Original Study

A Phase II Trial of Erlotinib and Concurrent Palliative Thoracic Radiation for Patients With Non–Small-Cell Lung Cancer

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Abstract

A phase II trial of combined erlotinib and palliative radiation evaluated the patient-reported quality of life (QoL) in 40 patients with advanced non–small-cell lung cancer. Although the combination improved QoL overall, the improvement was not more substantial than that observed with radiation alone. Future trials might identify subgroups of patients with metastatic disease who could benefit from combined targeted therapies and radiation.

Background: The downstream signaling pathways of the epidermal growth factor receptor might influence radiation resistance. Data from preclinical work support the hypothesis that erlotinib concurrent with radiation therapy (RT) might increase cancer cell killing. The present trial was designed to examine the efficacy and toxicity of combined erlotinib and palliative chest thoracic RT in non–small-cell lung cancer (NSCLC). **Materials and Methods:** Patients with newly diagnosed stage III-IV (American Joint Committee on Cancer, version 6) or recurrent NSCLC received 3 weeks of erlotinib at a dose of 150 mg daily, starting 1 week before palliative thoracic RT to 30 Gy in 10 fractions within 2 weeks. The primary outcome was a change in the quality of life, as measured by the Lung Cancer Symptom Scale (LCSS) question on the "symptoms of lung cancer" from baseline to 4 weeks after treatment. **Results:** A total of 40 patients were recruited from 2 institutions. Of the 40 patients, 22 (55%) were men, with an average age of 71 years, and 60% had stage IV disease. A total of 26 patients (65%) completed the full course of erlotinib, and 35 (88%) completed the planned RT. Twenty-five patients (62.5%) reported LCSS scores at 4 weeks after treatment, with an average change (improvement) of −12.5 U (95% confidence interval, −23.0 to −1.9; $2P = .023$). This was less than the a priori hypothesis of a change of −17.5 U. The median overall and progression-free survival was 5.2 and 3.2 months, respectively. **Conclusion:** The present single-arm, phase II trial did not demonstrate additional symptomatic benefit from concurrent erlotinib therapy with standard palliative thoracic RT for patients with locally advanced or metastatic NSCLC.

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Introduction

Non–small-cell lung cancer (NSCLC) is a leading cause of cancer-related deaths in both men and women.[1] Although new targeted therapy agents continue to be developed and improve the outcomes of patients with NSCLC,[2] radiation therapy (RT) remains a key modality for palliative and curative treatment of NSCLC.[3,4]

Recognizing the important role that RT can play, the outcomes for most stages of NSCLC would improve if the therapeutic ratio of RT could be enhanced. Clinically useful modifiers of RT, commonly referred to as radiation sensitizers, are agents that preferentially enhance the cytotoxicity of RT. Radiation sensitizers of benefit in the clinic have historically been limited to systemic chemotherapy agents; however, such drugs as cisplatin have toxicity profiles that limit their applicability, especially in the older, unwell population with significant comorbidities. In these patients, palliative RT alone offered in short courses (5-10 fractions) is frequently considered.[4] Trials on the use of palliative RT in advanced,

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metastatic, or recurrent NSCLC have often focused on patient quality of life (QoL) as an important primary outcome. A simple oral agent with limited toxicity that improves the local response to RT would have obvious merit in improving QoL in patients unable to tolerate lengthy courses of RT and/or the effects of cytotoxic systemic agents.

Erlotinib is a small molecule (quinazolinamine) that acts through direct and reversible inhibition of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) by competitively inhibiting the intracellular adenosine triphosphate-binding domain. The effects of erlotinib might not be limited to cytostasis by cell cycle arrest but might induce tumor cell death by the induction of apoptosis.[5] Erlotinib is an orally active agent that has been well tolerated in clinical trials. Although the benefits of erlotinib combined with standard chemotherapy for patients with NSCLC have not been impressive, as a single agent for patients in whom first- or second-line chemotherapy has failed, it has demonstrated a significant survival advantage in an unselected population.[6] A rationale exists to consider it as a radiosensitizer. A landmark phase III trial in advanced head and neck squamous cell carcinoma demonstrated improvements in local control and overall survival (OS) with the addition of the EGFR inhibitor cetuximab to RT.[7,8] The downstream signaling pathways of EGFR influence radiation resistance,[9] and preclinical work supports the hypothesis that erlotinib/EGFR therapy concurrent with fractionated RT can increase cancer cell killing.[10-12] Before the present study, in vivo work was limited. One study demonstrated no additional toxicities with an erlotinib/RT combination.[13] Combined, the single-agent activity of erlotinib as a secondary treatment for NSCLC and the potential synergistic effect (without added toxicity) with RT demonstrated preclinically, made it an intriguing therapeutic option. Therefore, the present trial was designed to specifically address whether erlotinib administered concurrently with palliative thoracic RT in patients with NCSLC demonstrated any evidence to suggest improved efficacy, specifically QoL, or safety signals of concern.

Materials and Methods

Patient Population

Eligible patients were required to have histologic evidence of unresectable locally advanced (stage IIIa or IIIb), metastatic (stage IV) (American Joint Committee on Cancer, version 6) or recurrent NSCLC and considered to be appropriate candidates for palliative thoracic RT. All patients were required to be $>$ 18 years old and willing and capable of completing the QoL assessments at baseline and after treatment, as described in the trial protocol. Patients with previous exposure to an EGFR antibody or TK inhibitor were not eligible for the present trial nor were patients who were planning to undergo concurrent chemotherapy. Patients with an anticipated survival of $<$ 3 months or an Eastern Cooperative Group (ECOG) performance status score of $\geq$ 3 were also excluded. Patients with a history of interstitial lung disease or elevated liver enzymes and those requiring the ongoing use of medications known to inhibit or induce the cytochrome P450 group of enzymes were deemed ineligible.

All patients provided written informed consent. The research ethics boards of both participating sites approved the trial, and patients were registered by contacting the Ontario Clinical Oncology Group (Hamilton, ON, Canada).

Interventions

Thoracic RT was planned to be delivered to a total dose of 30 Gy in 10 fractions within a 2-week interval. This specific fractionation scheme is a generally accepted one in the palliative NSCLC setting,[4,14] and, in contrast to 20 Gy in 5 fractions (another commonly used fractionation scheme), it was selected to maximize the duration of overlap of the 2 therapies. Simple parallel opposed beams were intended as the usual treatment field arrangement, delivering a mid-plane dose of 30 Gy.

Erlotinib treatment (150 mg daily) was initiated 1 week (range, 5-10 days) before beginning RT. It was then continued until RT completion, such that participants were to receive a total of 3 weeks of erlotinib therapy, 1 week before and 2 weeks concurrent with RT. Erlotinib was discontinued for any patient who experienced serious adverse events (AEs). Because the study cohort was expected to experience significant medical comorbidity during the natural course of their illness, only grade 3 (Common Terminology Criteria for Adverse Events, version 3.0) or higher AEs were collected. The specific AEs included diarrhea, skin rash, interstitial lung disease, and ophthalmologic disorders. Figure 1 shows the study schema in detail.

Although patients who were planning to receive palliative systemic chemotherapy were not eligible to enter the trial. If deemed medically appropriate for disease progression during the active phase of erlotinib therapy, erlotinib was discontinued and chemotherapy started.

Outcomes

After the baseline assessment to establish the initial eligibility, the patients were assessed weekly for the 3 weeks of active therapy for the purposes of acute toxicity and tolerability. At 7 and 11 weeks after study entry (corresponding to 4 and 8 weeks after study treatment), a QoL assessment using the Lung Cancer Symptom Scale (LCSS) was performed, in addition to the toxicity and clinical assessments. The LCSS is one of the most widely used instruments and has well-established feasibility, reliability, content validity, and construct validity.[15,16] Patients were then examined every 2 months until evidence of clinical disease progression. A radiologic assessment with computed tomography was to be performed at 8 weeks after treatment (week 11 visit). Disease progression and OS were recorded as available between the scheduled visits.

Justification for Primary Outcome Measure

The primary outcome measure of the present study was the mean change in the LCSS "symptoms from lung cancer" question from baseline to week 7 (4 weeks after RT completion). The LCSS consists of 9 items that can be reported individually or combined as an overall scale to assess the effect of lung cancer on QoL. Item 7, which focuses on the overall "symptoms from lung cancer," was the most responsive to the fractionated course of RT in the supportive care (SC).15 trial,[17] which evaluated palliative RT for advanced lung cancer. Also, it correlated well with improvements in the other respiratory symptoms and QoL.