A Phase I Trial of the Farnesyltransferase Inhibitor L-778,123 and Radiotherapy for Locally Advanced Lung and Head and Neck Cancer

Stephen M. Hahn, Eric J. Bernhard, William Regine, Mohammed Mohiuddin, Daniel G. Haller, James P. Stevenson, Debbie Smith, Barnali Pramanik, Joel Tepper, Thomas F. DeLaney, Krystina D. Kiel, Briggs Morrison, Paul Deutsch, Ruth J. Muschel, and W. Gillies McKenna

Department of Radiation Oncology [S. M. H., E. J. B., D. S., W. G. M.], Department of Pathology and Laboratory Medicine [R. J. M.], Department of Medicine, and Division of Hematology Oncology [D. G. H., J. P. S.], University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-4283; Department of Radiation Medicine, University of Kentucky, Lexington, Kentucky 40536 [W. R., M. M.]; Department of Radiation Oncology, University of North Carolina, Chapel Hill, North Carolina 27599 [J. T.]; Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts 02114 [T. F. D.]; and Department of Radiation Oncology, Northwestern Memorial Hospital, Chicago, Illinois 60611 [K. D. K.]; and Merck Research Laboratory, Rahway, New Jersey 07065 [B. P., B. M., P. D.]

ABSTRACT

Purpose: Preclinical data have demonstrated that farnesyltransferase inhibitors (FTIs) are radiation sensitizers in selected cell lines. The objective of this Phase I trial was to determine the maximally tolerated dose of the FTI L-778,123 in combination with radiotherapy in non-small cell lung cancer (NSCLC) and head and neck cancer (HNC).

Experimental Design: L-778,123 was given by continuous infusion and dose escalated in conjunction with standard radiotherapy. The presence of a ras mutation was not required for study entry.

Results: Nine patients (six NSCLC patients and three HNC patients) were enrolled on two dose levels of FTI. No dose-limiting toxicities were observed at the first dose level of 280 mg/m²/day during weeks 1, 2, 4, and 5 of radiotherapy. One episode of dose-limiting toxicity, grade IV neutropenia, was observed in one of three patients treated at 560 mg/m²/day during weeks 1, 2, 4, 5, and 7. No episodes of dose-limiting mucositis, esophagitis, or pneumonitis were observed. Of the four patients with NSCLC with evaluable disease, three patients had a complete response to treatment and one patient had a partial response. A complete clinical response to treatment was observed in two patients with HNC. In vitro studies in tumor cells obtained from a NSCLC patient on this trial showed radiosensitization with FTI and that tumor cells accumulated in G2-M after L-778,123 treatment.

Conclusions: The combination of L-778,123 and radiotherapy at dose level 1 is associated with acceptable toxicity. Local responses have been observed in four NSCLC patients without a clear increase in radiotherapy-associated toxicities.

INTRODUCTION

There is increasing evidence that genetic mutations form the underlying basis for the development of cancer (1). An increased understanding of the genetic basis for cancer is likely to lead to the development of therapeutic agents that are specific for molecular targets, thereby improving the therapeutic index of cancer treatments.

Genetic changes in cells may also lead to the development of resistance to cancer therapies, including radiation (2). Activation of ras by mutation is a common finding in human tumors with a frequency of approximately 30% overall (3). There are several lines of evidence suggesting that the expression of mutant ras in human tumors may have a role in cellular resistance to radiation (4). Studies in rodent cells have shown an increase in radiation resistance after ras transfection (5–7). Human osteosarcoma cells transformed with EJras (HrasV12) also show increased radioresistance (4).

Ras genes encode M, 21,000 proteins that are intermediates in signal transduction pathways critical for cellular processes such as growth, differentiation, and apoptosis (8, 9). Ras protein function is dependent upon localization to the plasma membrane. A critical step in Ras localization is posttranslational modification through the addition of a farnesyl group to the COOH terminus of the protein (10, 11). Farnesylation is mediated by the enzyme farnesyltransferase (12). Treatment of ras-transformed fibroblasts and human tumor cell lines with inhibitors of farnesyltransferase reverses ras transformation and inhibits cell growth in vitro and in xenograft tumor growth in nude mice (13–16).

Several FTIs have been shown to reverse cellular resist-
Phase I Trial of FTI and Radiation

Radiosensitization has been observed in REF cells expressing activated H-ras and human tumor cell lines containing activated H- or K-ras, but not in cells expressing wild-type ras (18). Enhanced cytotoxicity from radiation in the presence of a FTI compared with non-FTI-treated animals was also observed in a murine xenograft of tumors with H-ras tumors (19). These data raise the possibility that the FTIs may selectively radiosensitize tumor cells containing activated mutant ras.

Based upon the preclinical data of FTI and radiation, we initiated a Phase I trial of the FTI L-778,123 and radiotherapy for patients with NSCLC and HNC. L-778,123 is a peptidomimetic inhibitor of farnesyltransferase (20). In a Phase I trial of prolonged continuous infusion of L-778,123 alone, the recommended Phase II dose was found to be 560 mg/m²/day by continuous infusion over 2 weeks. The DLTs of this regimen were grade IV neutropenia and prolongation of the corrected QT interval (QTc) on ECG. The primary objective of this trial was to establish the MTD and DLTs of L-778,123 in combination with radiation.

MATERIALS AND METHODS

Patient Selection

Patients were individuals of 18 years of age or older with a histologically documented NSCLC or HNC who, in the opinion of the investigators, required radiotherapy. Patients with maxillary sinus or nasopharyngeal tumors were excluded. Eligibility criteria also included placement of a central venous catheter, ECOG performance status of 0 or 1, life expectancy of ≥3 months, signed informed consent, and adequate hematological (neutrophil count ≥ 1,500/mm³, platelet count ≥ 100,000/mm³, or hemoglobin ≥ 9 g/dl), renal (creatinine ≤ 1.5 times normal), and hepatic function (bilirubin/alanine aminotransferase/aspartate aminotransferase ≤ 1.5 times normal, alkaline phosphatase ≤ 2 times normal). Patients were required to have serum sodium, potassium, calcium, and magnesium within 10% of the normal range. Exclusion criteria included significant psychiatric illness, alcohol or drug dependency, pregnancy or lactation, latex allergy or significant drug allergies, known HIV disease, recent chemotherapy, oral steroids, immunotherapy, radiation therapy or major surgery, use of medications that are potent inducers of the CYP3a (cytochrome P450 isofrom) pathway, use of β-hydroxy-β-methylglutaryl coA reductase inhibitors, abnormal protime or activated partial thromboplastin time, cumulative doxorubicin dose of ≥ 450 mg/m², history of significant ventricular cardiac dysrhythmias, prolonged QTc on ECG of ≥440 ms, recent myocardial infarction, active infection, retinal disorder, seizure disorder, and central nervous system malignancy. Patients were permitted to have received cytotoxic chemotherapy (including investigational therapies) before study enrollment as long as 30 days had elapsed from the last treatment. Cytotoxic chemotherapy was permitted after the initial post-FTI toxicity and response evaluation if clinically indicated.

Study Design

This was a Phase I dose escalation study of the FTI L-778,123 and radiotherapy. The primary objective of this study was to evaluate the safety and tolerability of L-778,123 and to determine the MTD when administered in combination with radiotherapy. Patients with locally advanced pancreatic cancer were also enrolled in this study as a separate dose escalation cohort. The protocol was approved by the Institutional Review Boards of the institutions involved in this study. Informed consent was obtained from each patient before treatment.

A minimum of three patients was enrolled in each dose level. Dose escalation was not permitted in individual patients. Safety evaluations were completed for the first three patients at a given dose level before initiating the next dose escalation. All three patients were observed for a minimum of 8 weeks after completing radiotherapy before dose escalation. If DLT was observed in one of three patients treated on a dose level, three additional patients were enrolled on the dose level. If no instances of DLTs were observed in three patients treated on a dose level, dose escalation was permitted to proceed in the next cohort of patients. DLTs were, in general, defined as grade III toxicities of any duration with the exception of neurological toxicity, esophagitis/pharyngitis, and radiation dermatitis. The exceptions to this general rule were that the following did constitute a DLT: (a) irreversible grade II neurological toxicity; (b) grade IV esophagitis/pharyngitis; (c) grade IV radiation dermatitis; and (d) QTc prolongation of ≥490 ms with at least a 10% increase from baseline or an increase of ≥80 ms from baseline irrespective of the absolute QTc. An interruption of radiotherapy lasting ≥2 weeks or two interruptions each lasting at least 1 week were also considered a DLT. Toxicity was scored with the National Cancer Institute’s Common Toxicity Criteria.

L-778,123 Administration

L-778,123 was provided by Merck Research Laboratory (Rahway, NJ). A 3-day supply of the drug in 250-ml sterile normal saline was prepared for patient administration. A central venous catheter was placed before drug administration. L-778,123 was administered as a continuous venous infusion with a Deltec CADD-PLUS model 5400 infusion pump starting on day 1 of radiotherapy. Two dose levels were evaluated in this study. Preclinical studies of FTI and radiotherapy suggested that a certain drug level might be required for radiosensitization. In addition, a continuous exposure of FTI over as many radiation fractions as possible was considered ideal. Therefore, the dose of L-778,123 used in dose level 1 was influenced by prior clinical experience with the drug (20) and the desire to achieve plasma levels in the range needed for radiosensitization. After completion of dose level 1, additional clinical data with L-778,123 became available that indicated that a more prolonged course of L-778,123 was well tolerated; therefore, a decision was made to escalate both the drug dose and duration of administration. The starting dose (dose level 1) of L-778,123 was 280 mg/m²/day for 7 days of each week during weeks 1, 2, 4, and 5 of radiotherapy. The second dose level was 560 mg/m²/day for 7 days of each week during weeks 1, 2, 4, 5, and 7 of radiotherapy. After three patients were enrolled on dose level 2, a decision was made by the manufacturer of L-778,123 not to pursue clinical development of the drug, and the study was closed to further enrollment.
External Beam Radiotherapy

Radiotherapy was started on day 1, concurrent with the initiation of the L-778,123 infusion. The radiation dose was prescribed at mid-separation on the central ray for two opposed equally weighted beams. For all other beam arrangements, the dose was prescribed at the center of the target area or at the intersection of central rays of the beams. Simulation for all fields was required. Computed tomography-based treatment planning was required for all NSCLC patients. Reproducible immobilization was required. The target volume was defined by shaped ports with custom-made blocks or multileaf collimation. Portal verification was required for all fields. Source-axis distance techniques were used, and each field was treated every session. Megavoltage equipment was required with a minimum peak photon energy of 6 MV for NSCLC patients.

Dose and Volume NSCLC Patients. The total radiation dose to gross disease was ≥65 Gy administered with standard fractionation. A total of 45 Gy was delivered to the gross tumor and areas at risk for microscopic disease (draining lymph nodes). An additional minimum of 20 Gy was delivered to gross tumor using a margin of 1.5–2 cm.

Dose and Volume HNC Patients. The total dose to gross disease was 70 Gy with standard fractionation. Fifty Gy were delivered to the gross tumor and areas at risk for microscopic disease. An additional 20 Gy were delivered to the gross tumor. The anterior, low neck field was treated to a depth of 3 cm for a total of 44–45 Gy. Electrons were used for the posterior neck fields and for gross nodal disease, if required. The posterior neck field received 60 Gy when gross nodal disease was present on the ipsilateral side.

Normal Tissue Doses. All attempts were made to keep the maximum spinal cord dose to ≤40 Gy. The maximum dose to the entire heart was not to exceed 40 Gy, and >50% of the heart volume was not to exceed 45 Gy.

Patient Evaluation

Vital signs and a 12-lead ECG for evaluation of the QTc were obtained on each patient on day 1 before and 0.5 and 3 h after the initiation of L-778,123 administration. If there was a question regarding the accuracy of the QTc interval measurement, a consulting cardiologist was asked to review the ECG. Cardiology consultation and in-patient monitoring were required for a QTc of >440 ms and <490 ms. L-778,123 was discontinued if the QTc was consistently ≥490 ms.

Patients were seen weekly during radiotherapy and then 4, 8, and 12 weeks after the completion of radiotherapy. Radiological assessment of tumor response was first obtained 8 weeks after the completion of radiotherapy and then regularly thereafter. Response reporting was based upon the best response achieved, observed in any follow-up scan. A complete response was defined as the disappearance of all measurable and evaluable disease. A partial response was defined as a ≥50% reduction in the sum of the products of perpendicular diameters of all measurable lesions, as well as the absence of any new lesions within the radiation treatment volume. Progressive disease was defined as an increase of ≥25% in the sum of the products of perpendicular diameters of all measurable disease or the appearance of new lesions within the radiation treatment volume.

Table 1 Patient characteristics (N = 9 patients)

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>ECOG status</th>
<th>Age (yrs)</th>
<th>Dose level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>NSCLC</td>
<td>0</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>HNC</td>
<td>1</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>NSCLC</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Stage III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Stage IIIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>HNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Stage IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Prior therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95</td>
<td></td>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td></td>
<td>Range</td>
<td>43–70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>280 mg/m²/dayᵃ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>HNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>560 mg/m²/dayᵇ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>HNC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ᵃ Dose level, 280 mg/m²/day during weeks 1, 2, 4, and 5 of radiotherapy.
ᵇ Dose level, 560 mg/m²/day during weeks 1, 2, 4, 5, and 7 of radiotherapy.

Stable disease was defined as disease that failed to fulfill the criteria for partial response or progressive disease.

Patient Characteristics

Nine patients (Table 1), five males and four females, were enrolled in this study. Six patients had NSCLC, two patients with unresectable stage IIa disease and four patients with stage IIIB disease. All three patients with HNC had unresectable stage IV disease. The median age of patients was 59 years (range, 43–70 years). The majority of patients had an ECOG performance status of 1. Six patients were enrolled on dose level 1, and three patients were enrolled on dose level 2.

Primary Cell Culture

Tumor tissue was obtained from a NSCLC patient who completed treatment on the Phase I clinical trial and subsequently developed an isolated adrenal metastasis. Appropriate Institutional Review Board approval and patient consent were obtained before performing these studies. The patient underwent resection of the adrenal metastasis, and tumor tissue was obtained for the purpose of establishing a primary cell line (the AdM cell line). Tumor tissue was minced, followed by enzymatic digestion for 20 min at 37°C in HBSS containing 166 units/ml collagenase XI, 0.25 mg/ml protease, and 255 units/ml DNase. Cells were recovered by straining through an 80-μm mesh and centrifugation of the resulting cell suspension at 500 × g. Cells were resuspended and propagated in DMEM supplemented with 10% fetal bovine serum (Atlanta Biologicals, Norcross, GA), 100 units/ml penicillin, and 100 μg/ml.
streptomycin. All experiments were carried out in cells at or before passage 10 in vitro.

**Radiation Cell Survival Studies**

Log-phase cultures of the AdrM cell line were treated with 1.5 μM L-778,123 or an equal volume of drug diluent (DMSO). After 24 h, pretreated and control cells were harvested, and single cell suspensions were plated in an inhibitor (0.25 μM L-778,123) or a diluent, respectively. Cells were irradiated with 1–6 Gy at ambient room temperature with a Mark 1 cesium irradiator (J. L. Shepherd, San Fernando, CA) at a dose rate of 1.6 Gy/min. One day after irradiation, drug-free medium was added to the cultures (final L-778,123 concentration in cultured cells = 0.08 μM). Plates were stained for colonies after 15 days (control cells) or 19 days (L-778,123-treated cells) of culture to allow for equal colony size formation. The surviving fraction was based on the plating efficiency of unirradiated cultures (control radiation survival) or L-778,123 (FTI-treated radiation survival). The surviving fraction at each radiation dose was defined as the number of colonies formed divided by the number of cells plated multiplied by the plating efficiency for unirradiated controls.

**In Vitro Studies and Flow Cytometry**

Log-phase growth cultures were plated at 2 × 10^5 cells/dish in 60-mm dishes. Replicate dishes were harvested for flow cytometric analysis of DNA content at the times indicated after the addition of 2.5 μM L-778,123 to the culture medium. Control cultures were treated with an equal volume of carrier solution (50% DMSO in H2O). Flow cytometry analysis was carried out using the ModfitLT v2.0 program.

**RESULTS**

**Toxicity.** The toxicities observed in this trial are shown in Table 2. One episode of dose-limiting hematological toxicity, grade IV neutropenia, developed in a NSCLC patient at the second dose level of 560 mg/m^2/day. This patient required two 1-week breaks from radiotherapy because of hematological toxicity. Metastatic disease was also documented. He was subsequently taken off study before completing treatment. Mild (≤grade II) anemia, neutropenia, and thrombocytopenia were otherwise observed (Table 2).

No patients developed radiation pneumonitis or myelitis. Three months after treatment, one NSCLC patient was admitted to the hospital for pneumonia, pleural effusion, and a pericardial effusion. The radiographic infiltrate did not correspond to the shape of the radiation portal, and the patient responded to antibiotic therapy. She was subsequently diagnosed with malignant pericardial spread of tumor.

Table 2 also shows the frequency and severity of esophagitis, mucositis, and radiation skin reaction in all patients. In the NSCLC group, one patient was treated at dose level 1 with grade I esophagitis. All other patients had grade I esophagitis (one patient at dose level 1 and two patients at dose level 2). Mucositis in the HNC patients was also mild. No grade III or IV radiation skin reaction was observed in any treatment group.
Other toxicities were mild and included fatigue, anorexia, nausea, and diarrhea (Table 2). Mild liver function test abnormalities were also observed. Among the various FTIs in clinical evaluation, QTc prolongation is a toxicity unique to L-778,123 (21). We observed two episodes of QTc prolongation. One patient treated on dose level 1 had a prolonged QTc in the setting of grade III hypokalemia and grade I hypomagnesemia. The electrolyte abnormalities were felt to be related to the effects of prior chemotherapy. FTI treatment was continued, and the patient was monitored overnight in the hospital. After electrolyte repletion, the QTc returned to baseline. A second patient treated on dose level 2 developed QTc prolongation, and L-778,123 was discontinued. After review by the attending cardiologist, the QTc prolongation was believed to be an artifact. Upon rechallenge with L-778,123, no QTc prolongation was observed. These episodes of QTc prolongation were not felt to represent DLTs. No patient was removed from the study because of QTc prolongation.

One patient treated on dose level 1 developed transient worsening of a baseline neurological condition manifested by word-finding difficulties and slurred speech during treatment with L-778,123 and radiation. She was admitted to the hospital and underwent an extensive evaluation. She was diagnosed with a transient aphasia secondary to narcotics. This patient also developed pancreatitis after an operation for removal of an isolated adrenal metastasis several months after the completion of protocol therapy. This episode was not felt to be treatment related. One patient with HNC suffered a decline in his performance status and had difficulty maintaining his hydration status, which was not felt to be therapy related. A synchronous NSCLC was discovered. He refused further protocol therapy and was taken off study 1 month after initiating treatment. He died 3 months after study entry.

Response. Ras mutational analysis was performed in six patients enrolled on this trial (five NSCLC patients and one HNC patient). In none of these patients was a ras mutation identified. Although efficacy of treatment was not the primary end point of this trial, responses were evaluated after the completion of therapy. All patients underwent restaging radiographic studies 8–12 weeks after the completion of treatment and regularly thereafter. Radiographs were compared with pretreatment studies. Three HNC patients were enrolled in this study. One patient completed treatment but was taken off the study (as described above) and died 3 months after study entry. Two other patients with stage IV HNC (hypopharynx and tonsil) completed treatment and underwent restaging. Both patients had no evidence of disease on follow-up computed tomography scans or nasopharyngoscopy. One patient remains alive and is without evidence of disease. The other patient suffered a cerebrovascular accident and was lost to follow-up.

Six patients with NSCLC were enrolled on this study. One patient had DLTs (as described above) as well as distant metastatic disease and was taken off study. One patient completed treatment but did not have measurable disease and subsequently died of metastatic disease. The remaining four patients completed protocol therapy. Three of the four patients had complete responses to radiation and L-778,123. The fourth patient had a partial response. No evidence of progression of the primary lesions has been observed for a period of 7–12 months after treatment. Three of the four patients with evaluable disease developed distant metastases. The fourth patient developed a malignant pleural effusion. The interpretation of response is complicated by the fact that three of the four NSCLC patients received cytotoxic chemotherapy after FTI and radiotherapy.

In Vitro Studies. A cell line, AdrM, was established from the adrenal metastasis obtained from a NSCLC patient treated in the Phase I trial. We initially asked whether L-778,123 would lead to radiosensitization of AdrM cells compared with untreated controls. Repeated attempts demonstrated that the drug alone was cytotoxic or cytostatic at doses as low as 1.25 μM. To determine the mechanism of the cytostatic effect, we analyzed the cell cycle distribution of cultures treated with FTI for 24–48 h. As shown in Fig. 1, there was an accumulation of cells in G2-M. Clonogenic cell survival was determined in the presence and absence of L-778,123 (Fig. 2). Greater radiation cytotoxicity was observed in the presence of L-778,123 administration compared with controls.

DISCUSSION

Local recurrence after a definitive course of radiation therapy remains a significant clinical problem and represents a common pattern of failure for many solid tumors. Among the potential causes for local failure are physiological factors such as hypoxia that may limit the effectiveness of radiation (22) and intrinsic cellular radioresistance (23). Intrinsic radioresistance has been demonstrated in some human cancers and has been correlated with a poorer prognosis (23). The biological basis of intrinsic radioresistance has not been fully defined. In tissue culture, the expression of oncogenes, including ras, raf, mos,
ets, and sis, has been shown to increase radiation resistance (5, 6, 23–27). In vitro studies have shown that transformation of REFs by H-ras and v-myc leads to radiation resistance compared with v-myc-transformed REFs (6). In addition, REF cells transformed with v-myc alone undergo elevated levels of apoptosis after exposure to radiation than REF cells transformed with H-ras and v-myc (7, 25, 28). Inhibition of mutant ras farnesylation with FTI has been shown to decrease cell survival in vitro and enhance tumor growth delay in vivo after radiation (18, 19). Although the reversal of intrinsic radioresistance with therapies against a molecular target represents the scientific basis for studying the FTI in combination with radiotherapy, evaluation of the reversal of intrinsic radioresistance was not possible in the current study. The primary goal of this study was to determine the MTD and to evaluate the toxicities of L-778,123 and radiotherapy.

The trend in cancer treatments for solid tumors over the past several years has been the use of combined chemotherapy and radiation for locally advanced malignancies (29–33). In several cancer sites, including NSCLC (29–31), HNC (32), and esophageal cancer (33), combined chemotherapy and radiation has led to an improvement in survival compared with radiation therapy alone. One of the major drawbacks of combined chemoradiotherapy, especially concurrent chemoradiotherapy in NSCLC, is the substantial toxicity associated with this treatment (34, 35). The increased risk of early and late toxicities of combined modality treatment, notably esophagitis and pneumonitis, underscores the narrow therapeutic index of current cancer therapies. In one study of carboplatin and paclitaxel administered concurrently with radiotherapy for NSCLC, a 52% frequency of grade III or IV esophagitis was reported (35). There is hope that new therapies designed for molecular targets in cancer could provide greater tumor selectivity and therefore provide a greater therapeutic index.

We chose to enroll both NSCLC and HNC patients in this study because we felt that it was likely that the spectrum of early and late toxicities from radiation would be similar and because ras mutations are present in some patients with these tumor types (9). Two dose levels of L-778,123 were evaluated in combination with radiotherapy. No DLTs were observed at the 280 mg/m²/day dose level. One DLT, grade IV neutropenia and thrombocytopenia and interruptions of radiotherapy, was observed in one patient treated at the 560 mg/m²/day level. Overall, however, hematological toxicity was mild.

The common toxicities of radiotherapy expected in patients with NSCLC and HNC were mucositis, esophagitis, dermatitis, and pneumonitis. Interestingly, only mild mucosal and skin toxicities were observed in this study. In NSCLC patients, no grade II or higher radiotherapy-related esophagitis was seen. This is in contrast to studies of combined concurrent cytotoxic chemotherapy and radiotherapy in NSCLC in which substantial rates of moderate and severe esophagitis are reported (34–37).

It is quite encouraging that local responses were observed in the four NSCLC patients with evaluable disease. It should be noted, however, that evaluation of the efficacy of L-778,123 and radiotherapy was not the primary end point of this Phase I study and is complicated by the use of cytotoxic chemotherapy in the post-FTI/radiotherapy period. In addition, because these patients were receiving both L-778,123 and radiation, it is impossible to sort out the relative contribution of each therapy to an individual patient’s response.

None of the four patients who responded to treatment with FTI and radiation were found to have a ras mutation. Despite this, L-778,123 led to radiosensitization in the cell line isolated from one of these patients. The proposed mechanism of action of the FTIs in human cancers is through the inhibition of farnesylation (including both mutant and wild-type Ras), leading to an interruption of downstream pathways that control a variety of critical cellular processes. Although FTIs would be expected to have their most profound effect on cells containing mutant ras that is constitutively activated, the inhibition of wild-type Ras could be important therapeutically in tumors, such as breast cancers, with other molecular abnormalities, such as activating mutations in receptor tyrosine kinases that signal through Ras (38–41). In addition, other proteins within the cell undergo farnesylation (9), and it has been proposed that FTI activity against transformed cells results from altered prenylation of proteins other than ras (42, 43). Insight into the mechanism of FTI action is likely to come from future translational research projects that identify predictors for tumor response to FTI treatment.

One possible mechanism for radiation sensitization with the FTIs is through cell cycle redistribution of cells into a more radiosensitive phase of the cell cycle such as G2-M. The in vitro studies performed in tissue obtained from one patient enrolled in this study demonstrate a G2-M block after treatment with L-778,123. Others have also reported similar cell cycle effects with selected FTIs (44, 45). Our data are preliminary and represent the evaluation of a human tumor cell line derived from one patient enrolled in this study. Definitive conclusions regarding the mechanism of FTI radiosensitization, including the role of cell cycle redistribution, cannot be made without additional studies.

It is not possible to determine the MTD for the combination of L-778,123 and radiotherapy because of the early termination of this study. L-778,123 at dose level 1 in combination with radiotherapy was tolerable without DLT; therefore, this study provides some needed clinical data regarding the safety of a selected FTI and radiation. Additional evaluation of L-778,123 with radiation would be required at dose level 2 or at intermediate dose levels to adequately determine the MTD. Given the decision to halt further clinical development of L-778,123, the investigation of FTIs with radiation will require additional studies with an alternative FTI. Also, additional clinical studies that define the molecular markers that predict responses to FTIs and translational studies that shed light on the mechanisms of the FTI-radiation action are needed.

REFERENCES


A Phase I Trial of the Farnesyltransferase Inhibitor L-778,123 and Radiotherapy for Locally Advanced Lung and Head and Neck Cancer


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/8/5/1065

Cited articles
This article cites 45 articles, 17 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/8/5/1065.full.html#ref-list-1

Citing articles
This article has been cited by 16 HighWire-hosted articles. Access the articles at:
/content/8/5/1065.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.