Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

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

Original Article

Continuous epidermal growth factor receptor-tyrosine kinase inhibitor administration in primary lung adenocarcinoma patients harboring favorable mutations with controlled target lung tumors dose not hinder survival benefit despite small new lesions

Ping-Chih Hsu [a], *Li-Chung Chiu* [a], *Shih-Hong Li* [a], *Chih-Hung Chen* [a], *Chih-Liang Wang* [a], *Kuo-Chin Kao* [a], *John Wen-Chang Chang* [b], *Chih-Wei Wang* [c], *Chih-Teng Yu* [a], *Fu-Tsai Chung* [a], *Cheng-Ta Yang* [a], *Chien-Ying Liu* [a,*]

[a] *Department of Thoracic Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*

[b] *Department of Oncology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*

[c] *Department of Pathology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*

ARTICLE INFO

Article history:
Received 14 December 2014
Accepted 28 July 2015
Available online 9 June 2016

Keywords:
Epidermal growth factor receptor-tyrosine kinase inhibitor
Overall survival
Progression-free survival
Progressive disease
Response Evaluation Criteria in Solid Tumors

ABSTRACT

Background: In this study, we investigated the efficacy of continuous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) administration in lung adenocarcinoma patients harboring favorable mutations regarding the progressive disease (PD) status with appearance of indolent new lesions.

Methods: From June 2010 to October 2012, 102 patients with lung adenocarcinoma, harboring favorable EGFR mutations and treated with EGFR-TKI were analyzed. Definite new lesions were detected during EGFR-TKI therapy, even though the primary target tumors were controlled.

Results: Of the 102 patients, 57 continued and 45 discontinued EGFR-TKI therapy. The median overall survival was 529 days for the discontinuation group and 791 days for the continuation group ($p = 0.0197$). Median survival time after the discontinuation of EGFR-TKI was 181 days and 115 days in the discontinuation and continuation groups, respectively ($p = 0.1776$), whereas median survival time after the appearance of indolent new lesions was 204 days and 262 days, respectively ($p = 0.0237$).

Conclusion: Continuous EGFR-TKI administration in favorable EGFR-mutative lung adenocarcinoma patients with controlled primary tumors did not hinder the survival benefit, despite the appearance of new lesions.

* *Corresponding author*. Department of Thoracic Medicine, Chang Gung Memorial Hospital at Linkou, 5, Fusing St., Gueishan, Taoyuan 333, Taiwan. Tel.: +886 3 3281200ext.8468; fax: +886 3 3287787.
E-mail address: cyliu01@cgmh.org.tw (C.-Y. Liu).

Peer review under responsibility of Chang Gung University.
http://dx.doi.org/10.1016/j.bj.2015.07.002

At a glance commentary

Scientific background of the subject

Some advance lung adenocarcinoma patients, harboring favorable epidermal growth factor receptor mutation, who were receiving epidermal growth factor receptor-tyrosine kinase inhibitor, were detected with small new lesions in the follow-up images, which defined progressive disease by RECIST criteria. However, these patients had controlled primary target lesions with stable clinical condition.

What this study adds to the field

For advance lung adenocarcinoma patients, harboring favorable epidermal growth factor receptor mutation, even the appearance of small new lesions while receiving EGFR-TKI. Continuous EGFR-TKI administration did not hinder the overall survival and survival time after the occurrence of new lesions in patients with controlled primary target lesions.

Lung cancer is a leading cause of cancer-related deaths in both male and female patients worldwide [1]. Nonsmall cell lung cancer (NSCLC) accounts for approximately 85% of primary lung cancers and approximately 40% are adenocarcinoma [2,3]. The prognosis of the most nonresectable lung cancers (approximately 80% of NSCLCs) is poor, with a mean survival of 8–14 months [4]. Anti-epidermal growth factor receptor (EGFR) agents have been developed as a treatment for NSCLC and as an alternative to conventional chemotherapy [5–8]. A subset of patients harboring favorable EGFR mutations, such as an exon 19 deletion and L858R, benefit from EGFR targeted therapy [9,10]. However, most patients eventually develop the progressive disease (PD) because of acquired resistance, which might be related to a second-site EGFR mutation, MET amplification, or other factors [11].

Previous reports have only described the progression of local lesions without the representation of systemic resistance; therefore, the clinical definition of acquired resistance for NSCLC is unclear [12–16]. Our preliminary data showed that lung adenocarcinoma patients treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) and who had progression-free survival (PFS) of more than 6 months, developed new lesions, but remained clinically stable when EGFR-TKI was continued [17]. However, these patients were selected based only on the clinical efficacy of EGFR-TKI treatment with more than 6 months of PFS and they did not undergo analysis of the EGFR mutation because gene analysis was not performed routinely in clinical practice in our institute before 2009. New lesions are considered when a lesion is identified through follow-up imaging of an anatomic location without lesions at baseline [18]. The appearance of one or more new lesions is defined as PD by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.0, published in 2000) [19].

However, according to the revised RECIST 1.1 guidelines (2009), the first appearance of new lesions might not definitively indicate PD. If new lesions cannot be identified initially, treatment can be continued until the next scheduled assessment. Nonetheless, follow-up imaging that confirms the development of new lesions should also confirm PD [18], after which therapeutic agents should be altered. However, acute deterioration of disease after EGFR-TKI withdrawal has been reported in EGFR-mutant lung cancer patients with acquired resistance [14]. Furthermore, in clinical practice, some patients with a first appearance of new malignant lesions and PD have been observed to regain disease stability when the original EGFR-TKI treatment is continued [17].

The present study was intended to determine whether the survival of a subset of patients with EGFR mutative lung adenocarcinoma, with controlled target lesions, and new malignant lesions could be affected by discontinuing EGFR-TKI based on the appearance of new lesions, which are defined by RECIST, a PD status.

Methods

Study population

From June 2010 to October 2012, 486 patients diagnosed with stage IIIB or IV primary lung adenocarcinoma were tested for EGFR mutation status and were screened. All the patients were enrolled in the NHI program of Taiwan and received comprehensive and updated therapy for NSCLC. The patients were evaluated to determine the stage of the disease before the start of treatment, at regular intervals, and for disease progression or relapse. The disease stage was determined according to a complete medical history; physical examination; imaging survey, including chest X-ray (CXR) and computed tomography (CT) of the chest and abdomen; and additional staging procedures such as magnetic resonance imaging (MRI) of the head, bone scintigraphy, and fluorodeoxyglucose positron-emission tomography (FDG-PET). Tumor response was assessed during therapy, based on RECIST Version 1.0 or 1.1, depending on the respective year. Patient's lung cancer-related symptoms such as dyspnea, cough, hemoptysis, chest pain, and metastatic-lesion-related symptoms were recorded at each clinical visit or hospitalization. Clinical information was prospectively recorded following the Chang Gung Memorial Hospital (CGMH) lung cancer protocol and retrieved from the Cancer Registry System of the Cancer Center of CGMH.

Patient selection

The inclusion criteria were: (1) Patients with EGFR mutations that were sensitive to EGFR-TKI; (2) patients who had received EGFR-TKI therapy; (3) patients who were receiving EGFR-TKI therapy with controlled target primary lung tumors and preexisting metastatic tumors; (4) appearance of small new lesions in the follow-up images during EGFR-TKI therapy, defined as PD by RECIST; (5) patients who were asymptomatic or exhibited stable preexisting symptoms or mild symptoms