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A single-arm phase II trial of pazopanib in patients with advanced non-small cell lung cancer with non-squamous histology with disease progression on bevacizumab containing therapy

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Abstract

Objectives—Platinum-based chemotherapy with bevacizumab is a standard therapy for patients with stage IIIB/IV non-small cell lung cancer (NSCLC) with non-squamous (NS) histology. Mechanisms of resistance to bevacizumab include increased VEGF signaling or activation of VEGF receptors. Pazopanib is a multi-targeted VEGF receptor tyrosine kinase with single agent activity in NSCLC.

Materials and methods—Stage IIIB/IV patients with adequate organ function, who progressed on a bevacizumab containing therapy were eligible if it had been ≤8 weeks since the last bevacizumab treatment. The primary end-point was disease control rate (DCR), defined as partial or complete response, or stable disease for ≥12 weeks. Patients were assessed radiographically every 2 cycles (6 weeks). A Simon 2-stage design was used, and if in the first stage ≤4 of 17 patients experienced disease control the trial was to have been stopped for futility. An unplanned analysis was performed after 15 patients were evaluable secondary to slow accrual.

Results—Between December 2010 and November 2013, 15 patients were treated on trial. The median age was 61 years (range 39–74), and all patients had stage IV disease. Of the 15 patients, 4 discontinued therapy prior to cycle 2 evaluation due to adverse events ($n = 3$) and medical illness ($n = 1$), 5 patients had progressive disease, 4 patients had stable disease for <12 weeks, and 2 patients had stable disease for ≥12 weeks. No responses were observed. The DCR observed was 13% (2/15), and the trial did not meet the criteria to proceed to the second stage. Episodes of grade 3 treatment related toxicities observed included: increased ALT ($n = 2$), increased AST ($n = 1$), anorexia ($n = 3$), fatigue ($n = 3$), hypertension ($n = 1$), infection ($n = 1$), mucositis ($n = 2$), nausea ($n = 3$), pericardial effusion ($n = 1$), and vomiting ($n = 1$).

Conclusion—Pazopanib has limited activity in NSCLC-NS in patients who have experienced disease progression on bevacizumab.

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Conflict of interest statement

None declared.

Keywords

Angiogenesis; Multi-targeted tyrosine kinase inhibitors; Targeted therapy; Second-line therapy; Clinical trial; Non-small cell lung cancer

Lung cancer remains the leading cause of cancer deaths in the United States, and is a leading cause of cancer deaths globally [1,2]. The majority patients with lung cancer have the non-small cell lung cancer (NSCLC) subtype, and have advanced stage disease at the time of diagnosis. The goals of treatment for patients with NSCLC and advanced stage disease are to extend overall survival (OS),improve quality of life, and reduce disease-related symptoms. For the minority of patients with an epidermal growth factor receptor(*EGFR*) tyrosine kinase mutation or an anaplastic lymphoma kinase(*ALK*) rearrangement first-line targeted therapy is an option [3, 4]. For patients with NSCLC without an *EGFR* or *ALK* molecular alteration treatment with platinum-based chemotherapy remains the standard of care. For patients with NSCLC and non-squamous histology, treatment with platinum-based therapy with bevacizumab, a monoclonal antibody against vascular endothelial growth factor A (VEGF), is a treatment option. Two phase-III trials compared platinum-based therapy with and without bevacizumab. Both trials demonstrated a statistically significant improvement in objective response rate (ORR) and progression-free survival (PFS), and one trial also demonstrated a statistically significant improvement in OS [5–7]. Unfortunately there is no predictive biomarker for bevacizumab benefit.

The median PFS observed in the phase III trials of platinum-based chemotherapy with bevacizumab was approximately six months, suggesting that acquired resistance to bevacizumab occurs in a relatively short period of time [5, 7]. The mechanisms of bevacizumab resistance remain unclear. Candidate mechanisms include increased production of VEGF, increased expression of VEGF receptors, and the development of non-VEGF dependent mechanisms of stimulating tumor vascular growth [8]. Multi-targeted vascular endothelial growth factor receptor inhibitors inhibit the VEGF receptor tyrosine kinases. This trial was designed in 2009 following the presentation of data demonstrating that pazopanib has single agent activity in NSCLC [9]. We hypothesized that patients who previously benefitted from and tolerated the VEGF antibody bevacizumab might, upon disease progression, have a higher probability of benefit from intracellular tyrosine kinase inhibition of VEGF.

1. Patients and methods

Patients with stage IIIB or IV NSCLC with non-squamous histology who had documented radiographic progression on a bevacizumab-containing therapy, and who were ≤8 weeks since last bevacizumab treatment were eligible for enrollment. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0–2, measurable disease by Response Evaluation criteria in Solid Tumors (RECIST) version 1.1, and adequate organ function [10]. Patients with treated brain metastases who were asymptomatic and who were not requiring steroids were eligible.

Patients with gastrointestinal abnormalities that could increase the risk of bleeding (e.g. peptic ulcer disease, known intraluminal metastatic lesion, and active inflammatory bowel disease), history of GI bleeding within the previous 6 months, prolonged QT interval, unstable cardiovascular disease, a cerebrovascular event with in the previous 6 months, uncontrolled hypertension, hemoptysis within the previous 6 weeks, or lesions infiltrating the major pulmonary vessels were excluded. Concomitant use of medications that inhibit the CYP2A4, CYP2C8, and CYP2D6 was prohibited 14 days prior to starting the study drug, and patients who were not able to discontinue the concomitant medication were ineligible. The trial was reviewed by the Institutional Review Board of all the participating centers, and all patients provided written informed consent prior to any study related tests or procedures. The trial was registered at Clinicaltrials.gov (National Clinical Trials number: NCT01262820)[11].

2. Treatment

Patients who were enrolled and eligible for the trial were treated with pazopanib 800 mg daily. Cycle duration was 21 days. Blood pressure was monitored weekly for the first 6 weeks. Other toxicities, including laboratory evaluations of complete blood count, urine protein/creatinine ratio, serum chemistries and liver function tests were evaluated every 3 weeks. Patients underwent disease assessment with radiographic imaging every 6 weeks. Patients continued on pazopanib until disease progression, unacceptable toxicity, study withdrawal or death.

3. Study design

The primary end-point was the disease control rate (DCR) defined as a complete response, partial response, or stable disease of ≥12 weeks duration. Patients who discontinued therapy for reasons other than disease progression were censored at the date of treatment discontinuation. The null hypothesis that the DCR was less than 25% was tested against the one-sided alternative that the DCR was higher than 25%. A Simon two-stage mini–max design was used, and if disease was not controlled in at least 5 of the first 17 patients, the trial would have been terminated [12]. If at least 5 of the first 17 patients experienced disease control, 19 additional patients were to be enrolled (a total of 36 patients). This design yielded a type I error rate of 0.05, and power of 0.80 when the true disease control rate was 45%. Trial accrual was slower than anticipated and the trial was analyzed after 15 patients were evaluable to assess whether enrollment should continue.

4. Results

Between April 2010 and January 2014, 22 patients provided informed consent for the trial; 7 patients were considered ineligible and 15 patients were enrolled and treated on trial. Reasons for ineligibility were concomitant medication ($n = 2$), >8 weeks from last bevacizumab treatment ($n = 2$), concurrent medical illness ($n = 2$), and did not meet multiple eligibility criteria ($n = 1$).The median age was 61 years (range 39–74), 8 patients were women, and all patients had stage IV disease. Of the 15 patients, 4 discontinued therapy prior to cycle 2 disease evaluation due to adverse events ($n = 3$) and medical illness ($n = 1$),

and 5 patients experienced progressive disease. Four patients experienced stable disease-2 patients for <12 weeks and 2 patients for ≥12 weeks. The DCR observed was 13% (95% confidence interval (CI), 0.02–0.40).The median progression-free and overall survivals observed were 10.9 weeks (95% CI, 8.1–18.9) and 24.1 weeks (95% CI, 20.3–33.7),respectively.

The reasons for treatment discontinuation were disease progression ($n = 9$), adverse events ($n = 4$), and medical illness ($n = 2$). Episodes of grade 3 treatment related toxicities observed include increased alanine aminotransferase ($n = 2$), increased aspartate aminotransferase ($n = 1$), anorexia ($n = 3$), fatigue ($n = 3$), hypertension ($n = 1$), infection ($n = 1$), mucositis ($n = 2$), nausea ($n = 3$), pericardial effusion ($n = 1$), and vomiting ($n = 1$).

5. Discussion

This trial accrued 15 of the planned 17 patients in the first-stage of the Simon two-stage design. Early data analysis performed due to slow accrual demonstrated insufficient efficacy to justify additional accrual. This data suggests that pazopanib has limited activity in non-squamous NSCLC patients who have experienced disease progression on a bevacizumab-containing regimen. An ongoing European Organization of Research and Treatment of Cancer (EORTC) phase II/III study (NCT01208064) evaluates pazopanib as compared to placebo in patients who have not progressed after four cycles of first-line chemotherapy [11]. The primary end-point is OS, and the results of this trial will better define the role of pazopanib in advanced NSCLC.

Since the design of this trial several studies have evaluated the efficacy of multi-targeted tyrosine kinase inhibitors of VEGF as single agents or in combination with chemotherapy or another targeted agent. Phase III trials have demonstrated improvements in PFS, however, none have revealed an improvement in OS in the intent-to-treat patient population [13–19]. One trial compared docetaxel with the multi-targeted tyrosine kinase inhibitor nintedanib to docetaxel with placebo and showed a statistically significant survival advantage in the adenocarcinoma subset [17]. However, none of these trials enriched for patients who were previously treated with bevacizumab. In previous trials 3–8% of patients enrolled were previously treated with bevacizumab [16–18]. At this time there is limited data investigating the impact of prior bevacizumab therapy on second-line anti-angiogenic therapy.

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