Efficacy and Safety of Oxaliplatin and Gemcitabine with Bevacizumab in Advanced Non-small Cell Lung Cancer

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Introduction: We conducted a multicenter phase II study to evaluate the efficacy and safety of oxaliplatin and gemcitabine with bevacizumab in patients with advanced non-small cell lung cancer (NSCLC).

Methods: Patients with chemotherapy-naive, nonsquamous, stage IIIB or IV NSCLC received gemcitabine 1000 mg/m^2 on days 1 and 8, oxaliplatin 130 mg/m^2 on day 1, and bevacizumab 15 mg/kg on day 1 every 21 days for 4 cycles. Patients with stable disease or response received maintenance bevacizumab every 3 weeks until progression. Primary end point was median time to progression (TTP).

Results: Nineteen of 44 eligible patients had partial response in the intent-to-treat analysis for an objective response rate of 43% (95% confidence interval [CI], 26.3–60.1%); 16 patients had stable disease for a disease control rate of 80% (95% CI, 72.0–87.0%). Median TTP was 5.5 months (95% CI, 3.8–6.9 months), which approached that seen in phase III studies. Median survival was 13.7 months (95% CI, 7.3–21.8 months). The most common grade 3 or 4 adverse events were hypertension (11%), neutropenia (9%), diarrhea (7%), dyspnea (7%), and thromboembolic events (7%). Pulmonary hemorrhage was not observed.

Conclusions: The results of this phase II study suggest that oxaliplatin and gemcitabine with bevacizumab was active and reasonably well tolerated. Median TTP approached that in phase III studies. This combination represents another treatment option for advanced NSCLC.

Key Words: Bevacizumab, Gemcitabine, Oxaliplatin, Advanced non-small cell lung cancer.

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Combination chemotherapy has become the standard treatment for patients with advanced non-small cell lung cancer (NSCLC).[1] Only minor differences have been detected among platinum-based doublets in large randomized phase III studies.[2–4] Oxaliplatin with gemcitabine is a theoretically attractive doublet because of its synergy in human cancer cell lines[5] and favorable safety profile in phase II studies.[6–8] Specifically, oxaliplatin is associated with less nephrotoxicity than cisplatin[9] and less myelosuppression than carboplatin.[10] Preliminary clinical studies of this combination have yielded efficacy outcomes in the range of other commonly used platinum-based doublets.[6–8] Furthermore, a recent phase III study indicated that the addition of bevacizumab to a standard regimen such as carboplatin and paclitaxel significantly improved response rate, TTP, and survival.[11]

Based on this rationale, we conducted a phase II study to investigate the efficacy and safety of oxaliplatin and gemcitabine with bevacizumab as first-line therapy in eligible patients with advanced NSCLC. The dosages of oxaliplatin and gemcitabine were based on a phase I study[12] in which the combination was well tolerated with primarily hematologic toxicity at the maximum tolerated dose; sensory neuropathy was relatively uncommon and reversible. Four cycles of the 3-drug combination were administered and followed by maintenance bevacizumab. The duration of induction therapy was based on randomized studies in which 3 or 4 cycles resulted in less toxicity and provided benefits comparable to those of 6 or more cycles.[13–15] The dosage and schedule of bevacizumab were based on the phase III study.[11]

MATERIALS AND METHODS

Eligibility

Patients were eligible if they had histologically or cytologically confirmed advanced (stage IIIB with malignant pleural effusion or stage IV or recurrent disease) nonsquamous NSCLC and had not received prior systemic treatment. Patients had to have measurable disease without central nervous system metastases and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients also had to have adequate hematologic (absolute neutrophil count $>1500/\mu L$ and platelets $>100{,}000/\mu L$), hepatic (total bilirubin <1.5 mg/dL and transaminases $<5\times$ the upper limit of normal), and renal function (serum creatinine $\leq 1.5\times$ upper limit of normal and urinalysis $<1+$ protein). Women of childbearing potential and sexually active males had to use

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contraception. Exclusion criteria were pregnancy or lactation; unresolved adverse events from radiation therapy; deep-vein thrombosis or pulmonary embolus within 1 year; ongoing therapeutic anticoagulant; uncontrolled hypertension; serious nonhealing wound ulcer, bone fracture, or major surgical procedure within 3 weeks; history of gross hemoptysis; prior malignancy; or other medical conditions that would limit compliance with study requirements. All patients provided written informed consent. The Institutional Review Board approved the study, which was conducted in accordance with federal and institutional guidelines.

Treatment Plan and Evaluation

This was an open-label phase II study. Patients received intravenous (IV) gemcitabine 1000 mg/m^2 over 30 minutes on days 1 and 8 followed by IV oxaliplatin 130 mg/m^2 over 2 hours on day 1 followed by IV bevacizumab 15 mg/kg over 90 minutes on day 1. Anaphylaxis precautions were observed during bevacizumab administration. If bevacizumab was well tolerated, the second infusion was shortened to 60 minutes and subsequent infusions to 30 minutes. Antiemetic administration was allowed at the discretion of the investigators. Granulocyte colony-stimulating factor could also be administered according to American Society of Clinical Oncology guidelines.[16] Treatment was administered every 21 days for a maximum of 4 cycles. Patients with complete or partial response or stable disease after 4 cycles received maintenance IV bevacizumab 15 mg/kg every 3 weeks until relapse or progression.

Toxicity was assessed every cycle using National Cancer Institute Common Toxicity Criteria Version 3.0. Dose modifications were based on worst toxicity for any organ system for the previous cycle. Dose escalations were not permitted. The gemcitabine dose was first reduced to 900 mg/m^2 and, for second occurrence of selected toxicities, to 800 mg/m^2. The oxaliplatin dose was reduced to 100 mg/m^2. For absolute neutrophil count $<500/\mu$L for ≥ 7 days or febrile neutropenia, both drugs were delayed until recovery to $\geq 1000/\mu$L and administered at the first reduction level. For platelets $<50{,}000/\mu$L, gemcitabine was delayed until recovery to $\geq 75{,}000/\mu$L and administered at the first reduction level. For second occurrence of platelets $<50{,}000/\mu$L, both drugs were delayed until recovery, and gemcitabine was administered at the second reduction level and oxaliplatin at the first reduction level. Similar reductions and delays were specified for gemcitabine on day 8. For nonhematologic toxicities other than nausea, vomiting, and alopecia, both drugs were reduced to the first level for grade 3 toxicity and stopped for grade 4 toxicity. In addition, oxaliplatin was reduced for paresthesia or dysesthesia that was grade 2 and persistent or grade 3, and was stopped for grade 3 or 4 acute hypersensitivity or anaphylactic reaction; the infusion duration was prolonged to 4 to 6 hours for acute laryngopharyngeal dysesthesia. Bevacizumab was generally delayed until recovery from grade 3 toxicity and discontinued upon second occurrence of grade 3 toxicity or first occurrence of grade 4 toxicity, such as hemorrhage, uncontrolled hypertension, proteinuria, or venous thrombosis.

Patients were evaluated at baseline and at the beginning of each cycle. Evaluations generally included history, physical examination, vital signs, complete blood count with differential and platelet count, serum chemistries, urinalysis, and assessment of ECOG performance status and neurologic function. Computed tomography (CT) scans of potential disease areas and brain imaging by CT scan or magnetic resonance imaging were performed at baseline. If clinically indicated, bone scan, skeletal survey, or magnetic resonance imaging was performed at the beginning of each cycle. CT scans were performed for tumor assessment after cycles 2 and 4 and then every 12 weeks during maintenance therapy. Response Evaluation Criteria in Solid Tumors[17] were used to categorize response to treatment as complete response, partial response, stable disease, or progressive disease.

The primary end point was median TTP, defined as time from registration to tumor progression or death. TTP was censored at the last known progression-free date for patients who remained on or were removed from study without objective tumor progression, received nonstudy antitumor treatment, or were lost to follow-up without disease progression. Patients who completed therapy without disease progression were censored on the last follow-up date. Secondary endpoints were response rates, median duration of survival, and adverse events.

Statistical Analysis

Target sample size was 50 evaluable patients, which yielded statistical power of 80% to detect the difference between the null (median TTP of 4.6 months) and alternative (median TTP of 6.7 months) hypotheses, with an exponential maximum likelihood estimate and a one-sided significance level of 0.05.[18] Kaplan-Meier method was used to estimate TTP and survival.[19] Descriptive statistics were used for baseline characteristics and secondary endpoints.

Study populations were defined prospectively. The intent-to-treat population included all eligible patients, whether or not they received any study drug. The safety population included all patients who received at least 1 dose of any study drug. The efficacy-evaluable population included all patients who received at least 2 cycles of treatment with at least 1 follow-up tumor assessment and who had no protocol violations related to efficacy evaluation.

RESULTS

Forty-five patients were enrolled at four institutions between November 2004 and August 2006. The study was stopped short of the predefined target enrollment of 50 patients because accrual rate decreased over time. One patient was excluded from all analyses because he was retrospectively found to have metastatic colon cancer. The median duration of follow-up in 44 eligible patients was 13.3 months (range, 1–31 months). Most eligible patients were males and had stage IV adenocarcinoma (Table 1). All had an ECOG performance status of 0 or 1.

The median number of chemotherapy cycles was 4 (range, 1–6). Thirty-one patients received 4 cycles, including four patients who received two additional chemotherapy cycles because of the likelihood of continuous benefit as

TABLE 1. Patient and Disease Characteristics at Baseline in 44 Patients with NSCLC

Characteristic	Number of Patients (%), Unless Otherwise Stated
Median age in years (range)	64.5 (42–81)
Sex	
Males	31 (70)
Females	13 (30)
Race or ethnicity	
Caucasian	29 (66)
Hispanic	12 (27)
African-American	2 (5)
Other	1 (2)
ECOG performance status	
0	19 (43)
1	25 (57)
Disease stage	
IIIB	8 (18)
IV or recurrent disease	36 (82)
Histology	
Adenocarcinoma	25 (57)
Other	19 (43)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

determined by the treating physician. Reasons for stopping chemotherapy before four cycles were progressive disease ($n = 10$), noncompliance ($n = 2$), and adverse event ($n = 1$). Nineteen doses were omitted, usually gemcitabine on day 8; 13 doses were reduced; and three were delayed. A total of 26 patients received maintenance bevacizumab, with a median of 5 cycles (range, 1–23 cycles). Reasons for stopping maintenance bevacizumab were progressive disease ($n = 21$), adverse event ($n = 3$), and unhealed wound after ankle surgery ($n = 1$); one patient continued to receive bevacizumab at the time of evaluation.

Partial response was observed in 19 of 44 patients for an objective response rate of 43% in the intent-to-treat analysis (95% confidence interval [CI], 26.3–60.1%; Table 2). Sixteen patients had stable disease for a disease control rate of 80% (95% CI, 72.0–87.0%). Of 39 patients who received at least two cycles, 19 had partial responses (49%; 95% CI, 32.6–64.8%) and 16 had stable disease for a disease-control rate of 90% (95% CI, 84.4–95.0%).

TABLE 2. Best Response to Treatment in 44 Patients with NSCLC

Type of Response	Number of Patients (%)
Partial response	19 (43%; 95% CI, 26.3–60.1%)
Stable disease	16 (36%)
Progressive disease	8 (18%)
Not evaluable[a]	1 (2%)

CI, confidence interval; NSCLC, non-small cell lung cancer.
[a]Not evaluable because of discontinuation before completion of cycle 1 due to adverse event.

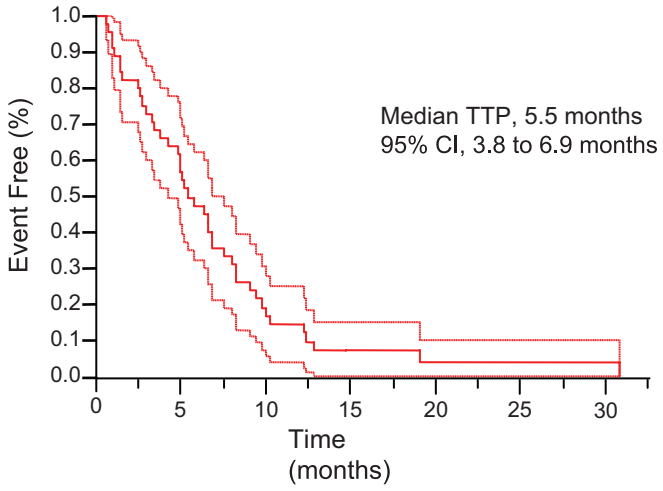

FIGURE 1. Kaplan-Meier estimate of time to progression (TTP, solid line) and 95% confidence interval (CI, dashed lines) in intent-to-treat analysis of 44 patients with non-small cell lung cancer, including two censored patients who did not have progressive disease (data not shown).

Median TTP, including two censored patients whose disease had not progressed, was 5.5 months in the intent-to-treat analysis of 44 patients (95% CI, 3.8–6.9 months; Figure 1). Median survival, including 16 censored patients who remained alive, was 13.7 months (95% CI, 7.3–21.8 months; Figure 2). The 1-year survival rate was 55%.

The most common grade 3 or 4 hematologic adverse event during combination therapy was neutropenia (9%; Table 3). The most common grade 3 or 4 nonhematologic adverse events were hypertension (11%), diarrhea (7%), dyspnea (7%), and thromboembolic events (7%). Thromboembolic events occurred in three patients. The first had grade 4 ischemic bowel, necessitating discontinuation of all treatment after the first cycle. The second had grade 3 acute coronary event, necessitating discontinuation of bevacizumab after the

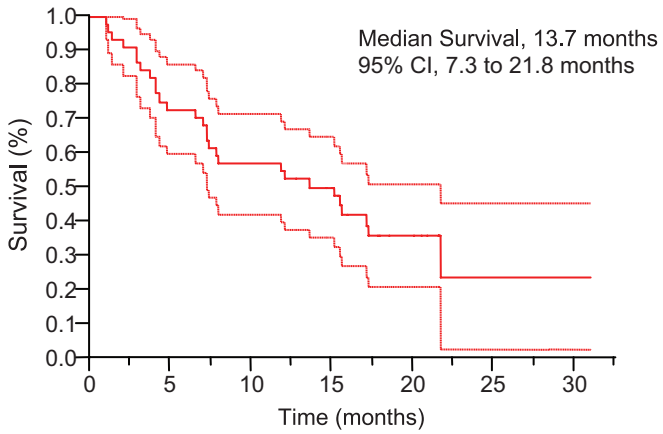

FIGURE 2. Kaplan-Meier estimate of overall survival (solid line) and 95% confidence interval (CI, dashed lines) in intent-to-treat analysis of 44 patients with non-small cell lung cancer, including 16 censored patients who did not have progressive disease (data not shown).

TABLE 3. Grade 3 or 4 Adverse Events

	Number of Patients (%)	
Adverse Event	**Gemcitabine, Oxaliplatin, Bevacizumab (n = 44) Grade 3 or 4[a]**	**Maintenance Bevacizumab (n = 26) Grade 3 or 4**
Hematologic events		
Neutropenia	4 (9)[a]	0
Thrombocytopenia	3 (7)[a]	1 (4)
Anemia	1 (2)	0
Nonhematologic events		
Hypertension	5 (11)[a]	1 (4)
Diarrhea	3 (7)	0
Dyspnea	3 (7)	0
Thromboembolic events	3 (7)[a]	0
Fatigue	2 (5)	0
Nausea and vomiting	2 (5)	0
Stroke (hemorrhagic)	1 (2)[ab]	1 (4)
Allergic reaction	1 (2)	0
Neuropathy (sensory)	1 (2)[c]	0

[a]Each asterisk indicates 1 grade 4 event.
[b]One stroke was considered not related to treatment; the other was probably related to maintenance bevacizumab.
[c]One patient had grade 2 neuropathy; none had grade 3 or 4 neuropathy.

first cycle but allowing continuation of gemcitabine and oxaliplatin. The third had grade 3 pulmonary embolism and bilateral deep venous thrombosis in the lower extremities, which were judged possibly related to treatment by the treating physician; the treatment was stopped because of progressive disease. In addition, one patient had a grade 3 allergic reaction after the first cycle, characterized by dyspnea and diaphoresis with grade 3 nausea and vomiting; treatment was continued for a total of seven additional cycles of bevacizumab. No patients experienced grade 3 or 4 neuropathy or nephrotoxicity.

Grade 3 adverse events during bevacizumab maintenance were hypertension (4%), stroke (4%), and thrombocytopenia (4%). Specifically, bevacizumab was discontinued in one patient after cycle 3 because of grade 3 hypertension and in another patient after cycle 8 because of cerebellar hemorrhagic stroke with thrombocytopenia. In an additional patient, bevacizumab was discontinued after cycle 9 because of grade 2 epistaxis.

DISCUSSION

At the time this study was conceived and implemented, bevacizumab use in advanced NSCLC was experimental and, at least in the United States, primarily limited to combination with carboplatin and paclitaxel. Because of its favorable safety profile[6–10] and preliminary evidence of clinical activity,[6–8] our goal was to test the efficacy and safety of oxaliplatin and gemcitabine with bevacizumab. Criteria were predefined to decide whether this regimen, if proven tolerable, would merit further testing in a phase III setting. To the best of our knowledge, this is the first completed phase II trial of this combination as first-line therapy in patients with advanced NSCLC.

Treatment was associated with tolerable toxicity in our study. Although bevacizumab has been reported to increase the hematologic toxicity of carboplatin with paclitaxel[11,20] and cisplatin with gemcitabine,[21] grade 3 or 4 hematologic toxicity occurred in <10% of our patients. This finding was consistent with the lower incidence of myelosuppression secondary to oxaliplatin and gemcitabine compared with other platinum-based doublets.[6] The most common nonhematologic event in our patients, hypertension, has been observed in previous studies of bevacizumab in NSCLC[11,20,21] and other solid tumors,[22–24] usually responded to antihypertensive therapy, and was reversible upon completing bevacizumab.

The lack of pulmonary hemorrhage in our study was noteworthy. We followed the same exclusion criteria used in the large phase III trials.[11,20] Nevertheless, severe pulmonary hemorrhage was noted in approximately 1% to 3% of those patients, a rate too low for replication in our sample size. On the other hand, concern about an increased risk of pulmonary hemorrhage due to gemcitabine, perhaps related to thrombocytopenia, was not substantiated in our study.

Two patients had hemorrhagic stroke, but one may not have been related to treatment. The only other bleeding events were grade 2 epistaxis during maintenance bevacizumab and grade 1 events (data not shown). Therefore, the incidence of grade 3 or 4 bleeding events was 5% in our patients, approximating the 4% incidence in phase III studies.[11,21] Three patients had thromboembolic events, including one pulmonary embolism with bilateral deep venous thrombosis, one acute coronary event, and one ischemic bowel. These complications have been described in patients with NSCLC[11,20,21] and other solid tumors.[22–24] For example, in the largest study of bevacizumab in patients with NSCLC ($N = 1043$),[21] ischemic events, including arterial thromboembolic events, occurred in 5% of patients who received cisplatin with gemcitabine compared with 2% or 3% of those who received the doublet plus bevacizumab 7.5 or 15 mg/kg, respectively. The corresponding incidences of venous thromboembolic events were 6%, 7%, and 7%.[21]

Our response rate of 43% compared favorably with the range of 25% to 31% associated with oxaliplatin and gemcitabine alone in phase II studies[6–8] and 30% to 35% associated with bevacizumab and platinum-containing doublets in randomized studies.[11,20,21] The median TTP of 5.5 months approached that in phase III trials,[11,20,21] but did not meet the predefined level of 6.7 months for further evaluation. Six additional patients were needed to satisfy the target sample size of 50 patients, and it remains unclear whether enrolling those additional patients would have significantly altered the outcome. The median duration of survival of 13.7 months was quite promising and, again, comparable to that of platinum doublets with bevacizumab in previous trials.[11,20] Nevertheless, survival data must be interpreted cautiously in phase II studies, even when conducted at multiple institutions, and was not the primary end point of our study.

Oxaliplatin-based doublets continue to be evaluated as first-line therapy in patients with advanced NSCLC. Oxali-

platin with gemcitabine had similar activity and milder hematologic toxicity compared with carboplatin and gemcitabine or the same regimen followed by docetaxel in a large phase II randomized study.[6] Oxaliplatin and pemetrexed also showed efficacy comparable to that of carboplatin and pemetrexed in a prior trial.[10] Oxaliplatin with docetaxel showed promising results in a recent pilot study[25]; and this combination is now being studied with the addition of bevacizumab in an ongoing multicenter phase II trial. Lastly, and importantly, a phase III study of gemcitabine plus either oxaliplatin or carboplatin (or cisplatin) has been completed and results are pending.

In summary, oxaliplatin and gemcitabine with bevacizumab was reasonably well tolerated, showed efficacy similar to that of other platinum doublets in combination with bevacizumab, and represents another treatment option in our armamentarium for patients with advanced NSCLC. Further phase III trials will depend on the results of ongoing and recently completed trials.

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