A Phase II Study of Oxaliplatin, Pemetrexed, and Bevacizumab in Previously Treated Advanced Non-small Cell Lung Cancer

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Introduction: Single agent chemotherapy is standard for second and third line treatment of non-small cell lung cancer (NSCLC). Combination therapy to date has not proven to be superior to single agents in this setting, often adding toxicity without any additional efficacy. We investigated the activity and tolerability of the combination of oxaliplatin, pemetrexed, and bevacizumab in patients with previously treated advanced NSCLC.

Methods: This multicenter phase II trial evaluated the safety and efficacy of the combination of pemetrexed (500 mg/m^2), oxaliplatin (120 mg/m^2), and bevacizumab (15 mg/kg), given every 21 days, in patients with previously treated advanced NSCLC. Eligibility criteria included performance status 0 to 1, nonsquamous histology, and at least one prior chemotherapy regimen. Patients with treated brain metastases were allowed. The primary end point was response rate, with secondary endpoints of progression-free survival and overall survival.

Results: Thirty-six patients were enrolled on this study. Treatment was well tolerated; the most common grade 3 toxicity was hypertension, which was easily managed with oral medications. The nine (25%) patients with treated brain metastases had no episodes of cerebral hemorrhage. Of the 34 patients evaluable for tumor response, none had complete response, nine (27%) had partial response, 15 (44%) had stable disease, and 10 (29%) had progressive disease. Median progression-free survival was 5.8 months (95% confidence interval 4.1–7.8 months) and median overall survival was 12.5 months (95% confidence interval 7.3–17 months).

Conclusions: Treatment with oxaliplatin and pemetrexed in combination with the targeted antiangiogenic agent bevacizumab yielded promising efficacy with manageable toxicity in the previously treated advanced NSCLC population.

Key Words: Non-small cell lung cancer, Oxaliplatin, Pemetrexed, Bevacizumab, Previously treated.

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Lung cancer is the leading cause of cancer-related death in the United States.[1] Most patients with non-small cell lung cancer (NSCLC) are diagnosed with advanced disease, and platinum-based chemotherapy regimens are the backbone of first-line treatment.[2] Bevacizumab, a monoclonal antibody to vascular endothelial growth factor, is the first molecularly targeted treatment to show benefit when added to first-line chemotherapy for NSCLC, improving median survival from 10 to 12 months.[3] Early-phase clinical trials suggest that bevacizumab may also add benefit when combined with second-line therapies for NSCLC.[4]

Despite these advances, the prognosis for patients with advanced NSCLC is limited and virtually all patients will progress. Finding better second and third-line therapies is critical to improving survival. Currently, docetaxel, pemetrexed, and erlotinib are approved for second-line treatment of NSCLC. Response rates for these agents in large phase III trials are generally less than 10%, with progression-free survival (PFS) that ranges from 2 to 3 months, and median overall survival (OS) of 6 to 8 months.[5–8]

Although combination chemotherapy is standard for first-line treatment, in previously treated patients combination therapy to date has had no clear benefit over single agents, often adding toxicity without additional efficacy. However, many of these studies were performed with older chemotherapeutics. More modern regimens are worth exploring, especially if they are thought to render better response rates and survival, or to combine more easily into multidrug regimens with tolerable side effects.

The combination of oxaliplatin and pemetrexed has been of particular interest because it has demonstrated both good efficacy and a tolerable side effect profile. Although it is a member of the platinum family, oxaliplatin has activity in

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cisplatin-resistant cell lines.[9] More importantly, clinical studies have confirmed that oxaliplatin retains activity in individuals previously treated with cisplatin or carboplatin.[10,11] The combination of oxaliplatin and pemetrexed was compared with carboplatin and pemetrexed as first-line therapy for NSCLC in a randomized phase II study.[12] Response rates were 27 and 33%, respectively, and not statistically different. Toxicity in the oxaliplatin/pemetrexed arm was quite low, suggesting that this is a tolerable combination with potential efficacy in a population previously exposed to platinum.

We investigated the activity and safety of the regimen of bevacizumab, oxaliplatin, and pemetrexed in the previously treated advanced NSCLC setting with the hope that the favorable profile of oxaliplatin with pemetrexed in platinum-treated patients and the antiangiogenic activity of bevacizumab would combine to yield a powerful yet manageable regimen. We elected to include patients with definitively treated brain metastases in this study. The presence of any brain metastasis was an exclusion criteria in Eastern Cooperative Oncology Group (ECOG) 4599, the randomized phase III trial that compared chemotherapy alone with chemotherapy with bevacizumab in the first-line setting.[2] However, a substantial proportion of patients with advanced NSCLC have brain metastases. Furthermore, studies in patients with malignant glioma suggest that bevacizumab can be given safely to patients with brain tumors.[13] Therefore, to study this regimen in a typical population of patients with advanced relapsed and refractory NSCLC, we included patients with stable and fully treated brain metastases.

PATIENTS AND METHODS

Patients/Eligibility

Eligibility criteria included stage IIIB (by pleural or pericardial effusion), stage IV, or recurrent NSCLC, nonsquamous histology, age ≥18 years, ECOG performance status of 0 to 1, life expectancy ≥12 weeks, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), at least one prior chemotherapy regimen, and adequate bone marrow, renal and hepatic function. Patients were not eligible if there was a history of bleeding diathesis or coagulopathy, arterial thrombotic event such as myocardial infarction or stroke in the previous 6 months, gross hemoptysis within the prior 4 weeks, major surgical procedures in the previous 4 weeks, minor surgical procedures in the previous 7 days, serious nonhealing wound, ulcer, or bone fracture, or history of abdominal fistula, gastrointestinal perforation, or intraabdominal abscess. Patients with current venous thrombosis, active coronary artery disease with symptoms of unstable angina, uncontrolled arrhythmia, uncontrolled hypertension, or ongoing infection, were ineligible. Patients could not have received previous therapy with oxaliplatin or pemetrexed. Brain metastases were allowed as long as they had been treated and were not hemorrhagic.

Treatment Plan

Patients received pemetrexed 500 mg/m^2, oxaliplatin 120 mg/m^2, and bevacizumab 15 mg/kg on day 1 of every 21 day cycle. A maximum of two dose reductions were allowed based on nadir counts or clinically significant nonhematologic toxicities. All patients received 1000 micrograms of vitamin B-12 intramuscularly at least 1 week before the start of treatment and again every 9 weeks, and folic acid 1 mg daily starting at least 1 week before therapy and continuing throughout treatment. Patients were premedicated with dexamethasone (4 mg twice daily the day before, the day of, and the day after chemotherapy). Growth factors were allowed at the discretion of the treating physician. Tumor measurements were assessed by means of computed tomography scan or magnetic resonance imaging using RECIST after every two cycles. In the absence of progressive disease or unacceptable toxicity, patients continued on the study drugs for a maximum of six cycles.

Statistical Analysis

The primary objective was to estimate the response rate of patients treated with bevacizumab, oxaliplatin, and pemetrexed. A two-stage phase II design was used, with an interim analysis and an early stopping rule for inactivity. Sample size was calculated based on Simon's method.[14] The first stage included 15 patients. If at least two of these patients achieved a partial or complete response by RECIST, enrollment proceeded with an additional 20 patients. This design provided a 92% probability of identifying an active regimen if the true response rate were truly 25%, the level regarded as the minimum to declare the triplet regimen clinically active. In contrast, there was a 6% probability of failing to declare the regimen inactive assuming a true response rate of 5% or less.

Secondary objectives were to assess PFS and OS. OS was defined as the time from date of registration to date of

TABLE 1. Patient Characteristics

Patient Characteristic	n (%)
Median age (range)	62 (40–81)
Male	18 (50%)
Female	18 (50%)
Stage at study entry	
IIIB (wet)	2 (6%)
IV	34 (94%)
ECOG PS	
0	13 (36%)
1	23 (64%)
Histology	
Adenocarcinoma	29 (80%)
BAC	1 (3%)
Large cell	2 (6%)
NSCLC nos	4 (11%)
No. prior regimens	
1	24 (66%)
2	7 (19%)
3	2 (6%)
4	2 (6%)
5	1 (3%)
Presence of brain mets	
Yes	9 (25%)
No	27 (75%)

death. PFS was the time from registration until documented progression or death from any cause, whichever occurred first. Survival analyses were performed using the Kaplan-Meier method.

RESULTS

Thirty-six patients were enrolled between January 2005 and October 2006 from four institutions. All patients received therapy with pemetrexed, oxaliplatin, and bevacizumab. The median number of cycles received was 5.5; range was 1 to 6. At the time of analysis, 31 patients had progressed and 29 patients had died. Two patients were not assessable for response; one patient died and another withdrew from the study before the first scheduled restaging scans. The median follow-up for all patients was 11 months, and clinical data were collected through December 2007.

The baseline patient and clinical characteristics are listed in Table 1. There were nine patients with treated brain metastases. All patients had received prior chemotherapy, with all but two having had a prior platinum-based combination. There were no patients who had received prior bevacizumab. Details of prior treatment regimens are included in Table 2.

Efficacy

Thirty-four patients were assessable for response. The response rate was 27%, with no complete responses, nine (27%) partial responses, 15 (44%) patients with stable disease, and 10 (29%) with progressive disease. The median PFS was 5.8 months (95% confidence interval 4.1–7.8 months); see Figure 1. The median OS was 12.5 months (95% confidence interval 7.3–17 months); see Figure 2.

Twenty-one (59%) patients received additional therapies after participating in this study. Thirteen (36%) received one subsequent therapy, six (17%) received two subsequent therapies, one (3%) received three subsequent therapies, and one (3%) received four subsequent therapies.

TABLE 2. Prior Treatments

One prior regimen	
Carboplatin/paclitaxel	9
Carboplatin/paclitaxel/TLK286	8
Carboplatin/gemcitabine	1
Cisplatin/docetaxel	1
Surgery → carbo/paclitaxel/RT	1
EP 50/50 with RT-consolidation taxotere	1
Carboplatin/paclitaxel/RT	1
Carboplatin/paclitaxel/RT-consolidation carboplatin/gemcitabine	1
Surgery → adjuvant carboplatin/paclitaxel	1
Two prior regimens	
Carboplatin/paclitaxel → gefitinib/erlotinib	2
Carboplatin/paclitaxel → gemcitabine/docetaxel	1
Cisplatin/gemcitabine/LY293111 → carboplatin/docetaxel	1
Cetuximab/navelbine → erlotinib	1
Carbo/paclitaxel/RT–surgery–carbo/paclitaxel → erlotinib	1
Surgery-EP 50/50/RT → carboplatin/paclitaxel/TLK286	1
Three prior regimens	
Carboplatin/paclitaxel → docetaxel → erlotinib	1
Carboplatin/paclitaxel RT-consolidation cisplatin/gemcitabine → erlotinib → HKI272	1
Four prior regimens	
Gefitinib → erlotinib → carboplatin/gemcitabine → HKI272	1
Carboplatin/gemcitabine → docetaxel → etoposide → erlotinib	1
Five prior regimens	
Gemcitabine → navelbine/docetaxel → cpt-11 → gefitinib → erlotinib	1

Toxicity

There was one fatal toxicity from hemoptysis. This occurred in a 56-year-old woman with stage IV NSCLC (including metastases to brain, liver, adrenal) who had progressed after whole brain radiotherapy and two cycles of cisplatin and docetaxel chemotherapy. Her tumor histology was poorly differentiated non-small cell carcinoma, not otherwise specified. She started second-line therapy on the study protocol and received two cycles of pemetrexed, oxaliplatin, and bevacizumab. Two days after receiving cycle 2, she experienced sudden, massive hemoptysis, and expired at home. Her primary lung mass was central in the chest, encasing the left main bronchus and left main pulmonary artery. There were no tumor cavitations observed in her baseline scan obtained before the start of treatment.

There were no other grade 4 or 5 toxicities observed. The most common grade 3 toxicity was hypertension, occurring in six (17%) patients. One patient developed new hypertension during cycle 5 of treatment which resolved with addition of a beta-blocker. Five patients had known hypertension and were on antihypertensive drugs before start of therapy, and required an increase in their oral regimen. All cases of hypertension were manageable with oral medication adjustment alone. Other grade 2 to 4 toxicities are noted in Table 3.

DISCUSSION

The standard wisdom in the treatment of advanced NSCLC in the second-line and third-line setting has been that combination therapy has no advantage over single agent therapy, only adding toxicity with little additional efficacy. The development of novel targeted drugs offers a chance to re-examine this paradigm and ask if combinations of newer agents might prove superior.

We have demonstrated in a multi-institution phase II trial that a combination of oxaliplatin, pemetrexed, and bevacizumab administered to previously treated advanced NSCLC patients is well tolerated and efficacious, with a response rate of 27%, median PFS of 5.8 months, and median OS of 12.5 months. Although this single-arm phase II study is not definitive, our results are provocative and raise hope that with modern chemotherapeutics and novel targeted agents, improvement in outcomes with second-line therapies and beyond may be possible. Table 4 summarizes selected agents that are commonly used in the second-line setting, with their associated response rates and survival statistics. Although most of these trials were randomized phase III trials and should not be directly compared with our results, it is

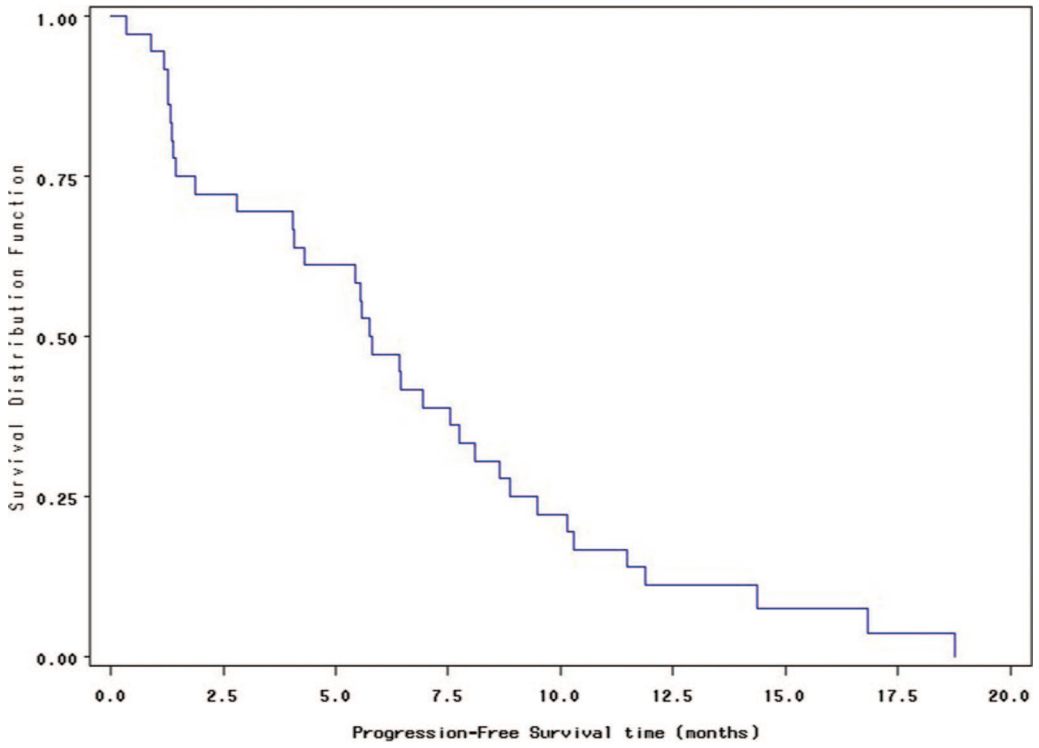

FIGURE 1. Progression-free survival.

clear that the promising treatment outcomes we obtained with oxaliplatin, pemetrexed, and bevacizumab in a phase II trial in this population are worthy of further study.

Treatment with the combination of oxaliplatin, pemetrexed, and bevacizumab was well tolerated. The most common grade 3 toxicity was hypertension, a well-described

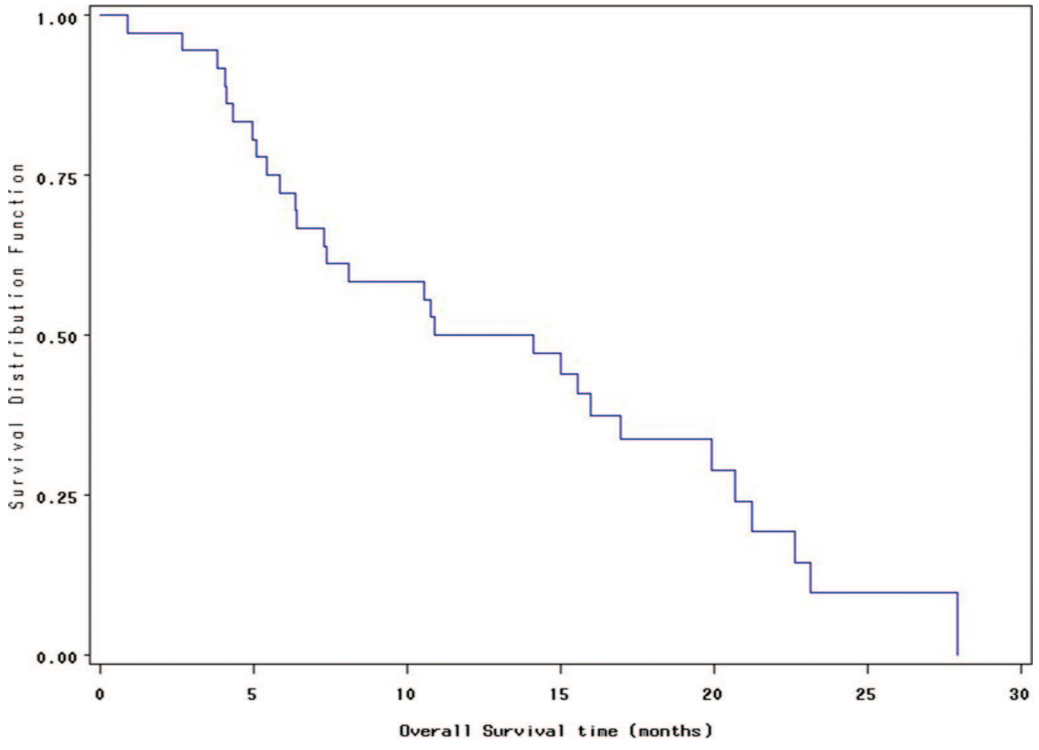

FIGURE 2. Overall survival.

TABLE 3. Toxicities

Toxicity	Grade 2	Grade 3	Grade 4	Grade 5
Neutropenia	3	1	0	0
Febrile neutropenia	0	0	0	0
Anemia	1	1	0	0
Thrombocytopenia	2	1	0	0
Fatigue	11	3	0	0
Nausea	1	1	0	0
Vomiting	1	1	0	0
Dehydration	1	1	0	0
Constipation	5	1	0	0
Abdominal pain	4	1	0	0
Infectious colitis	0	1	0	0
Port infection	0	1	0	0
Face pain	0	1	0	0
Hypertension	0	6	0	0
Neuropathy	3	1	0	0
Elevated ALT/AST	3	1	0	0
Hemoptysis	0	0	0	1
Dyspnea	8	1	0	0
Wheeze/bronchospasm	1	1	0	0
Allergic reaction	0	1	0	0
Pain	4	0	0	0
Depression	1	0	0	0
Dizziness	1	0	0	0
Cough	8	0	0	0
Alopecia	2	0	0	0
Anorexia	2	0	0	0
Rash	1	0	0	0
Fever without neutropenia	1	0	0	0
Headache	2	0	0	0
Hyperglycemia	1	0	0	0
Diarrhea	3	0	0	0

class effect of antiangiogenic therapy, which was easily manageable with standard antihypertensive medications. There was one fatal pulmonary hemorrhage. Although the patient did not have squamous cell histology, which was an exclusion criteria, the primary lung mass was a large central tumor encasing the major pulmonary vessels. There were no central nervous system bleeding complications, including the nine patients who had previously treated brain metastases. Although central nervous system metastases still remain an exclusion criteria for the standard use of bevacizumab in NSCLC, an ongoing phase II trial (known as the PASSPORT trial) is investigating the safety of bevacizumab in patients with treated brain metastases in nonsquamous advanced NSCLC.

The addition of bevacizumab to platinum-based chemotherapy in the first-line setting is clearly the standard of care for patients who meet the appropriate eligibility criteria. ECOG 4599 showed the benefit in OS of bevacizumab added to carboplatin and paclitaxel in the first-line treatment of advanced NSCLC.[3] Also in the first-line setting, the AVAIL study randomized patients to cisplatin and gemcitabine, with or without bevacizumab at dose levels of 7.5 or 15 mg/kg.[15] Both the 7.5 and 15 mg/kg dose levels showed an improvement in PFS when compared with chemotherapy alone. Our study was designed before the results of AVAIL were first reported, and it is not known whether a 7.5 mg/kg dose would have yielded similar results in our study.

In addition to treatment in the first-line setting, bevacizumab in the second-line therapy for NSCLC may improve outcomes. In a recently reported randomized phase II trial, patients with recurrent or refractory advanced NSCLC were treated with either chemotherapy (pemetrexed or docetaxel) alone, or chemotherapy or erlotinib in combination with bevacizumab.[4] Similarly to our study, patients enrolled on this trial had not received bevacizumab as part of prior chemotherapy regimens. PFS and OS, although not statistically significant, favored the bevacizumab arms. Median PFS was 4.8 and 4.4 months in the bevacizumab with chemotherapy or erlotinib arms respectively, compared with 3.0 months in the chemotherapy alone arm. OS also favored the bevacizumab arms, with median OS of 12.6 or 13.7 months in the bevacizumab with chemotherapy or erlotinib arms, respec-

TABLE 4. Therapies for NSCLC in Second Line and Beyond

Drug	Phase of Study	No. Prior Regimens	RR (%)	TTP (wk)	Median Survival (mo)
Docetaxel[5]	III	≥1	7.1	10.6	7.0
Best supportive care				6.7	4.6
Docetaxel 100 mg/m^2	III	≥1	10.8	8.4	5.5
Docetaxel 75 mg/m^2			6.7	8.5	5.7
Vinorelbine/ifosfamide			0.8	7.9	5.6
				PFS (mo)	
Pemetrexed[7]	III	1	9.1	2.9	8.3
Docetaxel			8.8	2.9	7.9
Erlotinib[8]	III	≤2	8.9	2.2	6.7
Placebo			<1	1.8	4.7
Chemotherapy[a] + placebo[4]	Randomized II	1	12.2	3.0	8.6
Chemotherapy[a] + bevacizumab			12.5	4.8	12.6
Erlotinib + bevacizumab			17.9	4.4	13.7

[a] Pemetrexed/docetaxel.

tively, compared with 8.6 months in the chemotherapy alone arm. Response rates were 12.5% with chemotherapy and bevacizumab and 17.9% with erlotinib and bevacizumab.

Interestingly, a recently reported phase III trial showed in a prespecified subset analysis that patients with adenocarcinoma or large cell histology may derive more benefit from pemetrexed in combination with cisplatin in the first-line setting.[16] As squamous histology was an exclusion criteria in our trial, most of our patients had either adenocarcinoma or large cell histology, and may be a subset of patients who might be expected to do well with pemetrexed.

In conclusion, treatment with a chemotherapy regimen of oxaliplatin and pemetrexed in combination with the targeted antiangiogenic agent bevacizumab yielded promising efficacy results with manageable toxicity in previously treated advanced NSCLC patients. Our results suggest that aggressive treatment of fit patients in the second-line setting and beyond could improve outcomes, and this regimen should be investigated in further trials. A randomized trial comparing oxaliplatin, pemetrexed, and bevacizumab to pemetrexed and bevacizumab would be warranted to further investigate the comparative benefit of this combination.

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