Lung Cancer 88 (2015) 187–194

Contents lists available at ScienceDirect

Lung Cancer

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

# Liver metastasis predicts poorer prognosis in stage IV lung adenocarcinoma patients receiving first-line gefitinib

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ARTICLE INFO

*Article history:*
Received 9 October 2014
Received in revised form 1 February 2015
Accepted 13 February 2015

*Keywords:*
Lung cancer
Adenocarcinoma
Gefitinib
Liver metastasis
Epidermal growth factor receptor tyrosine kinase inhibitor

ABSTRACT

*Objectives:* Gefitinib is currently used as a first-line therapy in patients of advanced non-small cell lung cancer (NSCLC) with susceptible epidermal growth factor receptor (EGFR) mutations. However, treatment outcomes of these patients vary. This study was conducted to evaluate the impact of specific metastatic sites on treatment outcomes of patients with stage IV lung adenocarcinoma with susceptible EGFR mutations receiving first-line gefitinib, focusing on the impact of liver metastasis.
*Materials and methods:* Between October 2009 and April 2014, patients of stage IV lung adenocarcinoma harboring EGFR mutation in exon 19 or 21, who received first-line gefitinib treatment, were enrolled in two hospitals and followed until December 22, 2014. The impacts of various clinical features, including sex, age, smoking history, performance status, EGFR mutation site, metastatic sites, etc., on progression-free survival (PFS) and overall survival (OS) were analyzed.
*Results:* A total of 148 patients were eligible for analysis. Patients with liver metastasis on initial diagnosis ($n = 19$) had shorter PFS and OS than those without liver metastasis did (median of PFS, 6.7 vs. 11.2 months, $p < 0.0001$; median of OS, 9.2 vs. 17.5 months, $p < 0.0001$). Multivariable Cox regression analysis showed liver metastasis was an independent poor prognostic factor for PFS (HR = 2.939 [95% CI: 1.729–4.997], $p < 0.0001$) and OS (HR = 3.300 [95% CI: 1.708–6.373], $p = 0.0004$).
*Conclusion:* Liver metastasis predicts poorer PFS and OS in stage IV lung adenocarcinoma patients with susceptible gene mutations receiving first-line gefitinib. Further study is warranted to elucidate the underlying mechanisms and find treatment modalities to improve prognosis of these patients.


## 1. Introduction

Cancers are the leading causes of death worldwide, and about 20% of them are related to lung cancer [1,2]. In Taiwan, lung cancer has been the most common cause of cancer death for more than 10 years [3]. Adenocarcinoma is the most common type of lung cancer, accounting for about 57% of lung cancer in Taiwan [4,5]. Lung cancer is usually diagnosed at advanced stage, with more than

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http://dx.doi.org/10.1016/j.lungcan.2015.02.012
0169-5002/

35% of patients diagnosed at stage IV, so the treatment outcome remains unsatisfying [4].

In the past decade, gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has become widely used for treating advanced non-small-cell lung cancer (NSCLC). Since a rapid and often dramatic clinical response to gefitinib was noticed in some patients, much effort has been made to identify the subpopulation of patients having better response to this magic bullet [6]. Although some clinical features, including female, never smokers, Asian ethnicity and adenocarcinoma, have been identified to predict better treatment response, the most robust predictor for a better outcome remains the presence of a mutation of the EGFR gene in the tumor [6–10]. The presence of sensitizing mutations located in exon 19 or 21 of the EGFR gene predicts longer progression-free survival (PFS) [10–12].

In Taiwan, gefitinib has been covered by the National Health Insurance as the first-line therapy for advanced lung adenocarcinoma with susceptible EGFR mutations since June, 2011. Because its better tolerability as compared with traditional chemotherapy, most patients with stage IV lung adenocarcinoma with susceptible EGFR mutations use gefitinib as their initial treatment in Taiwan. However, even in this selected population, the treatment response to gefitinib varies. Patients harboring EGFR exon 19 deletion might have better PFS than those with exon 21 mutation, whereas no significant difference was noted in the overall survival (OS) [12]. In addition to EGFR mutation site, some clinical features have also been found to predict treatment outcome of EGFR-TKI, including smoking history, physical size, number of metastatic sites, performance status, and so on [11–17]. However, whether a specific metastatic site affects outcome in stage IV EGFR-mutated lung adenocarcinoma patients receiving first-line gefitinib monotherapy has not been studied yet. A Swedish study of metastatic lung cancer found liver and bone metastases signaled significantly poorer OS as compared with nervous system metastasis, while liver metastases seemed a stronger predictor; however, the treatment modalities were not discussed in this study [18]. Besides lung cancer, the presence of bone and liver metastases had a negative impact on survival in patients with renal cell carcinoma receiving targeted therapy as well [19].

In this study, we therefore evaluated the impact of specific metastatic sites on treatment outcome of patients with stage IV lung adenocarcinoma harboring susceptible EGFR mutations receiving first-line gefitinib, focusing on the impact of liver metastasis.

## 2. Patients and methods

### 2.1. Patient identification

In this retrospective study, patients of stage IV lung adenocarcinoma diagnosed between October 2009 and April 2014 in two hospitals (one medical center and a community-based hospital) in southern Taiwan were identified and were followed until December 22, 2014. The lung cancer diagnosis was confirmed pathologically according to World Health Organization pathology classification. On initial diagnosis, all patients received extensive examinations, such as computed tomography, abdominal ultrasonography, whole body bone scan, brain imaging and so on. The tumor staging was designated according to the seventh American Joint Committee on Cancer staging system by a special committee constituted of clinical pulmonologists, medical oncologists, chest surgeons, radiologists, pathologists and radiation oncologists. Patients were included if: (1) they had adequate tumor specimens for EGFR mutation examination, (2) the exam revealed a common susceptible EGFR gene mutation in either exon 19 or exon 21, and (3) they received gefitinib as their initial treatment (i.e., those who received chemotherapy or surgery before starting gefitinib treatment were not included). Those who had previous history of other malignancies were excluded. Patients with brain metastasis were excluded if they did not receive radiotherapy for their brain metastasis.

Baseline clinical characteristics, including age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status at the beginning of gefitinib treatment, smoking status and tumor histology, were determined by retrospective chart review. Smoking status was categorized as current smoker, ex-smoker (quit $\geq$5 years before diagnosis), or never smoker (<100 lifetime cigarettes).

Mutations in EGFR gene were analyzed by EGFR RGQ kit (Qiagen, U.K.), which utilized amplification refractory mutation specific (ARMS) PCR and Scorpion technologies for the detection, and/or direct sequencing. The detection method was developed and validated by the Division of Molecular Diagnostics, Department of Laboratory Medicine, Kaohsiung Medical University Hospital (KMUH).

Initial treatment response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on serial imaging studies using the RECIST 1.1 criteria [20]. The primary outcome of this study was PFS defined by the duration between the start of gefitinib and the onset of progression. The secondary outcome was OS defined by the duration between the start of gefitinib and time of cancer-related death.

The study protocol was approved by the KMUH Institutional Review Board (KMUH-IRB-20120278).

### 2.2. Statistical analyses

Age, sex, smoking history, initial performance status, EGFR gene mutation site (exon 19 or 21), thyroid transcription factor 1 (TTF-1) immunostaining, metastatic sites on initial diagnosis and initial treatment response were summarized and compared between patients with or without liver metastasis. Categorical variables and continuous variables were compared using $\chi^2$ test (or Fisher's exact test as applicable) and Student's *t*-test, respectively.

Survival times were estimated using the Kaplan–Meier method, with differences between the groups compared using the log-rank test. Cox proportional hazards regression analysis was used to identify the effect of different clinical features on PFS and OS. After univariate analyses, all variables were included to obtain a maximal model of multivariable analysis to assess the independent effect of different variables. We also used backward variable selection method, keeping only variables with *p*-value less than 0.1, to develop a reduced multivariable model. All statistical analyses were performed using SAS system (version 9.3 for Windows, SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at a two-sided *p*-value of <0.05.

## 3. Results

### 3.1. Patient characteristics

A total of 198 patients with stage IV lung adenocarcinoma with susceptible EGFR gene mutations were enrolled. After excluding patients having concomitant or prior cancer in another organ, patients having operation or chemotherapy before taking gefitinib and those with brain metastasis who did not receive cranial radiotherapy, data of the remaining 148 patients having a common susceptible EGFR gene mutation in either exon 19 or exon 21 and taking gefitinib as their first-line treatment were further analyzed. The median time from the diagnosis to initiation of gefitinib was 13 days. The clinical characteristics of the study population,