Phase I/II Study of Gemcitabine and Exisulind as Second-Line Therapy in Patients with Advanced Non–small Cell Lung Cancer

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Background: The study was designed to evaluate the safety and efficacy of exisulind, a selective apoptotic antineoplastic drug, in combination with gemcitabine as second-line therapy in patients with progressing advanced non–small cell lung cancer.

Methods: Patients whose disease progressed more than 3 months from completion of first-line chemotherapy were eligible for this phase I/II trial. Primary end points were maximally tolerated dose and time to progression. Patients in the phase I portion of the study were treated with gemcitabine (1250 mg/m^2) in combination with three escalated dose levels of exisulind. Treatment involved six cycles of gemcitabine and exisulind followed by exisulind maintenance. The study was subsequently expanded to phase II.

Results: Thirty-nine patients (15 in phase I and 24 in phase II) were treated. The regimen was well tolerated with grade 3 fatigue and grade 3 constipation being dose-limiting toxicities. The maximally tolerated dose was not reached. Dose level 3 of exisulind (250 mg twice daily) in combination with gemcitabine was used for phase II. The overall response rates were 7% (phase I), 17% (phase II), and 13% (all). Median time to progression and median and 1-year survival, respectively, were 3.7 and 9.7 months and 33% (phase I); 4.3 and 9.4 months and 41% (phase II); and 4.1 and 9.4 months and 39% (all).

Conclusion: Although the study met its primary end point of improving time to progression (more than 4.1 months in phase II), we did not observe a clear survival advantage and thus do not plan to further investigate this schedule of gemcitabine and exisulind.

Key Words: Gemcitabine, Exisulind, Second-line therapy, Progressing non–small cell lung cancer.

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Chemotherapy has been the mainstay of treatment for patients with advanced non–small cell lung cancer (NSCLC). Although 19 to 32% of chemo-naive patients will respond to first-line standard cytotoxic doublets,[1–3] virtually all eventually face disease progression requiring further therapy. For such patients, docetaxel and pemetrexed are the only two cytotoxic drugs approved for use as second-line monotherapy, with dismal response rates of 6 to 9% and median survival of 6-8 months.[4–6] Therefore, more active regimens are clearly needed. In response to the need for effective therapies for patients with recurrent or refractory NSCLC, researchers have extensively investigated cytotoxic as well as molecularly targeted agents. Different agents with different targets, schedules, and regimens have been studied.

Gemcitabine (Lilly, Indianapolis, IN), an antimetabolite analogue of cytosine arabinoside, has significant clinical activity in several human tumors. The combination of gemcitabine and a platin is among standard first-line regimens for NSCLC in North America and other countries. A large phase III randomized trial conducted by the Eastern Cooperative Oncology Group has demonstrated that the combination of gemcitabine and cisplatin is at least as active as other new platinum-based regimens in chemo-naive patients with NSCLC.[1] In addition, a meta-analysis showed a statistically significant improvement in progression-free survival of gemcitabine-platinum regimens compared with other regimens containing a third-generation agent and platinum.[7]

Exisulind (sulindac sulfone) (OSI Pharmaceuticals, Melville, NY), a selective apoptotic antineoplastic drug, is an inhibitor of the enzyme cyclic GMP phosphodiesterase. By increasing cyclic GMP, exisulind activates protein kinase G and JNK1 pathway, thus inducing apoptosis of tumor cells.[8,9] The apoptotic and growth inhibition activity of exisulind has been demonstrated in various tumor cell lines, including lung cancer.[8,10–13] The combination of exisulind or its potent analog OSI-461 (previously known as CP-461) with cytotoxic drugs such as gemcitabine, vinorelbine, and irinotecan enhanced the inhibition of human lung cancer cell growth in culture.[14,15] In orthotopic lung cancer model systems, exisulind combined with docetaxel significantly increased apoptosis, inhibited tumor growth and metastasis, and prolonged survival.[11,16]

Based on preclinical data, we hypothesized that the combination of gemcitabine and exisulind would improve the response rate and survival in patients with NSCLC with disease progression after first-line chemotherapy. In this phase I/II study, we examined the safety and antitumor activity of this combination as second-line treatment in this patient population.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria for this study included: histologically confirmed NSCLC, disease progressing more than 3 months from completion of first-line chemotherapy; having undergone only one previous chemotherapy regimen for advanced disease; measurable or evaluable disease; an Eastern Cooperative Oncology Group performance status of 0 to 1; adequate bone marrow function (white cell count $\geq$4000/mm^3, neutrophils $\geq$1500/mm^3, and platelets $\geq$100,000/mm^3); liver function (bilirubin less than or equal to the upper limit of normal and transaminases $\leq$2.5 times the upper limit of normal); and kidney function (creatinine $\leq$1.5 mg/dl or creatinine clearance $\geq$60 ml/min). Patients had not undergone radiotherapy for at least 4 weeks. Patients with clinically stable brain metastases were eligible. Other than ibuprofen and naproxen, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, salicylates, and sulindac were not allowed during the study. Patients who previously received gemcitabine were ineligible.

Treatment Plan

The study consisted of two steps: phase I (step 1) to assess safety and to determine the maximally tolerated dose (MTD) and phase II (step 2) to evaluate the efficacy of the study regimen. Phase I portion involved three dose levels of exisulind (125 mg twice daily, 125 mg in the morning/250 mg in the evening, and 250 mg twice daily) given orally every day in combination with gemcitabine 1250 mg/m^2 given as a 30-minute intravenous infusion on day 1 and 8 of a 3-week cycle. Three patients were entered in each dose level in a traditional phase I dose-escalation design. Dose escalation was planned as followed: (1) If dose-limiting toxicity (DLT) occurs in two of the three patients at dose level 1 during cycle 1, we will conclude that the drug combination is too toxic and stop. (2) If DLT occurs in one of the three patients, an additional three patients will be added to further quantify the toxicity at that dose level. (3) Dose escalation will continue until DLT occurs in at least two of six patients. (4) MTD is the dose level preceding DLT in two of six patients, or dose level 3 if zero of three or one of six patients experiences DLT at that dose level. MTD is the chosen dose for step 2.

Toxicity evaluation was based on the National Cancer Institute Common Toxicity Criteria (version 2). DLTs were defined as grade 4 neutropenia for $\geq$7 days; grade 4 neutropenia accompanied by a fever (single elevation in oral temperature to $>$38.5°C, or three elevations to $>$38°C during a 24-hour period) that requires parenteral antibiotics; grade 4 thrombocytopenia; delay in gemcitabine and/or exisulind administration of more than 2 weeks; or other grade 3 or 4 non-hematological treatment-related toxicities.

Patients were examined and evaluated before each treatment cycle. To assess tumor response, computed tomographic scans were obtained, and tumors were measured after every two cycles of treatment. Response Evaluation Criteria in Solid Tumors criteria were used for tumor evaluation.[17] Patients with complete response (CR), partial response (PR), or stable disease (SD) continued on treatment for a total of six cycles of chemotherapy or until progressive disease (PD) or unacceptable toxicities developed. Patients with CR, PR, or SD after completing six cycles of chemotherapy were allowed to continue on exisulind maintenance. Patients with PD or unacceptable toxicities at any time were discontinued from protocol treatment.

Statistical Considerations

The primary end points of this study were to determine the MTD of exisulind in combination with gemcitabine and to evaluate time to progression (TTP) in patients with advanced NSCLC after failure of first-line chemotherapy. The secondary end point was to assess response rate and overall survival. Using standard approximations based on an exponential distribution for time to event and assuming that patient accrual was uniform over time, it was estimated that an observation of 18 disease progressions in step 2 was needed. This sample size provided 95% power to detect a 50% increase in median TTP from 3 months for historical control[18,19] to 4.5 months on the protocol therapy with gemcitabine and exisulind according a one-sided log rank test with the 0.1 level of significance. The rationale was that we were not so much concerned about falsely claiming efficacy of the new therapy, but we did not want to miss a promising therapy because of a small power. We planned to accrue a total of 24 patients with an additional follow-up after the last patient was enrolled until there was a total of 18 disease progressions for step 2 of the protocol.

According to this design (sample size estimation), the second-line therapy with gemcitabine and exisulind would be considered for further testing if the observed median TTP was $>$4.1 months, which corresponds to the 90% lower confidence limit for the true median TTP with the protocol therapy when 18 disease progressions were observed in the study.

Data were analyzed on an intent-to-treat basis. Time to event data such as TTP and overall survival were analyzed using the Kaplan-Meier method, separately for each step and also combined. TTP and survival were determined from the date of enrollment to the date of progression and of death, respectively. The objective response rate and qualitative and quantitative toxicities were summarized with descriptive statistics.

RESULTS

A total of 39 patients were enrolled in the study between April 2001 and April 2004. There were 15 patients in step 1 (phase I) and 24 patients in step 2 (phase II). Treatment was discontinued early during cycle 1 of therapy in one patient in step 1 because of grade 3 fatigue (DLT). One patient in step 2 was found ineligible during the course of

