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Afatinib in heavily pretreated advanced NSCLC patients who progressed following prior gefitinib or erlotinib: Compassionate use program in Korea

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ABSTRACT

Introduction: Afatinib, an irreversible ErbB family blocker, approved for first-line treatment of epidermal growth factor receptor (EGFR) mutated advanced non-small cell lung cancer (NSCLC). This study investigated experience of afatinib within a compassionate use program (CUP).

Methods: The afatinib CUP was an open-label, multicenter, single-arm program in Korea. We enrolled patients with stage IV NSCLC and who had received at least one line of previous cytotoxic chemotherapy and previous EGFR TKI treatment with either an EGFR mutation or documented clinical benefit. The starting dose of afatinib was 50 mg once daily.

Results: From August 2011 to September 2014, 332 patients received at least one dose of afatinib. Most patients were registered in the CUP for fourth- or fifth-line treatment with afatinib. Adverse events (AEs) occurred in 98.1% of patients, including 29.8% with serious AEs. The most common AEs (all grades) were diarrhea (90.1%) and skin rash (62.0%). Dose reductions occurred in 60.5% of patients and discontinuations due to AEs were reported in 11.1% of patients. The response rate and median time to treatment failure (TTF) were 27.4% and 3.3 months (CI 95%, 2.8–3.8 months), respectively, in this highly pretreated population. In subgroup analysis, ECOG PS 0 or 1 and immediate pretreatment with pemetrexed monotherapy or a platinum doublet were associated with a longer TTF for afatinib.

Conclusions: No additional or unexpected safety concerns were observed, and afatinib demonstrated moderate antitumor activity in advanced NSCLC patients with acquired resistance to gefitinib or erlotinib in a real-world setting.

1. Introduction

Lung cancer is a leading cause of cancer-related mortality in the world, with non-small cell lung cancer (NSCLC) accounting for about 85% of lung cancer [1,2]. The therapeutic landscape of NSCLC has been deeply changed over the last decade with the introduction of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and the discovery of EGFR activating mutations as the major predictive marker to these agents [3]. EGFR activating mutations are detected in about 30–40% of NSCLC from Asian patients and in 10% from Caucasian patients [4,5]. The two most common *EGFR* mutations, del19 and the Leu858Arg point mutation in exon 21, account for almost 90% of mutations-positive [6]. Several studies consistently demonstrated a significant superiority of EGFR-TKIs over standard platinum-based chemotherapy for NSCLC harboring EGFR mutations, leading to the sequential approval of gefitinib, erlotinib and afatinib as standard first-line treatment. However, almost all patients treated with EGFR tyrosine kinase inhibitors (TKI) eventually experience disease progression with acquired resistance after a median progression-free survival (PFS) of approximately 1 year (range, 8–14 months) [7–12].

Unlike the first-generation EGFR TKIs such as gefitinib and erlotinib, which are reversible inhibitors that selectively target EGFR, the

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second-generation EGFR TKI afatinib irreversibly blocks signaling from all relevant homo-dimers and hetero-dimers of the ErbB family of receptors (EGFR/ErbB1, HER2/ErbB2, ErbB3, and ErbB4) [13,14]. In two phase III studies in patients with *EGFR* mutation-positive advanced NSCLC (LUX-Lung 3, afatinib versus cisplatin/pemetrexed in patients recruited globally; LUX-Lung 6, afatinib versus cisplatin/gemcitabine in Asian patients), first-line afatinib monotherapy (40 mg/day, orally) significantly prolonged progression-free survival (PFS) compared with standard platinum-based chemotherapy regimens; afatinib was consequently approved in this setting [11,12]. In more recent analyses of these trials, afatinib was the first EGFR tyrosine kinase inhibitor to demonstrate an overall survival (OS) benefit over chemotherapy, even if limited to the subgroup of patients with EGFR exon 19 deletion [15]. Furthermore, in a randomized phase IIb trial, first-line afatinib significantly improved PFS, time to treatment failure and ORR versus gefitinib in EGFR mutation-positive NSCLC patients but OS was not significantly improved [16,17]. It has also demonstrated modest clinical activity in patients who had progressed following gefitinib and/or erlotinib [18,19].

Here we report the results of compassionate-use program (CUP) for afatinib in NSCLC patients who failed prior gefitinib and/or erlotinib in Korea.

2. Materials and methods

2.1. Study design and patients

The afatinib CUP was an open-label, multicenter, single-arm program conducted at 8 sites in Korea. The purpose of this CUP is to provide early access of afatinib in patients who are ineligible to participate in another afatinib phase III trial and for whom no other approved treatment is available.

Eligible patients were ≥18 years of age with pathologically confirmed stage IV NSCLC; failure of at least one line of cytotoxic chemotherapy and disease progression after clinical benefit on erlotinib or gefitinib. Clinical benefit was defined as stable disease for at least 6 months, or a complete or partial response, or the presence of an activating mutation of EGFR. Patients previously treated with afatinib in a clinical trial were excluded, as were those with a history of cardiac disease that is clinically significant, as judged by the investigator or uncontrolled cardiac disease and other life-threatening illness or organ system dysfunction, which in the opinion of the investigator, would compromise patient safety. The study protocol was approved by institutional review boards or independent ethics committees at each center, and the study was conducted according to International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written, informed consent.

2.2. Treatment

Afatinib was given as continuous oral treatment at a starting dose of 50 mg/day. Lower starting doses of 40 mg or 30 mg were allowed at the discretion of the treating physician. Dose reductions in 10-mg steps were allowed based on patient tolerability. No dose reduction is allowed below 30 mg. Treatment is continuous in the absence of disease progression or unacceptable adverse effects. Palliative radiation therapy was permitted for symptom control. During palliative radiotherapy, afatinib should be withheld and may be resumed once the patient has recovered from any radiation associated toxicity.

2.3. Assessments

There were no primary or secondary efficacy objectives, but disease assessments were performed per local standard practice according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events (AEs) were categorized and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

2.4. Statistical analysis

Data were collected on patient and disease characteristics, prior treatment, afatinib dose, adverse events and clinical outcome. Survival outcome of afatinib was determined by calculating the time to treatment failure (TTF) for each patient. TTF was defined as time from start of afatinib treatment to the end of treatment for any cause. Survival curves were estimated using the Kaplan–Meier method for TTF. A Cox proportional hazards model was applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The significance level was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 377 patients were enrolled in the Korean CUP from August 2011 to September 2014. Due to rapid disease deterioration, 45 patients received no afatinib treatment, resulting in 332 evaluable patients who received at least one dose of afatinib (Fig. 1). Patient characteristics are listed in Table 1. Most patients were female (63.3%), Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (73.2%), and adenocarcinoma histology (96.4%). All patients had received previous EGFR TKI treatment such as gefitinib (63.4%), erlotinib (31.9%), or both (3.6%), as their first (19.5%), second (55.9%), or subsequent (24.6%) line of therapy (Table 2). Objective responses to prior EGFR TKI were noted in 75% patients. Of 216 patients with known EGFR mutation prior to gefitinib or erlotinib therapy, exon 19 deletion was the most common, accounting for 59.3%, followed by L858R mutation at 25.9%. The majority of patients (76.5%) was registered in the CUP for fourth- or fifth-line treatment with afatinib. The median time from the last EGFR TKI dose until the first dose of afatinib was 8.6 months (range: 0.5–74.5 months). One hundred twenty-four patients (37.5%) received the first dose of afatinib ≤ 6 months after the last dose of previous EGFR TKI. Forty-nine (14.8%) patients received afatinib directly after the first-generation EGFR TKI.

3.2. Exposure

The starting dose of the CUP was defined as 50 mg/day afatinib. However, the actual starting dose could be varied by the treating physician's judgement. Accordingly, starting doses were unevenly distributed from 50 mg (81.9%) to 40 mg (17.8%) to 30 mg (0.3%). Dose

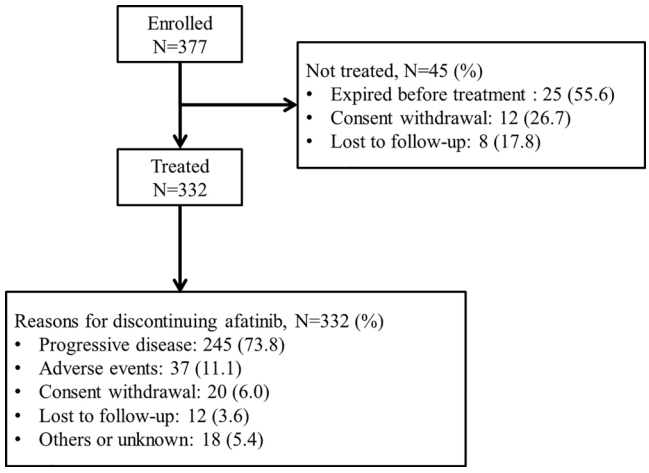

Fig. 1. Consort diagram.