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Advanced non-Small cell lung cancer patients at the extremes of age in the era of epidermal growth factor receptor tyrosine kinase inhibitors

Yu-Mu Chen[a], Chien-Hao Lai[a], Kun-Ming Rau[b], Cheng-Hua Huang[b], Huang-Chih Chang[a], Tung-Ying Chao[a], Chia-Cheng Tseng[a], Wen-Feng Fang[a,c], Yung-Che Chen[a,d], Yu-Hsiu Chung[a], Yi-Hsi Wang[a], Mao-Chang Su[a,c], Kuo-Tung Huang[a], Shih-Feng Liu[a], Hung-Chen Chen[a], Ya-Chun Chang[a], Yu-Ping Chang[a], Chin-Chou Wang[a,c], Meng-Chih Lin[a,*]

[a] *Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[b] *Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[c] *Department of Respiratory Care, Chang Gung University of Science and Technology, Chiayi Campus, Chiayi, Taiwan*
[d] *Graduate Institute of Clinical Medical Sciences, Chang Gung University College of Medicine, Kaohsiung, Taiwan*

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ABSTRACT

Objectives: The clinical characteristics and survival of very young (≤40 years) and very old (>80 years) patients with advanced non-small cell lung cancer (NSCLC) are distinct. However, the benefits of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) to patients at the extremes of age with NSCLC harboring *EGFR* mutation have not been well studied. We retrospectively studied the effect of extreme age on patients' clinical characteristics and prognosis.
Materials and methods: Of 1510 lung cancer patients diagnosed between November 2010 and March 2014, 555 patients who were tested for *EGFR* mutations were included. Patients were divided into the following groups according to age: young (≤40 years), lower medium (41–60 years), higher medium (61–80 years), and very old (>80 years).
Results: Of the 555 patients, 20 (3.6%) patients were aged ≤40 years and 60 (10.8%) patients were aged >80 years. Young NSCLC patients had a lower BMI ($p = 0.003$), more brain ($p = 0.016$) and bone metastases ($p = 0.002$) Very young lung cancer patients still have poor prognosis even they were EGFR mutant. (EGFR mutant vs. wild type patients, OS: 12 vs. 7.3 months, $p = 0.215$) Very old NSCLC patients had a lower BMI ($p = 0.003$) and poor ECOG PS ($p = 0.028$). Positive EGFR mutation test reverses poor prognosis of elderly NSCLC patients. (EGFR mutant vs. wild type patients, OS: 13.2 vs. 4.9 months, $p = 0.003$)
Conclusion: We observed *EGFR* mutations reverse the poor prognosis of old patients with NSCLC. However, young patients with lung cancer have a poor prognosis even if they harbor *EGFR* mutations.

1. Introduction

Very young and very old patients with lung cancer have a distinct clinical presentation and prognosis than middle-aged patients [1–8]. Because life span has been extended lately, the number of patients older than 80 years and diagnosed with lung cancer has been increasing [9]. Their prognosis is generally poor because of a high incidence of non-cancer deaths and because of their inability to undergo curative operations or tolerate cytotoxic agents in the pre-tyrosine kinase inhibitors (TKIs) era [6,7,9]. However, in the TKIs era, old age or even poor performance status is no longer a barrier to receiving therapy; only epidermal growth factor receptor (*EGFR*) mutation status is [10]. For patients diagnosed with lung

* Corresponding author.
E-mail addresses: blackie@adm.cgmh.org.tw (Y.-M. Chen), sugun01@gmail.com (C.-H. Lai), kmrau58@adm.cgmh.org.tw (K.-M. Rau), hch4902@seed.net.tw (C.-H. Huang), kuan2101@adm.cgmh.org.tw (H.-C. Chang), tychao@adm.cgmh.org.tw (T.-Y. Chao), cctseng@adm.cgmh.org.tw (C.-C. Tseng), wenfengfang@yahoo.com.tw (W.-F. Fang), yungchechen@yahoo.com.tw (Y.-C. Chen), ma4227@ms31.hinet.net (Y.-H. Chung), yihsi@adm.cgmh.org.tw (Y.-H. Wang), maochangsu@yahoo.com.tw (M.-C. Su), jelly@adm.cgmh.org.tw (K.-T. Huang), liuphysico@yahoo.com.tw (S.-F. Liu), chc1106@adm.cgmh.org.tw (H.-C. Chen), y7817@adm.cgmh.org.tw (Y.-C. Chang), b9002087@adm.cgmh.org.tw (Y.-P. Chang), ccwang5202@yahoo.com.tw (C.-C. Wang), linmengchih@hotmail.com (M.-C. Lin).

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cancer before 40 years of age, the prognosis is conflicting from previous studies [2–5,11–14]. These patients often suffer from a delayed diagnosis and tend to have more aggressive tumor behavior [3–5,11,12]. On the other hand, they also have fewer comorbidities, and are more willing to receive aggressive therapies [3,13,15,16].

The administration of EGFR-TKIs has prolonged life spans in patients who harbor the *EGFR* mutations [14,17–19]. It would be very interesting to study the incidence of positive *EGFR* mutations in very young and very old lung cancer patients and see if EGFR-TKIs can reverse the poor prognosis of very old NSCLC patients. Thus, we conducted a retrospective study to understand the effect of extreme age on *EGFR* mutation status, progression free survival (PFS), and overall survival (OS) in the TKIs era. We also compared these clinical parameters to those of patients with wild-type *EGFR* status.

2. Material and methods

2.1. Patient and clinical characteristics

We conducted a retrospective study between November 2010 and March 2014 at Kaohsiung Chang Gung Memorial Hospital in Taiwan. Patients were followed up until November 2015. Adult patients with histologically or cytologically newly confirmed stage IIIB or IV NSCLC receiving *EGFR* mutation test were included.

Baseline assessments including clinical parameters, chest radiography, chest computed tomography, bone scintigraphy, and brain magnetic resonance imaging were performed within 4 weeks of treatment initiation.

Clinical parameters included age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and history of diabetes mellitus. Patients were divided into the following groups according to age: young (≤40 years), lower medium (41–60 years), higher medium (61–80 years), and very old (>80 years). This study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital with approval number: 102-4571b. The need for informed consent was waived.

2.2. EGFR *mutation testing*

Tumor specimens were obtained using bronchoscopy, computed tomography (CT)-guided biopsy, pleural effusion cytology, or surgical procedures. The *EGFR* mutational analysis was performed using SCORPIONS and ARMS polymerase chain reaction with fragments amplified from genomic DNA extracted from paraffin-embedded tissues (QIAGEN EGFR RGQ PCR KIT). Exon 19 deletion and L858R mutations were defined as common mutations. Other mutations or compound mutations were defined as uncommon mutations.

2.3. Treatment response evaluation

Patients underwent routine chest radiography every 2–4 weeks and chest CT every 2–3 months to evaluate tumor responses. Disease progression was determined by the clinician according to the Response Evaluation Criteria in Solid Tumors criteria 1.1 [20]. Severity of side effects was determined by the Common Terminology Criteria for Adverse Events [21].

The primary endpoint was PFS defined as the first day of chemotherapy or EGFR-TKI administration until disease progression, death before documented progression, or the last visit during the follow-up period. The secondary endpoint of OS was defined as the first day of chemotherapy or EGFR-TKIs administration until death, loss to follow-up, or last follow-up.

2.4. Statistical analyses

Statistical analyses were performed using MedCalc (version 14.10.2). PFS and OS analyses were performed using the Kaplan-Meier method and the log-rank test. P value < 0.05 was considered significant in statistical tests.

3. Results

3.1. Patient characteristics

Among 1510 lung cancer patients diagnosed between November 2010 and March 2014, 563 patients with advanced NSCLC were screened for *EGFR* mutations (Fig. 1). Of these patients, 316 were positive for *EGFR* mutation test. Ten patients were lost to follow-up. The final analysis data set consisted of 555 patients. The median follow-up time was 33.5 months and the longest follow-up time was 57.8 months. Clinical characteristics of all patients are shown in Table 1. All EGFR-mutant NSCLC patients received first line EGFR-TKIs, and 224 of 247 EGFR wild type received chemotherapies. At the last follow-up, 22.2% (123/555) patients were alive.

The median PFS and OS were 7.0 and 13.6 months in all patients, 10.6 and 20.2 months in patients with the *EGFR* mutation, and 3.5 and 8.2 months in patients with wild-type *EGFR*, respectively.

3.2. Clinical characteristics of NSCLC patients with mutant and wild type EGFR

When comparing patients with mutant and wild type *EGFR* in baseline clinical characteristics, significant differences in sex (patients with mutant vs. wild type *EGFR*: 57.1% women vs. 41.3%, $p < 0.001$), smoking history (patients with mutant vs. wild type *EGFR*: smoker 31.2% vs. 46.2%, $p < 0.001$), and tumor histology (patients with mutant vs. wild type *EGFR*: adenocarcinoma 92.2% vs. 76.1%, $p < 0.001$) (Table 1).

There was no significant difference in body mass index (BMI), diabetes mellitus (DM) history, ECOG PS, tumor stage, or number and sites of distant metastases including bone, brain, liver and pleura between patients with mutant and wild type *EGFR* (Table 1).

3.3. Clinical characteristics of young, middle-aged, and old NSCLC patients

Young NSCLC patients had a lower BMI ($p = 0.003$), more brain metastases ($p = 0.016$), more bone metastases ($p = 0.002$), and more sites of distant metastases ($p = 0.001$) than middle-aged patients (Table 2). In subgroup analyses, lower BMI in young lung cancer was only seen in EGFR wild type patients (Table 2). More brain metastases, bone metastases, and total distant metastasis sites in young lung cancer were only seen in EGFR mutant patients (Table 2). Very old NSCLC patients had a lower BMI ($p = 0.003$) and poor ECOG PS ($p = 0.028$) than middle-aged patients (Table 2). In subgroup analyses, lower BMI and poor PS in very old lung cancer were both only seen in EGFR wild type patients, not in EGFR mutant patients. (Table 2).

3.4. Prognosis in very young and very old NSCLC patients

Among all NSCLC patients (Fig. 2A,B) and the subgroup with the *EGFR* mutation (Fig. 2C,D), young patients had a shorter PFS and OS than middle-aged patients; in contrast, elderly patients had a shorter OS but non-inferior PFS compared to middle-aged patients. However, among patients with wild-type *EGFR* (Fig. 2E,F), young