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A Phase II Study of Dasatinib in Patients with Chemo-sensitive Relapsed Small Cell Lung Cancer (CALGB 30602)

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Abstract

Introduction: SRC is an oncogene with an essential role in the invasiveness and metastasis of solid tumors including small cell lung cancer (SCLC). Dasatinib is a potent inhibitor of SRC as well as other tyrosine kinases. The primary objective of this study was to determine the efficacy of second-line dasatinib in patients with chemo-sensitive (relapse or progression ≥90 days after completing first-line therapy) SCLC.

Patients and Methods: Patients with measurable disease, performance status (PS) 0-1, no more than 1 prior platinum-based chemotherapy regimen, and adequate hematologic, hepatic, and renal function were eligible. Dasatinib was administered orally at 70 mg twice daily continuously (1 cycle = 21 days) until disease progression or unacceptable toxicity. Response was determined after every 2 cycles. Patients were followed until disease progression or death. The study was prospectively designed to simultaneously discriminate between complete plus partial response rates of 5% versus 20% and progression-free survival (PFS) rates at 6 weeks of 50% versus 70.7% in 53 evaluable patients with at least 92% power. The study was to be terminated early and declared negative if 1 or less objective response and 14 or fewer instances of PFS ≥ 6 weeks were observed among the initial 27 patients; however, patient accrual continued while the initial 27 patients were evaluated.

Results: Between 4/2007 and 12/2008, 45 patients were enrolled, but one patient never received any protocol therapy and one patient was ineligible: male/female, 17/26; white/black/unknown, 40/2/1; median age, 64 (range, 35-84) years; and PS 0/1, 12/31. No objective response was recorded among the 43 eligible and treated patients. Among the initial 27 patients, only 13 instances of PFS ≥ 6 weeks were observed. With a median follow up time of 7.1 months, median estimated overall survival and PFS times for the 43 eligible and treated patients were 17.0 and 5.9 weeks, respectively. Common reasons for removal of patients from protocol treatment were progressive disease (65%)

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and adverse events (26%). Toxicity was generally mild to moderate: grade 3 events of >5% frequency included fatigue, and pleural and pericardial effusions; and no grade 4 or 5 events were encountered.

Conclusions: Dasatinib did not reach our specified efficacy criteria in this clinical setting, and the study was terminated.

Keywords

Phase II; Dasatinib; Small cell lung cancer

INTRODUCTION

Lung cancer remains the leading cause of cancer deaths in both males and females in the United States.[1] Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer.[2] Progress in conventional treatment of SCLC has been slow in recent years.[3] Despite often dramatic initial responses to appropriate therapy, most patients with SCLC relapse and die, resulting in an overall five-year survival rate of approximately 10%. Treatment with platinum-based chemotherapy plus thoracic radiotherapy has resulted in impressive response rates of 80-90% in patients with potentially curable limited-stage disease, but median survival is only about 21 months and five-year survival is approximately 20%. In patients with extensive-stage disease, platinum-based chemotherapy also yields high initial response rates of 60-80%, but long-term survival is rare.

Salvage or second line chemotherapy for SCLC has been disappointing, and the only Food and Drug Administration (FDA)-approved drug, topotecan, results in transient responses in 6 to 37% of patients, depending upon the timing of relapse.[4-5] Patients with “refractory” disease (relapsing within 60-90 days of initial treatment) experience a worse response rate compared to those with “sensitive” relapse (more than 60-90 days from completion of initial therapy).[4-5] One randomized study supported the use of topotecan in the second line setting when compared with combination therapy with cyclophosphamide, doxorubicin and vincristine (CAV) in that there was equivalent efficacy but less toxicity.[6] Nonetheless, the time to progression in this study was 12-13 weeks. Clearly, novel approaches are needed in this disease.

Dasatinib, an aminothiazole analogue, is an orally administered inhibitor of protein tyrosine kinases that have been linked to human malignancies, including BCR-ABL, c-KIT, c-SRC, PDGFβ receptor, and EPHA2.[7-8] It is more potent than imatinib in inhibiting BCR-ABL and has been FDA-approved for use in chronic myelogenous leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia after imatinib failure or intolerance. C-KIT[9-12] and c-SRC[13-15] are expressed in SCLC. In cultured SCLC cell lines, c-SRC expression was found to be correlated with neuroendocrine differentiation of cells.[14] In a preclinical immunohistochemical analysis, c-SRC was expressed in 17 of 19 SCLC tumor tissues and considered a promising molecular target for therapy.[16] Blockade of c-SRC kinase decreased basal and neuropeptide-induced survival and proliferation of SCLC cells in liquid culture and semisolid medium.[17] Inhibition of neuropeptide-stimulated tyrosine phosphorylation and tyrosine kinase activity also stimulated apoptosis in SCLC cells.[18] Whereas c-SRC protein kinase activity was detected in SCLC cell lines and tissues, normal lung had low levels of kinase activity.[19]

The primary objectives of this phase II study were to determine (a) the efficacy of second-line dasatinib in chemo-sensitive SCLC (patients with relapse or progression ≥ 90 days after completing first-line therapy) and (b) the progression free survival (PFS) at 6 weeks of treatment. Secondary objectives were to document the objective response rate, progression-free and overall survival, and toxicity of dasatinib in this patient population.

PATIENTS AND METHODS

Patient Eligibility

All patients had pathologically documented SCLC and had received no more than one prior chemotherapy regimen. The disease had to have progressed or recurred after initial response to first-line, platinum-based chemotherapy with or without concurrent definitive radiation to the chest depending upon whether the patient initially presented with limited or extensive stage. The first-line chemotherapy had to be completed ≥90 days prior to documentation of relapse. Prior radiation therapy was allowed either in the context of combined modality treatment for limited stage disease, prophylactic cranial radiation, or palliative radiation initially or at relapse, but ≥ 2 weeks had to have elapsed since radiation. Patients with brain metastases were eligible as long as the brain metastases had been treated and patients were neurologically stable for ≥ 4 weeks. Prior treatment with dasatinib or other tyrosine kinase inhibitors was not permitted. Concurrent treatment with any other chemotherapeutic or investigational agent was not allowed. Measurable disease was required. Other eligibility criteria included age ≥ 18 years and Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Patients with significant cardiac disease (congestive heart failure, prolonged QTc, major conduction abnormality) and HIV-positive patients on combination anti-retroviral therapy were ineligible. Female patients who were pregnant or nursing were excluded. The required laboratory values at entry were: absolute neutrophil count (ANC) ≥ 1,500/μl; platelet count ≥ 100,000/μl; total bilirubin ≤ 1.5 × upper limit of normal (ULN); SGOT (AST) ≤ 2.5 × ULN; and serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 60 mL/min. The study had to be approved by the Institutional Review Board of each participating institution. Each patient had to give written informed consent.

Treatment Plan

Patients received dasatinib on an outpatient basis at a dose of 70 mg by mouth twice daily. Three weeks constituted one cycle of treatment. Treatment was continued daily until disease progression or intolerable toxicity. Dasatinib tablets were taken with or without food as desired and had to be swallowed with at least 8 ounces (240 mL) of water. Pill counts and medication calendars were used to monitor adherence. To avoid interactions with other drugs and substances, the protocol contained a detailed section that can be summarized as follows. Drugs with proarrhythmic potential were not permitted for 7 days before and during dasatinib treatment. Likewise, potent inhibitors or inducers of cytochrome P450 enzyme CYP3A4 were prohibited. Patients were also not allowed to consume grapefruit for 7 days before and during dasatinib treatment. Patients who required antacids used short-acting, locally-active agents but not within 2 hours before or 2 hours after the dasatinib dose.

Dasatinib (BMS-354825, NSC #732517, IND #73969) was supplied for this study by the Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute (NCI). Dasatinib was provided to the NCI under a Cooperative Research and Development Agreement between Bristol Myers Squibb Pharmaceuticals Co., Ltd., and the DCTD, NCI. Dasatinib was available in 20 mg and 50 mg tablet sizes.

The starting dose of dasatinib was 70 mg twice daily. A maximum of two dose reductions to 50 mg twice daily and 100 mg once daily was specified in the protocol if toxicity was encountered. Dasatinib was held for grade 3 and 4 neutropenia or thrombocytopenia and restarted at a lower dose once toxicity had improved to grade ≤ 2. Dasatinib was held for grade 2 hemorrhage, bleeding or coagulopathy and restarted once toxicity had improved to grade ≤ 1, but only one dose reduction was allowed. Recurrent grade 2 and any grade 3 or 4 hemorrhage, bleeding or coagulopathy required discontinuation of treatment. The electrocardiogram (ECG) was assessed for QTc prolongation, concomitant medications were reviewed, and electrolyte

abnormalities were corrected. For QTc prolongation ≥ 550 msec, dasatinib was stopped and only restarted if QTc < 480 msec after 14 days. For other non-hematologic toxicity of grade 3 or 4 severity, dasatinib was held, supportive therapy was maximized, and then a dose reduction instituted. Supportive care included measures for nausea, vomiting and diarrhea (such as granisetron and other antiemetics and loperamide for diarrhea) as well as measures to reduce fluid retention and inflammation (such as diuretics and steroids). Patients requiring radiation therapy during protocol treatment were considered to have progressed and were removed from protocol treatment.

Clinical Evaluation

Prior to enrollment on study and before each treatment cycle (21 days), a comprehensive history and physical examination were performed, and complete blood counts with differential and serum chemistries were obtained. Blood counts were obtained weekly during the first cycle. Staging studies were performed before enrollment and after every 2 cycles of therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) by the NCI were applied.[20] The Common Terminology Criteria for Adverse Events (CTCAE; Version 3.0) from the National Cancer Institute (http://ctep.cancer.gov) were used. After the protocol therapy was completed, patients were followed at least every 3 months for 1 year, then every 6 months for 3 years or until progression or death. Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairman. Statistical analyses were performed by CALGB statisticians.

Statistical Analyses

Topotecan is the only drug approved by the Food and Drug Administration of the United States for relapsed SCLC. In the trial of topotecan versus CAV in patients with progressive disease at least 60 days after completion of front-line chemotherapy, the response rates were 24.3% for topotecan and 18.3% for CAV.[6] Median times to progression were 13.3 weeks for topotecan and 12.3 weeks for CAV. The current study was prospectively designed to simultaneously discriminate between complete plus partial response rates of 5% versus 20% and progression-free survival (PFS) rates at 6 weeks of 50% versus 70.7% in 53 evaluable patients with at least 92% power. The study was to be terminated early and declared negative if 1 or less objective response and 14 or fewer instances of PFS ≥ 6 weeks were observed among the initial 27 patients. However, patient accrual continued while the initial 27 patients were evaluated because of the logistics of running this trial in a large cooperative group. Kaplan-Meier curves were used to describe progression-free survival and overall survival.[21] Progression-free survival was the time from randomization until disease progression, death, or last known follow-up. Survival was the time between randomization and death of any cause.

As part of the quality assurance program of the CALGB, members of the Audit Committee visit all participating institutions at least once every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 4 of the 45 patients in this study.

RESULTS

Patient Characteristics

Between July 2007 and December 2008, 45 patients were enrolled. One patient never started treatment. One patient was ineligible due to neutropenia. The median age of the 43 eligible and treated patients was 64 (range, 35-84) years. All patients had received prior chemotherapy

and 34 (79%) had received prior radiation therapy. The other demographic and baseline clinical characteristics are shown in Table 1.

Response

Table 2 shows the response to therapy. No complete or partial responses were observed. The rate of stable disease was 16%, and the median duration of stable disease was 12.3 weeks (95% confidence interval, CI, 6.3 - 33.9 weeks). The reasons for inadequate assessments of response included patient refusal to continue on protocol therapy and withdrawal of consent (n = 3), disease progression (n = 3), adverse event (chest pain and rash, n = 1), and early death (n = 1). One patient withdrew consent without giving a reason; one patient with bilateral pleural effusions who required thoracenteses which resulted in pneumothorax and atrial fibrillation with rapid ventricular response elected to be removed from protocol treatment; and one patient withdrew consent due to poor appetite and gastrointestinal symptoms that were more likely related to her malignant disease process than the protocol therapy. The patient with the early death was a 66 year old woman (active smoker) with superior vena cava syndrome from SCLC and with pulmonary, pleural and peritoneal involvement, intra-thoracic and intra-abdominal lymph node metastases, and liver metastases who was admitted to the hospital on day 8 of cycle #1 with respiratory insufficiency attributed to her advanced SCLC and exacerbation of chronic obstructive pulmonary disease; she did not improve despite intensive therapy and decided for comfort measures. The reasons for the discontinuation of protocol treatment were progressive disease (n = 28; 65%), adverse events (n = 11; 26%), withdrawal of consent (n = 3; 7%), and early death (n = 1; 2%).

Survival

Among the initial 27 patients, only 13 instances of PFS $\geq$ 6 weeks were observed. Among all 43 patients, the 6-week PFS rate was 43% with a 95% confidence interval (CI) of 30% to 61%. The median follow-up time was 7.1 months, and 32 patients have died. For all 43 patients, the progression-free survival was 5.9 weeks (95% CI, 5.7 - 6.6 weeks) and the overall survival was 17.0 weeks (95% CI, 14.6 -29.7 weeks).

Toxicity

The toxicity assessment included all 44 (43 eligible and 1 ineligible) patients who received the protocol treatment. The grade 3 treatment-related adverse events are listed in Table 3. The most common side-effect as defined by the Common Terminology Criteria for Adverse Events under constitutional symptoms was fatigue (asthenia, lethargy, malaise). The pleural and pericardial effusions were considered by the treating physician to be related to treatment rather than related to the malignant disease. The overall number of patients with grade 3 adverse events was 12 (27%). No grade 4 or 5 adverse events were encountered.

DISCUSSION

As stated in the statistical section, the study was to be terminated and declared negative if 1 or less objective response and 14 or fewer instances of PFS $\geq$ 6 weeks were observed among the initial 27 patients. These prospectively set targets were both met. So dasatinib did not reach our specified efficacy criteria in this clinical setting, and the study was terminated. A limitation of this study is that the expectations for this biologic, non-cytotoxic agent were arbitrarily set and perhaps too high. The study protocol allowed continuation of accrual after the initial 27 patients were entered. As a result 18 additional patients were enrolled although dasatinib was ultimately considered inactive. In the future, the trial design should call for suspension of accrual after the initial cohort of patients.

C- KIT[9-12] and c-SRC[13-15] are expressed in a variety of neoplasms, including SCLC. A limitation of this study is that tumor tissue of the patients was not assessed for the expression c-KIT or c-SRC. However, it does not appear that SCLC responds clinically to the inhibition of these tyrosine kinases by dasatinib. Single-agent therapy with tyrosine kinase inhibitors, such as dasatinib, may be ineffective in malignancies in which proliferation is not dependent on tyrosine kinase activity. It is also possible that activation mutations of tyrosine kinases are required for antitumor efficacy. A more comprehensive preclinical evaluation of dasatinib, including in vivo studies, should have been conducted before launching this trial. In this regard, our experience is similar to a phase II study of imatinib that also showed no activity in this disease.[22] In that study, tumors that were c-KIT positive were selected for the treatment with imatinib, but the presence of the molecular target was not sufficient for clinical efficacy. The redundancy of multiple aberrant growth and survival pathways may make any single therapeutic intervention unlikely to be successful in SCLC. Whereas progress has been made in non-small cell lung cancer with the tyrosine kinase inhibitor erlotinib and other drugs, therapeutic advances in SCLC have been sparse in over two decades.[3]

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TABLE 1

Patient Demographic and Initial Clinical Characteristics (n=43)

Characteristic	Number	%
Sex		
Male	17	40%
Female	26	60%
Race		
White	40	93%
Black	2	5%
Unknown	1	2%
Ethnicity		
Non-Hispanic	40	93%
Hispanic	3	7%
Performance status		
0	12	28%
1	31	72%
Disease sites		
Primary lung	31	72%
Contralateral lung	4	9%
Lymph nodes		
Hilar	19	44%
Mediastinal	24	56%
Supraclavicular	8	19%
Other	15	35%
Pleura	6	14%
Liver	21	49%
Adrenals	9	21%
Bone	9	21%
Brain	3	7%
Other	11	26%

TABLE 2

Response to Therapy (n=43)

Response	Number	%
Stable disease	7	16%
Progressive disease	28	65%
Inadequately assessed	8	19%

Table 3

Grade 3 Treatment Related Adverse Events (n=44)

	Number	%
Hematologic		
Hemoglobin	1	2%
Lymphocytes	1	2%
Non-hematologic		
Fatigue	6	14%
Pleural effusion	5	11%
Pericardial effusion	3	7%
Nausea	2	5%
Vomiting	2	5%
Anorexia	1	2%
Diarrhea	1	2%
Abdominal pain	1	2%
Rash/desquamation	1	2%