A Phase I Trial of the HIV Protease Inhibitor Nelfinavir with Concurrent Chemoradiotherapy for Unresectable Stage IIIA/IIIB Non-small Cell Lung Cancer

A Report of Toxicities and Clinical Response

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Background: The objective of this phase I trial was to determine dose-limiting toxicities (DLT) and the maximally tolerated dose of the radiosensitizer Nelfinavir in combination with concurrent chemoradiotherapy in locally advanced non-small cell lung cancer (NSCLC).

Methods: Nelfinavir (dose level 1: 625 mg orally [PO] twice a day; dose level 2: 1250 mg PO twice a day) was administered for 7 to 14 days before and concurrently with concurrent chemoradiotherapy to patients with biopsy confirmed IIIA or IIIB unresectable NSCLC. Five patients were treated at dose level 1; eight patients were treated at dose level 2. Patients were treated with concurrent chemoradiotherapy to a dose of 66.6 Gy. DLTs were defined as any treatment-related grade 4 hematologic toxicity requiring a break in therapy or nonhematologic grade 3 or higher toxicity except esophagitis and pneumonitis.

Results: Sixteen patients were enrolled and 13 patients received at least one dose of nelfinavir. Twelve patients were treated with nelfinavir and concurrent chemoradiotherapy. No DLTs have been observed at either dose level. The maximum tolerated dose of nelfinavir was therefore 1250 mg PO twice a day. Six patients experienced grade 4 leukopenia. One patient experienced grade 4 thromobcytopenia. Median follow-up for all 12 response-evaluable patients was 31.6 months and for survivors is 23.5 months. Nine of the 12 patients had evaluable post-treatment positron emission tomography/computed tomography with metabolic response as follows: overall response: 9/9 (100%); complete response: 5/9 (56%); and partial response: 4/9 (44%).

Conclusion: Nelfinavir administered with concurrent chemoradiotherapy is associated with acceptable toxicity in stage IIIA/IIIB NSCLC. The metabolic response and tumor response data suggest that nelfinavir has promising activity in this disease.

Key Words: Radiotherapy, Concurrent chemoradiotherapy, Locally advanced non-small cell lung cancer, Radiosensitizer.

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Approximately 50,000 patients are diagnosed annually with stage III non-small cell lung cancer (NSCLC). Five-year survival is extremely poor at 15 to 40%.[1] A standard therapeutic approach for patients with unresectable stage IIIA disease is definitive radiotherapy to a dose of 60 to 70 Gy given concurrently with a platin-based regimen.[2] One of the reasons for the poor cure rate in this disease is the inadequacy of local control with definitive radiotherapy. Le Chevalier et al.[3] observed that the 1-year local control rate was ~17% for patients with unresectable NSCLC treated to 65 Gy. A relationship has been shown between local failure and the subsequent appearance of distant metastases.[4] Furthermore, there is evidence to suggest an association between improved local control and better overall survival. In the CHART trial, hyperfractionated radiotherapy resulted in improved local control and survival.[5,6] A similar correlation between improved local control and survival was seen in the EORTC study comparing concurrent chemoradiation versus radiation alone for locally advanced NSCLC. Two-year local control improved from 19 to 31% with the addition of concurrent daily cisplatin. Two-year overall survival increased from 13 to 26% in the concurrent daily cisplatin arm.[7] Therefore, an improvement in local control repre-

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sents a principal goal in designing new strategies to treat NSCLC.

One approach to improve local control with definitive radiotherapy is to deliver escalating doses to the tumor bed. Although this approach has been used, it comes at the cost of greater, and potentially fatal, toxicity to the patient.[8,9] Another approach to improve the therapeutic ratio for tumor control is through concomitant administration of a radiosensitizing drug during standard dose radiotherapy.[10,11] Preclinical studies have shown that a class of protease inhibitors used to treat HIV, radiosensitize tumor cells both in vitro and in vivo.[12,13] The mechanism for this radiosensitization seems to be mediated, in part, through inhibition of P-I-3 kinase.[12]

Nelfinavir is a selective, nonpeptidic, inhibitor that binds with high affinity to the active site of the HIV protease. The most common side effects of this drug is diarrhea occurring in ~30% of patients.[14] This is controlled with over-the-counter antidiarrheals and usually is mild to moderate in nature not resulting in weight loss. Hyperglycemia and hyperlipidemia has been reported with prolonged use of all of the HIV protease inhibitors. Additionally, elevation of liver enzymes has been reported in HIV patients with hepatitis B and C infection as a result of immune reconstitution with elevation of the CD4 counts.[15] The standard dosing regimen for nelfinavir is 1250 mg given twice daily. This regimen was proven to be effective in a phase III randomized trial (AG-542) comparing dosing regimens of nelfinavir in HIV patients.[14] In vitro and in vivo studies confirm that AKT phosporylation by P-I-3 kinase is inhibited by nelfinavir when given at the serum concentrations that are routinely achieved with the standard HIV dosing regimen of 1250 mg twice daily.[12]

On the basis of these preclinical data, our group initiated a phase I trial of the HIV protease inhibitor nelfinavir with concurrent chemoradiotherapy for unresectable stage IIIA/IIIB NSCLC. The primary objective of this study was to determine the dose-limiting toxicities (DLTs) and the maximally tolerated dose of nelfinavir when administered with concurrent chemoradiotherapy. Response to therapy was assessed by positron emission tomography (PET) and computed tomography (CT).

MATERIALS AND METHODS

Eligibility

Patients aged 18 to 89 years with histologically proven NSCLC were enrolled onto this prospective trial. Patients had to be deemed unresectable by the thoracic oncology team at the University of Pennsylvania and planned for definitive chemoradiotherapy. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2 and not more than 10% unintended weight loss in the 6 months before enrollment. Patients were required to have sufficient hematologic and renal function to permit cisplatinum-based chemotherapy. Patients who had received prior thoracic radiotherapy were excluded. With long-term use of nelfinavir (≥3 years), there are reports of exacerbation of hyperglycemia in patients with type 2 diabetes.[16] This trial mandates a short course (8 week) of nelfinavir, therefore patients with type 2 diabetes were not excluded. As mentioned previously, the liver enzyme elevation in patients with hepatitis B or C receiving nelfinavir is believed to be due to immune reconstitution in HIV infected individuals and not drug effect.[15] Patients with history of HIV infection were excluded from this trial, however, patients with hepatitis B or C in the absence of HIV infection were not excluded. The Institutional Review Board at the University of Pennsylvania approved this study. All patients signed informed consent.

Trial Design

All subjects began taking daily oral nelfinavir (either 625 mg orally [PO] twice a day or 1250 mg PO twice a day) 7 to 14 days before the start of chemoradiotherapy. In preclinical studies, there was evidence of inhibition of Akt phosphorylation after 3 days of nelfinavir with no detectable phosphorylated Akt by immunoblot at the serum concentrations that are achieved with the dosing regimens that range from 625 to 1250 mg PO twice a day. Therefore, our starting dose level for this study was 625 mg PO twice a day with a top dose level of 1250 mg PO twice a day.[12] A 7- to 14-day interval was chosen to ensure inhibition of Akt phosphorylation before initiation of chemoradiotherapy. Nelfinavir was continued at the prescribed dose level (either 625 mg PO twice a day or 1250 mg PO twice a day) during the complete course of concurrent chemoradiotherapy and discontinued on the last day of radiotherapy (Figure 1). All patients underwent CT-based treatment planning. All fields were treated every session. The gross tumor volume, clinical target volume, and planning target volume are defined according to ICRU 50. Elective irradiation of regional lymph nodes was allowed. All patients were treated using involved field technique to 66.6 Gy in 1.8 Gy/fraction. Normal tissue doses: the maximal spinal cord dose was limited to 45 Gy. No more than 30% of the total lung volume received greater than 20 Gy. No more than 50% of the total cardiac volume received greater than 40 Gy. To account for respiratory excursion, a four-dimensional CT was performed and an internal target volume generated. Before availability of a four-dimensional CT, patients with lower lobe tumors underwent fluoroscopy and a margin was generated based on diaphragmatic excursion. Upper lobe tumors were treated with an empiric 1.2 cm three dimensionally expanded margin to the clinical target volume to account for both set-up variance and tumor excursion.

Standard chemotherapy consisting of cisplatinum and etoposide was administered as concurrent therapy with radiation in accordance with the standard Southwest Oncology Group regimen.[17,18] Cisplatinum 50 mg/m^2 was administered on days 1, 8, 29, and 36, with pretreatment and posttreatment hydration and a polyantiemetic regimen. Etoposide 50 mg/m^2 was administered days 1 to 5 and 29 to 33.

Toxicity and Response Assessment

DLTs were defined as any treatment-related grade 4 hematologic toxicity requiring a break in therapy for greater than 14 days or nonhematologic grade 3 or higher toxicity except esophagitis and pneumonitis. This definition of DLT was chosen as treatment breaks in chemotherapy commonly occur because of hematologic toxicity in