLC, and patients developing these lesions may be more susceptible to ICH.[14] Clinical data from patients with central nervous system malignancies have suggested that sunitinib has a manageable and predictable safety profile in this setting.[31,35,36] To date, this is the largest prospective clinical trial designed to evaluate the efficacy as well as the safety of an antiangiogenic agent in NSCLC patients with brain metastases. Importantly, no cases of ICH due to sunitinib treatment were observed. Recent studies, including the phase II PASSPORT study of bevacizumab in 106 NSCLC patients with irradiated brain metastases, reported no cases of ICH (efficacy was not formally evaluated).[20] Similarly, in 37 NSCLC patients with irradiated brain metastases who were enrolled in the BETA lung study evaluating bevacizumab plus erlotinib, no increased risk of cerebral hemorrhage was observed.[37] Furthermore, the NCCN has since amended their guidelines to permit the use of bevacizumab in eligible NSCLC patients with treated brain metastases; however, at the present time, the American Society of Clinical Oncology continues to advise against administering bevacizumab to these patients. Our study, combined with the safety data in the PASSPORT and BETA studies, indicates that treatment with antiangiogenic agents does not increase the incidence of ICH in NSCLC patients with irradiated brain

TABLE 3. Treatment-Emergent (All-Causality) Nonhematologic Adverse Events Occurring in >10% of Patients and All Hematologic Laboratory Abnormalities (Maximum CTCAE Grade)

	Grade 1/2	Grade 3	Grade 4	Total
Adverse event ($N = 64$)				
Fatigue	19 (30)	5 (8)	0	24 (38)
Decreased appetite	14 (22)	2 (3)	0	16 (25)
Constipation	14 (22)	2 (3)	0	16 (25)
Cough	15 (23)	0	0	15 (23)
Nausea	12 (19)	2 (3)	0	14 (22)
Dyspnea	7 (11)	6 (9)	0	13 (20)
Diarrhea	12 (19)	0	0	12 (19)
Hypertension	9 (14)	3 (5)	0	12 (19)
Vomiting	11 (17)	1 (2)	0	12 (19)
Asthenia	9 (14)	2 (3)	0	11 (17)
Mucosal inflammation	10 (16)	1 (2)	0	11 (17)
Arthralgia	8 (13)	0	0	8 (13)
Abdominal pain upper	7 (11)	0	0	7 (11)
Hematologic laboratory abnormality ($N = 61$)				
Lymphopenia	24 (39)	11 (18)	1 (2)	36 (59)
Anemia	34 (56)	0	1 (2)	35 (57)
Leukopenia	27 (44)	4 (7)	1 (2)	32 (52)
Thrombocytopenia	28 (46)	0	1 (2)	29 (48)
Neutropenia[a]	19 (31)	8 (13)	0	27 (44)

All other grade 4 nonhematologic adverse events: cardiac tamponade, duodenal ulcer, dysphagia, hemoptysis, lung infection, mental impairment, musculoskeletal chest pain oral pain, oropharyngeal pain, pleural effusion, pulmonary embolism, and respiratory failure (all $n = 1$).

[a] Febrile neutropenia was reported in one patient (grade 3). All other grade 3 nonhematologic adverse events: hypokalemia ($n = 4$), hyponatremia ($n = 2$), pain ($n = 2$), hypotension ($n = 2$), peripheral neuropathy ($n = 2$), and abdominal pain, aphthous stomatitis, blood magnesium decreased, blood potassium increased bone pain, cerebral ischemia, chest pain, confusional state, convulsion, epilepsy, facial palsy, fracture, hemiapraxia, hemiparesis, hemoptysis, herpes virus infection, hypophosphatemia, hypovolemia, infection, liver function test abnormal, mental status changes, muscular weakness, myopathy, neck pain, pericarditis, pneumonitis, pyelonephritis, and tumor pain (all $n = 1$).

CTCAE, Common Terminology Criteria for Adverse Events.

metastases. However, patients with advanced NSCLC and brain metastases should continue to be monitored carefully when treated with targeted antiangiogenic agents.

In this study, treatment with sunitinib was associated with only marginal antitumor activity (the primary end point of this study was not met); however, the PFS of 9.4 weeks, TTP of 15.1 weeks, and OS of 25.1 weeks were similar to time-to-event data reported in other studies of patients with brain metastases. A study of 41 patients with NSCLC and brain metastases treated with the targeted anti-epidermal growth factor receptor (anti-EGFR) agent, gefitinib, reported PFS of 12 weeks and OS of 20 weeks but a superior response rate of 10% (four PRs).[11] Two studies have examined chemotherapy regimens in patients with brain metastases and again TTP ranged from 12 to 19 weeks and OS ranged from 21 to 33 weeks, although the response rates were consistently higher than that reported here (ranging from 28 to 50%).[7,9] Comparisons between studies are hampered by differences in patient populations, such as level of pretreatment (note that 11 patients in the current study received sunitinib as first-line therapy) and performance status. However, despite the low ORR (1.6%) in the current study, intracranial antitumor activity was observed with 1 of 23 patients experiencing an intracranial PR and 7 experiencing SD. Intracranial responses and regression of brain metastases after treatment with sunitinib have also been reported in sunitinib-treated patients with advanced RCC and metastatic breast cancer.[35,38–43]

FLSI and FBrSI scores did not change significantly from baseline throughout the treatment period. During some treatment cycles, there was meaningful improvement in some common symptoms associated with lung cancer, including cough, dyspnea, and weight loss. Patients who were most able to tolerate treatment may have been more likely to complete questionnaires in the later cycles of this study, hence the potential for bias must be considered when interpreting these results.

AEs were consistent with those reported in other studies of single-agent sunitinib, including studies of intermittent dosing schedules (schedule 4/2; 4 weeks on treatment followed by 2 weeks off treatment) in NSCLC[22,30] and in RCC and gastrointestinal stromal tumors.[44,45] Fatigue and asthenia were frequently reported, occurring at any grade in 38% and 17% of patients, respectively. Although some reports have linked these AEs to hypothyroidism, we observed seven patients (11%) who were receiving thyroid replacement therapy and had hypothyroidism at study entry. Treatment-emergent hypothyroidism was reported in only one patient (2%) on study. The patient had no prior history of hypothyroidism, developed grade 2 hypothyroidism, and received levothyroxine therapy; the AE resolved within 4 weeks.

In this study, sunitinib on a continuous daily dosing schedule was safe and manageable, and no cases of ICH were observed. However, given the marginal antitumor activity reported in this study, no future trials of sunitinib in patients with NSCLC and brain metastases are planned. Given the poor prognosis of patients with brain metastases resulting from NSCLC, new treatment options are needed—particularly as these patients are often excluded from clinical trials.

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