Lung Cancer 71 (2011) 65–69

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

A multicenter phase II study to evaluate the efficacy and safety of gefitinib as first-line treatment for Korean patients with advanced pulmonary adenocarcinoma harboring EGFR mutations

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ARTICLE INFO

Article history:
Received 19 January 2010
Received in revised form 7 March 2010
Accepted 1 April 2010

Keywords:
Gefitinib
Adenocarcinoma
EGFR
Mutations
Lung
Cancer
Chemotherapy

ABSTRACT

This study was designed to prospectively evaluate the efficacy and safety of first-line gefitinib treatment in patients with advanced pulmonary adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutations and to explore the molecular factors affecting the efficacy of gefitinib. Tumor tissue, derived from either the original tumor or the metastatic or recurrent site was taken from chemo-naïve pts with advanced (stage IIIB, IV, and recurrent) pulmonary adenocarcinoma. Tumor genomic DNA underwent direct sequencing for EGFR exons 18, 19, 20, and 21. Patients with EGFR mutations received 250 mg of gefitinib daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression free survival (PFS), overall survival (OS) and tolerability. Out of 147 screened patients, 45 pts (31%) had EGFR mutations and received gefitinib. The most common EGFR mutations were in-frame exon 19 deletions (29 pts, 64%) and L858R point mutation in exon 21 (15 pts, 33%). One patient had atypical mutation of L861Q in exon 21. The ORR was 53.3% (95% CI, 38.6–67.9) and disease control rate (DCR) including stable disease was 86.7%. The median progression free survival (PFS) was 398 days and the median overall survival (OS) was 819 days. Treatment was well tolerated. Grade 3/4 adverse events (AEs) were reported by 6 patients and treatment-related Grade 3 AEs by 3 patients. There were no treatment-related Grade 4 AEs. Exploratory subgroup analysis according to the EGFR mutation subtypes was carried out. The ORR and DCR were higher in patients with exon 19 deletions than those with L858R (62.1% vs 33.3%; $P = 0.0705$ and 96.6% vs 66.7%; $P = 0.0062$, respectively). All 4 patients with progressive disease had a L858R mutation. No secondary resistant mutations such as T790M mutation or insertions in exon 20 were found in those patients. In addition, OS was significantly better in patients with exon 19 deletions than those with L858R (24-month OS rate was 72.1% vs 32.0%, $P = 0.0148$). Gefitinib as the first-line treatment for Korean patients with advanced pulmonary adenocarcinoma harboring EGFR mutations was effective and well tolerated. Subgroup analysis suggests that the benefit from gefitinib treatment was more prominent in patients with the exon 19 deletion mutations (ClinicalTrials.gov number, NCT00344773).

1. Introduction

Primary lung cancer is the leading cause of cancer death in Korea [1]. Platinum based chemotherapy is a well established first-line therapy in the palliative setting for patients with advanced disease, with response rates of 20–45% and median survival of 8–11 months [2–4]. Gefitinib is an orally administered epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) which has shown non-inferior survival compared with docetaxel

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doi:10.1016/j.lungcan.2010.04.005

in pretreated patients with advanced non-small-cell lung cancer [5]. Responsiveness to EGFR-TKIs has previously been shown to correlate with somatic mutations in the region of the EGFR encoding the tyrosine kinase domain [6,7]. Increased responsiveness to EGFR-TKIs has also been found in women, never or light smokers, pulmonary adenocarcinomas, and patients of Asian origin and has been linked to the relatively high incidence of EGFR mutation in these patient subgroups [8–10].

Recently, gefitinib showed superiority to carboplatin/paclitaxel in terms of progression free survival (PFS) and objective response rate (ORR) in the phase III IPASS study in never/light ex-smokers with advanced pulmonary adenocarcinoma in East Asia, a result primarily driven by the EGFR mutation-positive subgroup [11]. However, while several studies have shown the importance of EGFR genotypes as a predictor of responsiveness to EGFR-TKIs, few have prospectively selected patients on the basis of EGFR genotypes. In most studies, EGFR mutation analysis was performed after the commencement of either EGFR-TKI treatment or cytotoxic chemotherapies.

There have been a few small studies that tested the feasibility and efficacy of EGFR genotype-based patient selection for first-line gefitinib treatment. Those studies showed promising efficacy of gefitinib as the first-line treatment for patients with advanced non-small cell lung cancer harboring EGFR mutations, with response rates of 55–76% and median progression free survival of 9–9.7 months [12–14].

This study prospectively evaluated the efficacy and safety of gefitinib as first-line treatment in Korean patients with advanced pulmonary adenocarcinoma harboring EGFR mutations. It also explored the molecular factors affecting the efficacy of gefitinib in this patient population.

2. Patients and methods

This multicenter, phase II, single arm study (ClinicalTrials.gov number, NCT00344773) was conducted at seven major hospitals in Korea. The protocol and all related materials were approved by the local institutional review boards. The study was conducted in compliance with Good Clinical Practice, guidelines of the International Conference on Harmonisation, and the Declaration of Helsinki. Written informed consent was required from all patients before participation.

2.1. Patient population

Adult patients were eligible for EGFR screening if they had histological evidence of advanced (stage IIIB with malignant effusion, metastatic, or recurrent) pulmonary adenocarcinoma including bronchioalveolar carcinoma. Only patients with an EGFR mutation were eligible for gefitinib treatment. No prior palliative chemotherapy, biological, or immunological therapy was allowed, but prior adjuvant or neoadjuvant anticancer therapy completed more than 3 months before enrollment was allowed. Patients were required to have measurable lesions according to the Response Criteria in Solid Tumors (RECIST) criteria [15], a World Health Organization Performance Status 0-2 [16], a life expectancy of at least 12 weeks, and adequate hematologic, hepatic, renal function. Patients with central nervous system metastasis without definitive treatment, known hypersensitivity to gefitinib, clinically active interstitial lung disease, medically uncontrolled systemic disease, or prior malignancies other than basal cell carcinoma or cervical cancer *in situ* were not eligible. Pregnant or lactating women were excluded.

2.2. EGFR mutation screening

Patients were required to provide a paraffin embedded tumor tissue block or cut sections from the original tumor, metastatic site, or recurrent site to perform EGFR mutational analysis. Mutation analysis of EGFR exons 18, 19, 20 and 21 was performed centrally as previously described [8] at the ISU-ABXIS, Seoul Korea. Briefly, DNA was extracted from five 5-μm paraffin sections, containing a representative portion of each tumor block, using QIAamp DNA Mini kits (Qiagen, Hilden, Germany). One hundred nanograms (ng) of DNA were amplified in a 20 μl reaction solution containing 2 μl of 10× buffer (Roche, Mannheim, Germany), 1.5 mM of $MgCl_2$, 0.3 μM of each complementary primer, 250 μM of deoxynucleoside triphosphate, and 2.5 units of DNA polymerase (Roche). Amplifications were performed using a 5 min initial denaturation at 94 °C; followed by 30 cycles of 1 min at 94 °C, 1 min at 55 °C, and 1 min at 72 °C; and a 10 min final extension at 72 °C. Polymerase chain reaction products were purified using a QIAgen Gel Extraction kit (Qiagen) and DNA sequenced using an ABI-PRISM BigDye Terminator v3.1 (Applied Biosystems, Foster, CA, USA) with both forward and reverse sequence-specific primers. Sequence data were generated using an ABI PRISM 3100 DNA Analyser (Applied Biosystems), and sequences were analyzed using Sequencer 3.1.1 software (Applied Biosystems) to compare variations.

2.3. Treatment and evaluation

Patients received 250 mg of daily oral gefitinib continuously until disease progression, unacceptable toxicity, or patient refusal (whichever was sooner). Dose modification was not allowed. After discontinuation of gefitinib treatment, the patients were treated according to standard clinical practice at the discretion of the investigators.

Safety assessment including medical history taking, physical examination, and laboratory evaluation were performed at baseline and at the conclusion of each cycle using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Efficacy was assessed with computed tomography (CT) scans every 8 weeks until discontinuation or as clinically indicated. Any patients who discontinued study drug for reasons other than disease progression were to continue, where possible, to have objective tumor assessments every 12 weeks until progression. Responses were defined and categorized using RECIST criteria. All partial and complete responses were confirmed at least 4 weeks later with repeat imaging and a designation of stable disease required lack of progression for 12 weeks or more.

2.4. Statistical methods

The primary efficacy end point was ORR. All efficacy analyses were performed in the intent-to-treat (ITT) population, defined as all patients who had EGFR mutations and received gefitinib. The response rate was estimated by population proportion test supported by a 95% confidence interval (CI). The hypothesis of this study was that the ORR would be equal to 45% (one-sided proportion test). Calculation of sample size was based on Fleming's single stage method with a power of 80% and a type I error of 5% and estimated that 38 patients were required to be evaluable for response. Allowing for a dropout rate of 15%, 45 patients with EGFR mutation-positive tumors were to be allocated to the study drug treatment. The secondary end points were PFS, overall survival (OS), and safety profiles of gefitinib. Median PFS and OS were calculated using Kaplan–Meier product limit estimates [17]. PFS by EGFR mutation subtype was analyzed using a Cox proportional hazard model. Toxicity analysis was performed in the patients who received at least one dose of gefitinib. The incidence and percent-