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Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor

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ABSTRACT

Introduction: A feasibility study was performed to examine the safety and toxicity profile of daily gefitinib (250 mg) administration with concurrent definitive thoracic radiation therapy (TRT) in patients with unresectable non-small cell lung cancer (NSCLC) of stage III.
Methods: Patients received a 14-day induction therapy with gefitinib at 250 mg daily. TRT was initiated on day 15 in 2-Gy fractions administered five times weekly to a total dose of 60 Gy. The primary end point of the study was the rate of treatment completion. Mutation status of the epidermal growth factor receptor gene (*EGFR*) was evaluated for patients with available tumor specimens.
Results: Nine eligible patients enrolled in the study received induction gefitinib monotherapy. Two patients were unable to begin TRT because of the development of progressive disease during the first 2 weeks of the protocol. Three of the remaining seven patients treated with gefitinib and concurrent TRT were unable to complete the planned treatment (two because of pulmonary toxicity and one because of progressive disease), and the study was therefore closed according to the protocol definition. Tumor samples were available for eight patients. *EGFR* mutations (deletion in exon 19) were detected in two patients, both of whom achieved a partial response and exhibited an overall survival of >5 years.
Conclusions: Our results do not support further trials of gefitinib and TRT for unselected NSCLC patients. This therapeutic strategy may hold promise, however, for locally advanced NSCLC in patients with sensitizing *EGFR* mutations.

1. Introduction

Lung cancer remains the most common cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) is a heterogeneous disease that accounts for ~80% of lung cancer cases, and about one-third of individuals with newly diagnosed NSCLC present with locally advanced disease not amenable to curative resection [2]. The current standard of care for patients with unresectable locally advanced NSCLC is concurrent chemotherapy and definitive thoracic radiation therapy (TRT); however, most treated individuals experience disease recurrence, with the 5-year survival rate being only ~20% [3–5]. Further improvement in treatment outcome for patients with locally advanced NSCLC will require the development of more effective combined-modality therapies.

The expression and activity of the epidermal growth factor receptor (EGFR) are important determinants of radiation sensitivity in several cancers including NSCLC [6–9]. Irradiation of tumor cells has been shown to activate EGFR via ligand-dependent and ligand-independent mechanisms, possibly accounting for the radiation-induced acceleration of tumor cell repopulation and the development of radioresistance [9,10]. Such radiation-induced activation of EGFR-dependent processes provides a rationale for combined treatment with radiation and EGFR inhibitors. Indeed, preclinical models have shown that EGFR inhibition enhances the antitumor activity of radiation [11–14]. Gefitinib is a small-molecule tyrosine kinase inhibitor (TKI) of EGFR that competes with ATP for binding to the tyrosine kinase pocket of the receptor, thereby inhibiting receptor tyrosine kinase activity and EGFR

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signaling pathways [15]. Although several clinical studies have examined the use of gefitinib in patients with advanced or metastatic NSCLC [15–17], no data have been available regarding the efficacy of single-agent gefitinib combined with TRT in individuals with locally advanced NSCLC. We have now performed a feasibility study of gefitinib with concurrent TRT in patients with locally advanced NSCLC in order to establish the safety and toxicity profile of this therapeutic strategy. Midway through this study, the discovery of somatic mutations in *EGFR* and of the association of such mutations with a high response rate to EGFR-TKIs had a profound impact on the treatment of metastatic NSCLC [18–20]. We therefore examined the potential relation between the presence of *EGFR* mutations as detected in diagnostic biopsy specimens and treatment outcome.

2. Materials and methods

2.1. Eligibility criteria

Patients with pathologically confirmed unresectable NSCLC of stage III were eligible for enrollment in the study, whereas those with T3N1 disease, contralateral mediastinal lymph node metastasis, malignant pleural effusion, pericardial effusion, or pleural dissemination were excluded. Additional eligibility criteria included no previous disease treatment, the presence of any measurable lesion, an Eastern Cooperative Oncology Group performance status score of 0–1, an age of ≤75 years, no history of malignancy within the previous 5 years, a leukocyte count of ≥4000/μL, a platelet count of ≥100,000/μL, a hemoglobin level of ≥9 g/dL, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤50 IU/L, a serum creatinine concentration of ≤1.2 mg/dL, and an arterial oxygen pressure (PaO_2) of ≥70 mm Hg. Patients were excluded if they had interstitial pneumonitis, uncontrolled diabetes mellitus, or any serious underlying disease or complications. Staging workup included a chest radiograph, computed tomography (CT) scans of the chest and abdomen, either a CT scan or magnetic resonance imaging of the brain, and a radioisotopic bone scan. All subjects provided written informed consent to participation in the study, which was approved by the Institutional Review Board of each participating center (Kinki University School of Medicine and Yokohama Municipal Citizen's Hospital) and was performed in accordance with the Declaration of Helsinki.

2.2. Gefitinib therapy

Patients started taking 250 mg of gefitinib per day orally 14 days before initiation of TRT and continued doing so during TRT. At the completion of TRT, patients were maintained on gefitinib at 250 mg daily until evidence of disease progression or toxicity for up to 1 year. In the event of development of toxicities of grade 2 or higher, gefitinib was postponed until the toxicities had improved to grade 1 or lower. In the case that cessation of TRT was warranted, gefitinib was withheld until resumption of the remainder of the concurrent phase of the treatment. If patients experienced toxicities of grade 3 or higher or any grade of pneumonitis related to gefitinib, the treatment was terminated.

2.3. Radiation therapy

TRT was administered from day 15 of gefitinib using a linear accelerator photon beam of 6-MV or more. Three-dimensional (3D) treatment planning systems using computed tomography were used at both hospitals. Lung inhomogeneity correction was not performed in dose calculation. Radiation doses were specified at the center of the target volume.

The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks. The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (#2) to subcarinal lymph nodes (#7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. For the primary tumors and the involved lymph nodes of 1 cm in the shortest diameter, a margin of 1.5–2 cm was added. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5–1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods such as the oblique opposing method. Appropriate PTV margin and leaf margin were added for CTV1 and CTV2.

The objectives were to restrict the relative volume of the normal lung treated with a dose of >20 Gy (V20) to <35%, and the maximum spinal cord dose was restricted to <44 Gy. If patients experienced grade 3/4 esophagitis or dermatitis, pyrexia of 38 °C or more, or a decrease in *P*aO2 of >10 mm Hg compared to baseline, TRT was withheld until esophagitis or dermatitis improved to grade 2 or clinically acceptable toxicity level. If patients experienced grade 1 or more pneumonitis related to gefitinib, TRT was terminated.Assessment of toxicity and responseAll eligible patients who received any portion of the treatment regimen were considered assessable for toxicity and response. A CT scan of the chest was performed within 14 days of initiation of study treatment and was repeated on day 14 of gefitinib monotherapy in order to exclude individuals with disease progression or pneumonitis related to gefitinib. Chest X-rays, complete blood counts, and blood chemistry analysis were performed weekly until completion of TRT. Toxicities were assessed with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors [21]. The initial tumor response was defined as the best response recorded within 3 months after the start of treatment. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of registration in the study until the first documented instance of disease progression or death, respectively, with the use of the Kaplan–Meier method. Follow-up assessments included a posttreatment CT scan at 4–12 weeks after completion of TRT.

2.5. Study design and statistical considerations

The primary end point of the study was the rate of treatment completion. Complete treatment delivery was defined as completion of the planned 60 Gy of TRT within 63 days and administration of gefitinib for >3 weeks during TRT. We selected a 90% completion rate as a desirable target level and a 75% completion rate as uninteresting with an alpha error of 0.1 and a power of 0.8, resulting in a requirement for 28 patients. If 24 or more treatment completions were achieved among the 28 total assessable patients, the treatment was considered worthy of further consideration. Secondary end points included estimation of the objective response rate as well as of PFS and OS.

2.6. Analysis of EGFR mutation

Tumor specimens (embedded in paraffin) were collected during previous diagnostic procedures. *EGFR* mutations that confer sensitivity to EGFR-TKIs were identified by the PCR-Invader method (BML, Tokyo, Japan). Some patients had already died before the initiation of our genetic analysis, preventing us from obtaining informed consent. The Institutional Review Boards therefore approved our study protocol with the conditions that samples