Phase II Study of Topotecan and Bevacizumab in Advanced, Refractory Non–Small-Cell Lung Cancer

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Abstract

Second-line therapies for non–small-cell lung cancer (NSCLC) provide modest disease control. Weekly topotecan in combination with bevacizumab was evaluated in advanced, refractory NSCLC. Median progression-free survival was 5.1 months and overall survival was 11.5 months. Based on its favorable disease control rate and tolerable side effect profile, this combination should be further evaluated in refractory NSCLC.

Background: This clinical trial evaluated whether topotecan in combination with bevacizumab improved progression-free survival (PFS) in patients with advanced, refractory non–small-cell lung cancer in a second-line setting. **Patient and Methods:** Patients aged 18 years old and older received topotecan (4.0 mg/m^2) on days 1, 8, and 15, and bevacizumab (10 mg/kg) on days 1 and 15 as intravenous infusions on a 28-day treatment cycle. Available tumor specimens were analyzed for *ISG15* gene expression as a biomarker of response to topotecan. **Results:** Forty-two patients were enrolled in the study, with a median age of 62.5 years and a median of 3 (range, 1-7) prior treatment regimens. Almost half (n = 18, 42.9%) of the patients received prior bevacizumab therapy. PFS was 5.1 months (95% CI, 3.7-7.8 months), and overall survival was 11.5 months (95% CI, 6.8-15.5 months). Response rates were as follows: 14.3% partial response, 54.8% stable disease, and 28.6% progressive disease. Hematologic toxicities included grade 3 thrombocytopenia (n = 7, 16.7%), neutropenia (n = 4, 9.5%), and anemia (n = 2, 4.8%). One toxic death occurred due to pulmonary hemorrhage, and one patient experienced a grade 4 pulmonary embolism. Grade 3 nonhematologic adverse events were uncommon (< 8%). There was a trend for improved median PFS, 3.5 months vs. 1.8 months ($P = .26$), in patients with high *ISG15* expression. **Conclusion:** Bevacizumab in combination with topotecan as a salvage therapy for metastatic non–small-cell lung cancer is well tolerated and is worthy of further investigation.

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Introduction

Non–small-cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths in the United States.[1] Second-line docetaxel, pemetrexed, and erlotinib for recurrent or refractory metastatic NSCLC improves progression-free survival (PFS) by a median of only 2 to 3 months.[2-5] New therapies for refractory NSCLC could be effective by targeting increased tumor vascularization and elevated levels of angiogenic factors both of which are associated with increased risk for metastases and worsened survival.[6,7] Regulation of vascular endothelial growth factor and its receptors have been implicated in the angiogenesis pathway. Inhibition of this pathway is being rigorously evaluated in a variety of malignancies. Bevacizumab, an antibody against vascular endothelial growth factor, has clinical activity in a number of malignancies, including renal cell carcinoma,[8] colorectal cancer,[9] NSCLC,[10] and glioblastoma.[11] When combined with standard chemotherapy, bevacizumab correlates with improved survival in several of these malignancies. Bevacizumab is currently approved for use with carboplatin and paclitaxel in locally advanced and metastatic nonsquamous NSCLC in a first-line setting.[10] Current approved second-line options for

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NSCLC only provide modest responses, in the approximately 10%. Whereas analysis of some data suggests that adding bevacizumab with these approved agents in recurrent and/or refractory NSCLC has improved responses, its role as a second-line therapy in this disease is still being investigated.[12] Novel combinations, that include bevacizumab, may provide better responses and could potentially improve survival in the second-line setting.

Topotecan is a topoisomerase-I inhibitor with activity in numerous tumor types, including NSCLC.[13] In patients with previously treated NSCLC, topotecan given intravenously (I.V.) at a daily dose of 1.5-2.0 mg/m^2 on days 1-5 of a 21-day cycle achieved a median overall survival (OS) that ranged from 32 to 38 weeks.[14] When topotecan was compared with docetaxel in a phase III trial, the median OS times and time to progression were similar, which suggests that topotecan may be a reasonable alternative to docetaxel in patients previously treated with platinum-based chemotherapy. Because cytopenias are a major dose-limiting toxicity of topotecan, attempts to modify the administration schedule of this drug have been evaluated. In ovarian cancer, topotecan was administered on a weekly schedule at a dose of 4 mg/m^2 given on days 1, 8, and 15 of a 28-day cycle; this schedule reduced the incidence of neutropenia without limiting efficacy compared with the standard dosing schedule on days 1-5.[15]

On the basis of these data, we explored a weekly dosing schedule of topotecan administered at 4 mg/m^2 I.V. on days 1, 8, and 15 given in combination with bevacizumab on days 1 and 15 of a 28-day cycle. The purpose of this study was to determine the efficacy and safety of combining topotecan and bevacizumab in patients with previously treated NSCLC, as measured by the primary outcome of PFS. In addition, an exploratory analysis of clinical tumor samples was performed to investigate ubiquitin-like protein, interferon stimulated gene 15 (*ISG15*) expression as a predictive biomarker for topotecan response in NSCLC on the basis of preclinical reports.[16,17]

Patients and Methods

Patient Selection

Eligible patients were aged 18 years and older, with histologically or cytologically confirmed nonsquamous NSCLC that was locally advanced or metastatic (ie, stage IIIB or IV). Additional eligibility criteria included failure of at least one or more prior therapies, an ECOG PS (Eastern Cooperative Oncology Group performance status) of 0 or 1, measurable disease as determined by RECIST (Response Evaluation Criteria In Solid Tumors), adequate bone marrow reserve (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L, hemoglobin level > 9 g/dL), adequate liver function (total bilirubin level < 1.5 times the upper limit of normal [ref. range 0.2-1.3 mg/dL]; alkaline phosphatase [ref. range 40-150 U/L], aspartate transaminase [ref. range 0-55 U/L], and alanine transaminase levels < 3.0 [ref. range 0-50 U/L] $\times$ the upper limit of normal or $< 5.0 \times$ the upper limit of normal if the liver was involved with the tumor), adequate coagulation parameters (international normalized ratio < 1.5, and partial thromboplastin time [ref. range 22-37 seconds] less than the upper limits of normal), adequate renal function (serum creatinine concentration < 2.0, urine dipstick for proteinuria $< 2+$ or for patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline a 24-hour urine collection, which demonstrated ≤ 1 g of protein in 24 hours), and no radiation or systemic therapy for at least 14 days before study enrollment and at least 30 days for investigational agents. All the patients provided written informed consent. This study was approved by the institutional review board at the University of Minnesota Medical School and Park Nicollet Institute, and it was registered at clinicaltrials.gov (NCT00365547).

Patients were excluded for any of the following reasons: pregnant or breast feeding; known hypersensitivity to any component of bevacizumab; inadequately controlled hypertension as defined by systolic blood pressure > 150 mm Hg or diastolic blood pressure > 100 mm Hg; a history of hypertensive crisis or encephalopathy; New York Heart Association grade II or greater congestive heart failure; a history of myocardial infarction, unstable angina, stroke, or transient ischemic attack within 6 months of starting in the study; untreated brain metastases (treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging during the screening period); a history of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month before enrollment; active malignancy other than NSCLC; major surgical procedure, open biopsy, or significant trauma within 28 days before enrollment into study; a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months before enrollment in the study; or serious nonhealing wounds, ulcer, or fracture.

Treatment Schedule

Topotecan was administered weekly at a dose of 4 mg/m^2 as a 30-minute I.V. infusion on days 1, 8, and 15. Topotecan was not given on day 22 of the 28-day treatment cycle. Bevacizumab was given at a dose of 10 mg/kg I.V. on days 1 and 15. The initial dose of bevacizumab was delivered over 90 minutes as a continuous I.V. infusion. If the first infusion was tolerated without infusion-related adverse events (fever or chills), then the second dose was given over 60 minutes. If the 60-minute infusion was well tolerated, then all subsequent infusions were administered over 30 minutes, unless adverse effects occurred. Treatment cycles were repeated every 28 days until disease progression or intolerance of the study drugs.

Assessments

A baseline clinical evaluation, including a history and physical examination, baseline laboratory data (complete blood cell count with differential, electrolytes, creatinine level, transaminase values, urine dipstick, and coagulation tests), and imaging, was performed before entry into the study. On day 1 of each treatment cycle, a history and physical examination was performed and repeated laboratory data were reviewed. A complete blood cell count with differential was performed and reviewed on days 1, 8, 15, and 22. Radiologic studies (computed tomography, magnetic resonance imaging) were performed at baseline and every 8 weeks (2 cycles) to assess disease response. Criteria for discontinuation of the study included the following: progression of disease, unwillingness or inability to comply with study requirements, withdrawal of consent, grade 4 hypertension (or grade 3 hypertension not controlled with medication), nephrotic syndrome, grade ≥ 2 pulmonary or central nervous system hemorrhage, any grade 4 hemorrhage, venous