Lung Cancer 104 (2017) 58–64

Contents lists available at ScienceDirect

Lung Cancer

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

Predictive factors for *EGFR*-tyrosine kinase inhibitor retreatment in patients with *EGFR*-mutated non-small-cell lung cancer – A multicenter retrospective SEQUENCE study

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ARTICLE INFO

Article history:
Received 21 August 2016
Received in revised form 5 November 2016
Accepted 10 December 2016

Keywords:
Lung cancer
Adenocarcinoma
EGFR mutation
EGFR TKI retreatment
Exon 21 mutation
Females
Drug holiday
Overall survival
Progression free survival

ABSTRACT

Background: Acquired resistance occurs in most non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations experiencing a response to *EGFR*-tyrosine kinase inhibitor (TKI) initially. We investigated *EGFR*-TKI retreatment in patients who had previously received *EGFR*-TKI followed by chemotherapy.

Materials and methods: This was a retrospective multicenter study. Patients with locally advanced or metastatic adenocarcinoma or TTF-1 (+) NSCLC, positive *EGFR* sensitive mutation, and *EGFR*-TKI reuse after initial EGFR-TKI followed by chemotherapy were enrolled. The objectives were to assess the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) of *EGFR* TKI switched retreatment.

Results: In total, 205 patients were enrolled, with a median age of 61.8 years (range 31.4–92.9). There was a larger proportion of females (62.9%) than males, and more never-smokers (73.2%) than ever-smokers. In the initial *EGFR*-TKI administration, 57.6% of patients showed a complete response (CR) or partial response (PR), and 34.6% had stable disease (SD); in the second-line chemotherapy, 13.7% had PR, and 58.0% had SD; in the *EGFR*-TKI retreatment, 7.3% had PR, and 37.1% had SD.

The median PFS of first-line *EGFR*-TKI was 8.0 months (95% CI 7.3–8.2), and retreatment *EGFR*-TKI was 4.1 months (95% CI 2.7–4.6). The median OS since the start of the first-line *EGFR*-TKI therapy was 35.9 months (95% CI 28.8–50.9), and since the start of *EGFR*-TKI retreatment was 12.6 months (95% CI 10.4–20.9).

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http://dx.doi.org/10.1016/j.lungcan.2016.12.002

In the univariable and multivariable regression analysis of factors associated with PFS of *EGFR*-TKI retreatment, time interval between the two *EGFR* TKIs equal to or more than 7 months was statistically significant (HR = 0.62, 95% CI 0.44-0.86; HR = 0.6, 95% CI 0.43–0.86), both $p < 0.01$. Females with exon 21 mutation also showed a significant difference between the two groups (HR = 0.51, 95% CI 0.30–0.86; HR = 0.52 (0.31–0.88), both $p < 0.05$).

Conclusions: *EGFR*-TKI retreatment was effective in prolonging survival, and was shown to be a worthwhile option for *EGFR*-mutated NSCLC patients after failure of first-line *EGFR*-TKI and chemotherapy. The survival benefit was especially pronounced in patients with longer drug holidays from the initial *EGFR*-TKI and in females with the exon 21 mutation.

1. Introduction

It has been well established that advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations treated with first-line tyrosine kinase inhibitors (TKIs) show a significantly better response rate and progression-free survival (PFS) than patients treated with chemotherapy [1–5]. The Iressa Pan-Asia Study (IPASS) and NEJ002 also demonstrated a better quality of life and extended time to symptom worsening in patients receiving gefitinib [6,7]. However, acquired *EGFR*-TKI resistance often develops after 10–14 months of first-line TKI treatment. There are several mechanisms that may explain *EGFR*-TKI acquired resistance. The *EGFR* T790M mutation accounts for the majority of cases (around 60%) of acquired resistance, while MET amplification appears in only 4% cases. Around 30% of cases of acquired resistance are still unknown [8]. Conventional cytotoxic chemotherapy is used as the second-line therapy following first-line TKI failure. *EGFR*-TKI sensitive tumors might regrow during the chemotherapy and suggest that retreating with TKI is a possibility [8]. The theory of a "drug holiday" in TKI retreatment for patients with a good response previously is supported in a few studies. However, most of these previous studies were retrospective, with small patient numbers, and not all of the patients' *EGFR* mutation status was known [9–11]. Therefore, we conducted a retrospective, non-interventional, multicenter, observational chart review study to explore the real-world clinical benefits of *EGFR* TKI retreatment for patients with NSCLC whose initial treatment was *EGFR*-TKI followed by chemotherapy.

2. Materials and methods

2.1. Study population

This study was designed to retrospectively review the medical and chemotherapy records of 200 patients with *EGFR* mutation positive NSCLC in 7 medical centers in Taiwan. Eligible patients were as follows: patients aged 20 years or older, diagnosed with locally advanced or metastatic adenocarcinoma or positive result of thyroid transcription factor 1 (TTF1) NSCLC with measurable disease by computed tomography (CT) scan; positive *EGFR* mutation result with at least one sensitive mutation, including, but not limited to, exon 19 deletions or exon 21 point mutation; and treated with *EGFR*-TKI followed by chemotherapy before retreatment of *EGFR*-TKI. The exclusion criteria were as follows: patients with *EGFR* mutation status of positive exon 20 T790M mutation only; patients who were confirmed to have squamous type NSCLC; and combined treatment with *EGFR*-TKI and other anticancer treatment regimen. This study was approved by the Institutional Review Board of each participating hospital.

2.2. Data records and response evaluation

Clinical data for analysis included patients' age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS) before the start of *EGFR* TKI retreatment, tumor stage, smoking status, *EGFR* subtypes, *EGFR* TKIs and prior chemotherapy treatment history. TNM (tumor, node, and metastases) staging was done according to the 7th edition of the American Joint Committee for Cancer (AJCC) staging system. Unidimensional measurements as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used in this study [12]. The objective of this study was to assess the objective response rate (ORR), disease control rate (DCR), PFS and overall survival (OS) of *EGFR* TKI switched retreatment.

2.3. EGFR *mutation test*

Methods used for *EGFR* testing included direct sequencing, and mutant type-specific sensitive methods, such as matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), scorpions amplification refractory mutation system (ARMS) and Cobas *EGFR* Mutation Test.

2.4. Statistical analyses

Univariate analysis by Fisher's exact test was conducted on ORR, DCR, and PFS to evaluate the effects of clinical factors relating to patient and disease characteristics, *EGFR* subtypes, and previous treatments. Multivariate analyses using logistic regression model with stepwise selection method were performed for ORR, DCR, and PFS. The Kaplan–Meier method was used to estimate PFS and OS. Differences in survival time between disease control status, *EGFR* mutation subtypes, and lines of therapy were analyzed using the log-rank test. Multivariate analyses using Cox proportional hazard model with stepwise selection method were performed for PFS and OS. All statistical tests were done with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Two-tailed tests and p values <0.05 for significance were used.

3. Results

A total of 205 patients were eligible for inclusion in the study analysis from October 2009 to September 2013. The median age was 61.8 years (range 31.4–92.9 years), with a preponderance of females (females vs. males: 62.9% vs. 37.1%) and more never-smokers (73.2%). Most patients had an ECOG PS score of 1–2 (72.2%). Exon 19 deletion (57.5%) and L858R (41.0%) were the major subtypes of *EGFR* mutation. Different medications were used in the initial and re-administered *EGFR*-TKI. Most patients (93.5%) received gefitinib, and 5.4% and 1.0% of patients received erlotinib and afatinib, respectively, in the first-line *EGFR*-TKI treatment. Up to 89.8% of patients received erlotinib, while only 4.4% and 5.8% of