Phase II Trial of Sunitinib Maintenance Therapy After Platinum-Based Chemotherapy in Patients with Extensive-Stage Small Cell Lung Cancer

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Introduction: The prognosis for patients with extensive-stage small cell lung cancer remains poor. This trial was designed to evaluate the efficacy and toxicity of maintenance sunitinib after platinum-etoposide chemotherapy.

Methods: Patients who demonstrated objective tumor response or stable disease after four cycles of platinum plus etoposide chemotherapy were eligible. Sunitinib was given at 50 mg daily for 4 weeks of a 6-week cycle until disease progression or unacceptable toxicity. The primary end point was 4-month progression-free survival (PFS) rate from initiation of sunitinib.

Results: Sixteen patients were enrolled. Responses to platinum-etoposide were complete response (CR)/partial response (PR)/stable disease (SD) = 3/11/2. The median number of weeks on sunitinib was 4 (range: 1.4–20). Reasons for sunitinib discontinuation were disease progression (50%), toxicity (31%), and patient request (19%). Median PFS from the start of sunitinib was 2.5 months (95% confidence interval [CI], 0.8–3.1). Further accrual would have failed to reach the target PFS rate, so the study was terminated. There were no objective responses to sunitinib, but four patients (25%) had disease stability for 15, 15, 17, and 20 weeks. Median PFS and overall survival from the start of chemotherapy were 6.2 months (95% CI, 4.1–6.5) and 8.2 months (95% CI, 6.2–14.7), respectively. Grade 3 to grade 4 toxicity included thrombocytopenia (25%), fatigue (19%), muscle weakness (13%), and hypothyroidism (6%).

Conclusions: Sunitinib did not seem to maintain disease stability after response to chemotherapy. Sunitinib was discontinued in half of patients due to toxicity or request to stop therapy. Although disease stability with sunitinib was noted in four patients, this approach does not seem to warrant further clinical study.

Key Words: Small cell lung cancer, Sunitinib, Maintenance.

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For more than two decades, the standard therapy for patients with extensive-stage small cell lung cancer (ES-SCLC) has been platinum-based chemotherapy, which induces objective tumor response in 60 to 80% of patients, median progression-free survival (PFS) of 4 to 6 months, and overall survival (OS) of 8 to 13 months.

Angiogenesis seems to be a relevant biological phenomenon in SCLC as these tumors have a high microvessel density, and preclinical studies indicate that SCLC cells express functional vascular endothelial growth factor (VEGF) receptors (VEGFR).[1–3] Sunitinib is a small molecule inhibitor of receptor tyrosine kinases involved in tumor proliferation and angiogenesis, specifically platelet-derived growth factor receptor (PDGFR), VEGFR, c-kit, FLT3, and RET. Given the potential dependence of SCLC on VEGF/VEGFR activation, the use of an antiangiogenic agent such as sunitinib in SCLC is an appealing therapeutic approach.

As nearly all patients with ES-SCLC develop disease progression within months of initial treatment, prolongation of PFS is a clinically meaningful end point for clinical trials exploring novel agents. We hypothesized that sunitinib maintenance therapy would delay or prevent recurrence and prolong survival in patients who achieved an objective response or stable disease with four cycles of induction chemotherapy. Therefore, we designed a phase II study to evaluate the efficacy and tolerability of maintenance sunitinib in patients with ES-SCLC who did not progress after induction chemotherapy.

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically documented ES-SCLC who had received no more than four cycles

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of front-line platinum plus etoposide chemotherapy and demonstrated a response or stable disease were eligible. ES-SCLC was defined as disease that extended beyond one hemithorax and regional lymph nodes. Other requirements included age ≥18 years, Zubrod performance status 0 to 2, absolute neutrophil count ≥1500/mm^3, platelet count ≥50,000/mm^3, serum calcium ≤12.0 mg/dl, serum creatinine ≤2.0 mg/dl, total bilirubin ≤1.5 times the institutional upper limit of normal, and aspartate aminotransferases (SGOT) and alanine aminotransferases (SGPT) ≤2.5 times the upper limit of normal. Patients were ineligible if they had grade ≥3 hemorrhage within 4 weeks of starting study treatment, any history of gross hemoptysis, symptomatic, uncontrolled central nervous system (CNS) disease, or required therapeutic anticoagulation. The trial was approved by the local institutional review boards, and signed written informed consent was obtained from all patients.

Treatment

Patients began maintenance sunitinib 4 to 6 weeks after day 1 of the fourth cycle of induction therapy to allow recovery from chemotherapy and to permit the administration of prophylactic cranial irradiation (PCI) if offered. Patients were treated with sunitinib (SUTENT, Pfizer Inc.) 50 mg orally once daily for 4 consecutive weeks followed by a 2-week rest period to form a 6-week cycle. Therapy continued until disease progression or unacceptable toxicity.

Dose Adjustment for Toxicity

Patients who developed grade 4 hematologic toxicity or grade 3 or 4 nonhematologic toxicity had treatment held until resolution to grade ≤2 or grade ≤1, respectively. Treatment was then restarted at a dose of 37.5 mg. A second dose reduction to 25 mg was also permissible. If sunitinib treatment was interrupted for longer than 14 days during a 4-week dosing period, then therapy was discontinued. The start of the next cycle could be delayed up to 2 weeks if additional time was required for recovery from treatment-associated toxicity.

Assessment of Response and Toxicity

Patients were considered evaluable for toxicity and response if they received at least one dose of sunitinib. Scans were performed after every two cycles to evaluate for response/progression. Response was assessed according to RECIST criteria.[4] Sunitinib was discontinued if a patient required a third dose reduction, developed progressive disease, or had life-threatening, irreversible, or unacceptable toxicity. Toxicity was graded according to the National Cancer Institute (NCI) Common Toxicity Criteria v3.0 (http://ctep.cancer.gov/reporting/ctc.html).

Statistical Analyses

The primary objective was to assess the 4-month PFS rate in patients treated with maintenance sunitinib. A two-stage Minimax Simon's design was used. Based on historical data, this treatment would be considered not interesting if the 4-month PFS rate from the start of sunitinib therapy was less than 35%, and it would be of definite clinical interest if the 4-month PFS rate was more than 55%.[5–7] With 21 patients in stage 1 and 39 total patients, the two-stage design had a 5% type I error and 80% power in testing the hypothesis, and the probability of early termination would be 0.706 if the true PFS rate was less than 35%. The trial was to be terminated at stage 1 if ≤8 patients were progression free at 4 months.

PFS on sunitinib therapy was defined as the time from initiation of sunitinib to progression of disease or death. Other end points included response rate, toxicity, PFS from initiation of induction chemotherapy, and OS defined as the time from the initiation of induction chemotherapy to death from any cause. All survival end points were estimated using Kaplan-Meier method.[8] The SAS System (Cary, NC) was used for all analyses.

RESULTS

Sixteen patients were enrolled onto the study between July 2007 and January 2009. Patient characteristics are summarized in Table 1. Fifteen patients received four cycles of carboplatin plus etoposide at standard doses, and one patient received cisplatin plus etoposide. Three patients had a complete response to induction chemotherapy, 11 had a partial response, and two had disease stability. Six patients received PCI after completion of chemotherapy and before initiation of sunitinib.

Toxicity

All sixteen patients received sunitinib maintenance therapy and were evaluable for toxicity analysis. Patients received a median of 4 weeks of sunitinib (range: 1.4–20.0). Disease progression was the main reason for discontinuation of treatment (n = 8, 50%). Five patients discontinued sunitinib due to toxicity: grade 4 hypertension (n = 1), grade 4 acute respiratory distress syndrome (n = 1), persistent grade 3 hand-foot syndrome (n = 1), and grade 3/4 asthenia/fatigue (n = 2). Three patients received sunitinib for 2.9, 3.7, and 20 weeks and then requested discontinuation of the drug, mainly due to persistent asthenia. One of the patients who opted to discontinue therapy refused further follow-up and has been censored from survival analyses.

TABLE 1. Patient Characteristics

Characteristics	No. (%)
Age (yr)	
Median	66
Range	34–80
Sex	
Male	8 (50)
Female	8 (50)
Performance status	
0	5 (31)
1	10 (63)
2	1 (6)
Response to induction chemotherapy	
CR	3 (19)
PR	11 (69)
SD	2 (12)
Received prophylactic cranial irradiation	6 (38)

TABLE 2. Worst Toxicity from Sunitinib Experienced per Patient (n = 16) Grade

Toxicity	1–2	3	4
Anemia	3	0	0
Neutropenia	4	0	0
Thrombocytopenia	4	3	1
Nausea/vomiting	11	0	0
Diarrhea	4	0	0
Rash	4	0	0
Thyroid dysfunction	1	1	0
Hypertension	1	0	1
Muscle weakness/myalgia	4	2	0
Acute respiratory distress syndrome	0	0	1
Dyspepsia	3	1	0
Oral mucositis	2	1	0
Hand/foot syndrome	1	1	0
Taste alteration	3	0	0
Anorexia	8	0	0
Fatigue/decline in PS	9	2	1

PS, performance status.

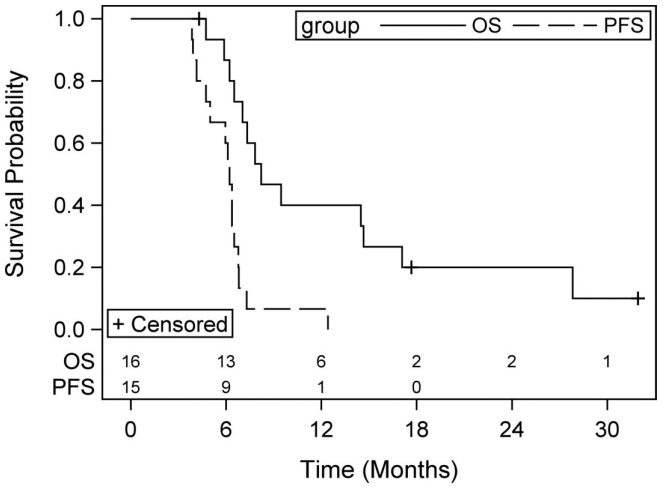

FIGURE 1. Intent-to-treat Kaplan-Meier estimates for overall survival (OS) and progression-free survival (PFS) for all patients, N = 16 (median OS: 8.2 months; median PFS: 6.3 months from the start of chemotherapy).

Toxicity is listed in Table 2. The most common grade 3 to grade 4 toxicities of sunitinib were thrombocytopenia (25%), fatigue (19%), muscle weakness (13%), and hypothyroidism (6%). One patient had grade 4 thrombocytopenia but did not experience bleeding. Three patients (19%) required one dose reduction of sunitinib due to toxicity during cycle 1. Of these, one patient required a second dose reduction after cycle 2.

Response and Survival

No objective responses were identified with maintenance sunitinib; however, four patients (25%) had stable disease for 15, 15, 17, and 20 weeks. The median PFS from the start of maintenance sunitinib was 2.5 months (95% confidence interval [CI], 0.8–3.1) with a 4-month PFS rate of 13% (95% CI, 2–33%). The median PFS and OS from the start of induction chemotherapy were 6.2 months (95% CI, 4.1–6.5) and 8.2 months (95% CI, 6.2–14.7 months), respectively. The 1-year survival rate from the start of induction therapy was 40% (95% CI, 15–65%). The intent-to-treat Kaplan-Meier estimates of PFS and OS for the 16 patients are presented in Figure 1. Because of slow accrual, a sufficient number of events occurred for analysis in the first 16 patients. The 4-month PFS rate from the start of sunitinib therapy would not have been able to reach our predetermined threshold required for study continuation even if the remaining five patients planned for stage 1 had been accrued and had met the 4-month PFS mark. The study was, therefore, discontinued early.

DISCUSSION

Preclinical data support the biologic activity and antitumor effect of sunitinib in SCLC; however, the inhibition of the specific receptor tyrosine kinase pathways that promote its antitumor effect remains unclear. One presumed mechanism is inhibition of the c-kit/stem-cell factor autocrine growth pathway. The significance of c-kit inhibition was evaluated by treating mice bearing human SCLC xenografts with sunitinib or imatinib.[9] Sunitinib resulted in significant tumor growth inhibition, whereas the effect of imatinib was less dramatic. Nevertheless, several clinical studies evaluating imatinib in patients with SCLC have failed to demonstrate a clinical benefit.[10–12] It is evident that SCLC does not have significant dependence on the c-kit pathway for survival, and its inhibition has not translated into clinical benefit for patients with SCLC.

The efficacy of sunitinib in SCLC preclinical models may be conferred by targeting other receptors vital for cell survival, such as VEGFR and PDGFR. For example, sunitinib inhibited SCLC tumor growth at drug concentrations that led to full PDGFR inhibition but only partial c-kit inhibition.[13] In contrast, sunitinib demonstrated greater inhibition of c-kit and PDGFR than VEGFR and PDGFR-β in gastrointestinal stromal tumors (GISTs) refractory to imatinib.[14,15] These studies highlight the heterogeneity of tumor signaling pathways between different tumor types and raise concerns about using preclinical models to predict clinical activity. The true contributions of these pathways to SCLC tumorigenesis, survival, and metastasis remain unknown.

Antiangiogenic agents such as sunitinib may enhance cancer cell death induced by chemotherapy through the inhibition of compensatory pro-survival pathways.[16,17] This effect may have been abrogated by our use of chemotherapy followed by sunitinib in a sequential fashion. Nonetheless, toxicities arising from this combination strategy may limit its efficacy. Indeed, a phase IB study of the combination of sunitinib 25 mg/d on days 1 to 14 with standard cisplatin and etoposide reported prolonged neutropenia and an unacceptable rate of treatment-related mortality despite the use of prophylactic granulocyte growth factors.[18]

The administration of sunitinib on a schedule of 4 weeks of treatment followed by 2 weeks of no treatment may be suboptimal. Studies in renal cell carcinoma have shown

that circulating soluble VEGFR2 levels, which are elevated pretreatment, decline after 4 weeks of sunitinib therapy but increase over the 2-week break.[19] In addition, FDG-positron emission tomography studies have shown a reduction in tumor metabolism while patients are taking sunitinib, but tumor progression and increased FDG avidity during treatment breaks.[20,21] Finally, toxicity from sunitinib may have obscured a small survival benefit. Six of the 16 patients discontinued sunitinib during the first cycle due to toxicity or patient request. Although all patients had a good performance status at enrollment, patients with SCLC frequently have difficulty tolerating further therapy. Prior chemotherapy and PCI may also have amplified the toxicity of maintenance sunitinib. Although sunitinib administration is convenient compared with cytotoxic chemotherapy, the toxicity profile should not be trivialized, especially in older patients who previously received chemotherapy.

In conclusion, our trial demonstrated no clear improvement in PFS or OS with maintenance sunitinib after platinum plus etoposide induction therapy in patients with ES-SCLC. Until we develop a better understanding of the molecular defects that drive tumor survival, growth, and metastasis in SCLC, an empiric treatment approach with sunitinib does not seem to warrant further investigation.

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