Paclitaxel Plus Bevacizumab in Patients with Chemosensitive Relapsed Small Cell Lung Cancer

A Safety, Feasibility, and Efficacy Study from the Hoosier Oncology Group

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Introduction: Bevacizumab when combined with carboplatin and paclitaxel improves response rates (RRs) and overall survival in patients with advanced non-small cell lung cancer. Paclitaxel has single-agent activity in relapsed small cell lung cancer (SCLC). Angiogenesis seems to play an important role in the pathogenesis of SCLC. This study evaluated the safety and efficacy of paclitaxel plus bevacizumab in patients with chemosensitive relapsed SCLC.

Methods: Patients with relapsed chemosensitive SCLC with an Eastern Cooperative Oncology Group performance status of 0 to 1 were eligible. They received paclitaxel 90 mg/m^2 intravenously on days 1, 8, and 15. Bevacizumab was administered at 10 mg/kg intravenously on days 1 and 15. Cycles were every 28 days. The primary endpoint was progression-free survival (PFS). Secondary endpoints included RRs, toxicity, and overall survival. Correlative studies evaluated vascular endothelial growth factor polymorphisms.

Results: Thirty-four patients were enrolled in the study. Median age was 66.5 (range, 38–88) years, male:female: 61.8%:38.2%, Eastern Cooperative Oncology Group performance status 0:1 47.1%:52.9%. Median progression-free survival was 14.7 weeks (equivalent to historical controls). Median survival time was 30 weeks. The overall RR was 18.1%. Stable disease rate was 39.3%, and 45.4% of patients had progressive disease. No unexpected toxicities were noted, and grade 3/4 toxicities were limited to neutropenia, fatigue, and dyspnea. None of the vascular endothelial growth factor polymorphisms evaluated were significantly associated with response.

Conclusions: The addition of bevacizumab to paclitaxel does not improve outcomes in relapsed chemosensitive SCLC.

Key Words: Relapsed small cell, Paclitaxel, Bevacizumab.

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Small cell lung cancer (SCLC) accounts for 13 to 15% of lung cancers with the majority of patients ultimately succumbing to their disease.[1] The majority of patients are diagnosed with extensive disease at presentation and are treated with platinum-based therapy. Depending on the duration of response to platinum-based therapy, patients are described as having chemosensitive or chemorefractory disease. Those with chemosensitive disease, typically defined as relapsing more than 60 to 90 days after completion of platinum-based therapy, frequently benefit from further chemotherapy at the time of disease progression. Multiple agents have activity in the second-line setting, but responses are typically brief (2–4 months), and survival times are short (median, 6 months). Paclitaxel also has single-agent activity in chemotherapy-naive patients with SCLC with a response rate (RR) of 30 to 50%.[2,3] In addition, paclitaxel is active in a chemorefractory population with SCLC.[4]

Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a recombinant vascular endothelial growth factor (VEGF) monoclonal antibody that was included in the first-line treatment paradigm of advanced non-small cell lung cancer after its combination with carboplatin/paclitaxel in the Eastern Cooperative Oncology Group (ECOG) 4599 study. This trial showed an improvement in RR and overall survival (OS) compared with chemotherapy alone.[5]

SCLC is a tumor with early hematogenous spread. Tumor microvessel count and VEGF expression were prog-

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nostic factors and correlated with worse survival ($p < 0.001$ and $p = 0.0008$, respectively) in patients with SCLC who underwent pneumonectomies or lobectomies.[6] VEGF was also reported to be expressed in 81% of patients with SCLC.[7]

Therefore, we initiated this study evaluating the safety and efficacy of the combination of paclitaxel and bevacizumab in relapsed chemosensitive SCLC. We used the dosing schedule evaluated as initial treatment in patients with metastatic breast cancer in which the combination resulted in an improvement in RR (36.9% versus 21.2%, $p < 0.001$) and progression-free survival (PFS; 11.8 versus 5.9 months, hazard ratio = 0.6, $p < 0.001$) over paclitaxel alone.[8]

PATIENTS AND METHODS

Eligibility criteria included age ≥18 years, histologic or cytologic diagnosis of SCLC, prior treatment with at least one platinum-containing regimen, ECOG performance status 0 to 1, and measurable disease by Response Evaluation Criteria in Solid Tumor (RECIST) Group response criteria. All patients had chemosensitive disease defined as relapse more than 60 days after completing initial treatment. Adequate hematologic, renal, and liver function at baseline were required. No therapies were allowed within 3 weeks of registration. Patients were excluded if they had evidence of brain metastases within 42 days of registration. All patients provided written informed consent before enrolling in the study. Local institutional review boards approved the protocol.

Treatment Plan

Patients received 90 mg/m^2 of paclitaxel as a 1-hour intravenous infusion on days 1, 8, and 15 and bevacizumab at 10 mg/kg intravenously on days 1 and 15. Cycles were repeated every 28 days. Patients were premedicated before paclitaxel per package insert. Bevacizumab was administered after the completion of paclitaxel on day 1 of cycle 1. After 4 to 6 cycles of treatment with the combination, patients were allowed to continue with bevacizumab alone as maintenance therapy until disease progression or intolerable side effects.

Statistical Analysis

The primary endpoint of the study was PFS defined as the interval from the start of therapy until disease progression or death. Secondary endpoints included RR as defined by the Response Evaluation Criteria in Solid Tumor criteria and OS time defined as time from initiation of first cycle to death. Other secondary endpoints included determination of adverse events, their severity, and all grade 3 and grade 4 toxicities.

The median PFS with historical controls (topotecan) is 14 weeks. With a total number of 34 patients, this study had 91% power and $\alpha = 5\%$, to detect an improvement in PFS to 24 weeks.

Laboratory Correlates

Correlative studies involved evaluation of VEGF polymorphisms and their correlation with RR. Fisher's exact test was used to correlate VEGF polymorphisms with response data.

TABLE 1. Baseline Characteristics ($n = 34$)

Characteristics	$n = 34$
Age (yr)	
Median	66.5
Range	38–88
Sex, *n* (%)	
Male	21 (61.8)
Female	13 (38.2)
ECOG PS	
0	16 (47.1)
1	18 (52.9)
Smoking history, *n* (%)	
Current	12 (35.3)
Former	20 (58.8)
Never	2 (5.9)
Prior treatment, *n* (%)	
1. Chemotherapy	29 (85.3)
2. Chemotherapy	5 (14.7)
Radiotherapy	18 (31)
Median number of days from previous regimen to registration (range)	142 (35–557)

ECOG PS, Eastern cooperative oncology group performance status.

Blood samples were collected in 6-mL lavender-top tubes from patients agreeable to laboratory correlatives. The following VEGF polymorphisms were evaluated: +936 C/T, −634 G/C, −2578 C/A, −1154 G/A, and −460 C/T. These specific polymorphisms were selected because of their known impact on modulating angiogenesis. Polymorphisms were assessed using standard polymerase chain-restriction fragment length polymorphism methods that are previously established and Taqman-based assays.[9]

RESULTS

Between April 26, 2006, and January 11, 2007, 34 patients were enrolled in the study. Baseline characteristics are summarized in Table 1.

Treatment Administered ($n = 33$)

The median number of cycles received on trial was 3 (range, 1–9). Approximately 60% of patients were able to receive the study regimen without dose modifications. Fifty percent of the patients required no dose delays. Only two patients continued on the maintenance bevacizumab phase after six cycles of paclitaxel plus bevacizumab.

Efficacy

Response results are available for 33 patients because one patient never received treatment. One complete response (CR) was observed, five patients achieved a partial response (PR) (15.1%) for an overall RR of 18.1%. Fifteen patients progressed (45.4%), and stable disease was noted in 13 patients (39.3%). The median PFS was 14.7 weeks (95% confidence interval = 7–15.7), and the median survival time (MST) was 30 weeks (95% confidence interval = 18–48).

TABLE 2. Hematologic Toxicities ($n = 34$)

Toxicity	Any Grade, *n* (%)	Grades 3–4, *n* (%)
Hematologic		
Neutropenia	9 (26)	6 (17.6)
Febrile neutropenia	0	0
Anemia	12 (35)	0
Thrombocytopenia	6 (17.6)	0

TABLE 3. Nonhematologic Toxicities ($n = 34$)

Toxicity	Any Grade, *n* (%)	Grades 3–4, *n* (%)
Fatigue	29 (85)	9 (26)
Dyspnea	20 (58.8)	5 (14.7)
Hypertension	9 (26.4)	0
Neuropathy	15 (44)	0
Nausea	17 (50)	0
Vomiting	4 (11.7)	0
Liver enzyme abnormalities		
Elevation in alkaline phosphatase	5 (14.7)	0
Elevation in AST	5 (14.7)	0
Diarrhea	12 (35)	0
Constipation	17 (50)	0
Anorexia	19 (55.8)	0
Mucositis	6 (17.6)	0
Hyperglycemia	5 (14.7)	0
Headache	11 (32.3)	0

AST, aspartate aminotransferase.

Safety/Toxicity

Toxicities noted in ≥10% of patients ($n = 34$) are presented in Tables 2 and 3. No unexpected toxicities were observed with the combination. Grade 1 pulmonary hemorrhage was noted in one patient. Three patients had grade 1 to grade 2 proteinuria. There were no febrile neutropenia episodes and no treatment-related deaths.

Laboratory Correlative Results

Data were available for 30 patients to assess VEGF polymorphisms and association with response. The frequencies of the various VEGF polymorphisms in different patient response groups are presented in Table 4. No associations were statistically significant, although the association of VEGF 1154GA with response approached statistical significance ($p = 0.0677$).

TABLE 4. Frequencies of VEGF Polymorphisms and Correlation with Responses ($n = 30$)

VEGF Polymorphism	CR/PR (%)	PD (%)	SD (%)
VEGF-2578			
AA	2 (6.6)	3 (10)	1 (3.3)
CA	3 (10)	5 (16.7)	5 (16.7)
CC	0 (0)	2 (6.6)	6 (20)
VEGF-1154			
AA	0 (0)	1 (3.3)	0 (0)
GA	5 (16.7)	6 (20)	4 (13.3)
GG	0 (0)	6 (20)	8 (26.6)
VEGF 936			
CC	3 (10)	10 (33.3)	10 (33.3)
CT	1 (3.3)	3 (10)	1 (3.3)
TT	1 (3.3)	0 (0)	1 (3.3)
VEGF-634			
CC	0 (0)	4 (13.3)	2 (6.6)
GC	3 (10)	2 (6.6)	4 (13.3)
GG	2 (6.6)	7 (23.3)	6 (20)
VEGF-1498			
CC	2 (6.6)	3 (10)	1 (3.3)
CT	3 (10)	6 (20)	5 (16.7)
TT	0 (0)	4 (13.3)	6 (20)

VEGF, vascular endothelial growth factor; SD, stable disease; PD, progressive disease; CR, complete response; PR, partial response.

DISCUSSION

The addition of bevacizumab to paclitaxel does not seem to improve PFS in patients with chemosensitive relapsed SCLC. The median PFS reported with this combination is similar to that reported with topotecan. In addition, the RR of 18.1% is similar to that of other regimens, and the MST was 7.5 months. The regimen seems safe, and no unexpected toxicities were observed.

Our study yielded comparable results with another phase II study, which combined topotecan with bevacizumab.[10] That trial included both chemosensitive and chemorefractory patients, was associated with more grade 3 to grade 4 toxicities, and reported a MST and PFS of only 32 and 18.4 weeks, respectively.

Other studies have evaluated bevacizumab combined with chemotherapy in previously untreated patients with SCLC. ECOG conducted a phase II trial that evaluated the addition of bevacizumab to cisplatin and etoposide. The combination was tolerable with no unexpected toxicities, but efficacy was not substantially different than expected with cisplatin plus etoposide alone.[11] The Cancer and Leukemia Group B evaluated the combination of cisplatin and irinotecan plus bevacizumab in 68 untreated patients with extensive stage SCLC.[12] Median PFS was 7.1 months, and MST was 11.7 months. These results compared favorably with outcomes from other trials, but the study failed to reach its primary endpoint of improving survival times compared with historical controls.[13] The Sara Cannon group evaluated bevacizumab combined with carboplatin and irinotecan in a similar patient population. The median time to disease progression was 9.1 months, and MST was 12.1 months.[14] Nevertheless, this regimen was associated with a significant incidence of grade 3 or more diarrhea and fatigue.

Collectively, this data suggest that bevacizumab is unlikely to substantially improve outcomes in unselected patients with SCLC. Our study also investigated whether subgroups of patients with certain VEGF polymorphisms may preferentially benefit from bevacizumab. Schneider et al.[15] were the first to describe VEGF polymorphisms that correlate with efficacy and toxicity with bevacizumab in patients with metastatic breast cancer. In their analysis,

VEGF-2578 AA and VEGF-1154 AA genotypes correlated with a superior median OS with a bevacizumab-containing regimen in advanced breast cancer. In this analysis, VEGF-634 CC and VEGF-1498 TT genotypes were associated with a decreased risk of significant hypertension with bevacizumab. This study is the first to evaluate VEGF polymorphisms in SCLC. We were unable to identify a VEGF polymorphism that was associated with response. Nevertheless, interpretation of VEGF polymorphisms and their impact on response in our study should be viewed with caution due to the small patient number, the even smaller patient number in different response subgroups, and the lack of grade 3 to grade 4 hypertension, a potential surrogate for benefit with VEGF-directed therapy. Furthermore, multiple association tests were performed; therefore, the traditional p value less than 0.05 for statistical significance may not be valid.

Patients with relapsed SCLC continue to be in need of improved therapy options. Continued understanding of the complex biology of this smoking-associated illness confirms the differences between SCLC and non-small cell lung cancer where multiple agents of benefit in the latter are ineffective in SCLC. Chemotherapy remains the cornerstone of therapy for patients with SCLC.

Novel therapies and strategies in the treatment of this disease continue to be explored.

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