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ORIGINAL ARTICLE

Treatment and survival status of patients with *EGFR* mutation-positive stage IV lung adenocarcinoma: five-year follow-up results in the Ordos Area of Inner Mongolia, China*

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Abstract

Objective We aimed to determine the epidermal growth factor receptor (*EGFR*) mutation status and treatment survival of patients with stage IV lung adenocarcinoma living in the Ordos area of Inner Mongolia, China.

Methods *EGFR* testing and first-line tyrosine kinase inhibitor (TKI) treatment rates of patients with stage IV lung adenocarcinoma were analyzed from June 2012 to June 2016. Kaplan-Meier survival curves were constructed to compare patients who received different treatment strategies and those harboring different *EGFR* mutation statuses.

Results *EGFR* testing and mutation rates were 65.60% and 52.90%, respectively, and improved continuously from June 2012 to June 2016. Among patients with *EGFR* mutations, 38.9% had *EGFR* 19 del, 48.2% had L858R, 4.2% had co-existing mutations in exons 19 and 21, and 8.4% had uncommon mutations. The median overall survival (OS) was 29.5, 26.5, and 16.0 months for patients receiving both TKI and chemotherapy, TKI alone, and chemotherapy alone, respectively (P = 0.047). The OS was 26.5 and 30.0 months for patients harboring *EGFR* 19 del and L858R mutations, respectively (P = 0.096).

Conclusion The high OS rates of stage IV lung adenocarcinoma patients living in the Ordos area may be attributed to continuous improvements in *EGFR* testing and first-line TKI treatment rates. In the era of TKIs, chemotherapy for increasing OS times should be emphasized.

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Key words: epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI); minority areas

Lung cancer is the leading cause of cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for 88% of lung cancer cases [1]. In China, lung cancer accounts for 25.24% of deaths among the 10 cancer types most commonly associated with mortality in cancer registration areas in 2009 [2]. In recent years, the percentage of patients with adenocarcinomas has increased significantly such that it has now become the most common cancer histologically [1].

Guidelines for NSCLC management strongly recommend testing for epidermal growth factor receptor (*EGFR*) gene mutations and administering tyrosine kinase inhibitors (TKIs) as first-line treatment in patients harboring such mutations because of the reported improvements in life quality and overall survival (OS) [3]. Previous national surveys showed that the rate of *EGFR* mutation testing was only 9.6% in China because of the limited access to relevant technology [4]. A multicenter survey from 12 tertiary hospitals showed an increased gene aberration testing rate of 71.4% compared with those reported in national surveys, although these hospitals were all affiliated with the medical universities in China, which reported high rates of lung cancer diagnoses and treatments [5]. Moreover, only 53.5% of *EGFR* mutation-

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positive patients received *EGFR* TKIs as first-line treatment at Guangdong Lung Cancer Institute, China [6]. Therefore, it is particularly important to continuously improve the *EGFR* testing and first-line TKI treatment rates in patients with stage IV lung adenocarcinoma.

The retrospective study aimed to identify the extent to which national treatment guidelines were adopted to customize care for lung adenocarcinoma patients living in the Ordos area of Inner Mongolia, China, between June 2012 and June 2017.

Patients and methods

Study population

In this retrospective observational survey, clinical data of patients with advanced lung adenocarcinoma were obtained from an electronic database at Department of Medical Oncology, Ordos Central Hospital, China, from June 2012 to June 2017. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ordos Central Hospital Committee on Human Research. All patients provided a written informed consent to participate in the study.

Data collection

The electronic database information included patient number, age, sex, ethnicity, smoking history, histological grade, genetic status, metastasis sites, and treatment. Smoking history was self-reported. "Never-smokers" were defined as patients who had smoked < 100 cigarettes over their lifetime. All patients had stage IV lung adenocarcinoma. Treatments were described as those administered since the diagnosis of stage IV lung adenocarcinoma and included chemotherapy, TKI therapy, and radiotherapy.

Statistical analysis

Data were presented as medians or numbers (percentages). We analyzed continuous changes in the *EGFR* exon 19 or 21 testing rate and first-line TKI treatment rate from June 2012 to June 2016. OS analysis was conducted in patients harboring *EGFR* 19 del only, L858R mutation only, and co-existing *EGFR* mutations in exons 19 and 21. OS was measured from the date of lung cancer diagnosis to death of any cause from June 2012 to June 2017. Patients were categorized into three groups based on the management modality they received: TKI and chemotherapy, TKI alone, and chemotherapy alone. Kaplan-Meier survival curves were constructed to compare the differences between groups. All statistical tests were two-sided P tests. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 19.0 software (IBM SPSS, Armonk, NY, USA).

Results

EGFR mutation status

Data of 288 patients with pathology-confirmed stage IV lung adenocarcinoma were included in the electronic database at Department of Medical Oncology, Ordos Central Hospital, China, between June 2012 and June 2017. Of these, 189 (65.60%) patients underwent *EGFR* testing, and testing specimens included biopsy tissues (140/189, 74.07%), pleural fluid samples (23/189, 12.17%), and blood (26/189, 13.76%). The detection of *EGFR* mutation was mainly performed using the amplification refractory mutation system [7], except for six patients who underwent *EGFR* sequencing between June 2012 and December 2013. Among the 189 patients who had *EGFR* testing, 100 (52.90%) had mutations in exon 18, 19, 20, or 21. Of the 100 *EGFR* mutation-positive patients, we excluded five whose mutations were not accurately reported. Among the remaining patients, 38.9% (37/95) harbored *EGFR* 19 del, 48.2% (46/95) had L858R, 4.2% (4/95) had co-existing *EGFR* mutations in exons 19 and 21, and 8.4% (8/95) harbored an uncommon mutation.

EGFR testing and fist-line TKI treatment rate

The *EGFR* testing rate improved continuously from June 2012 to June 2016 (Fig. 1). Additionally, the first-line TKI treatment rate of patients harboring *EGFR* mutations also improved continuously (Fig. 2).

EGFR mutation-positive patient treatment and survival status in the real world

From June 2012 to June 2017, 83.0% (83/100) of patients harboring *EGFR* 19 del or L858R mutations received first-line chemotherapy or TKI treatment; patients with co-existing *EGFR* mutations in exons 19 and 21 were excluded from the treatment analysis. The primary end point of the retrospective study was OS. Patients were categorized into three groups according to the management modality that they received (Fig. 3): group 1 included patients who received first-line TKI with second-line chemotherapy, first-line chemotherapy with second-line TKI, or first-line chemotherapy maintained by TKI (30.1%, 25/83); group 2 included patients who received TKI alone (63.9%, 53/83); and group 3 included who received chemotherapy alone (6.0%, 5/83). The median OS of the three groups was 29.5, 26.5, and 16.0 months, respectively ($P = 0.047$).

Comparison of OS for *EGFR* mutations in exons 19 and 21

Among the 53 patients harboring *EGFR* mutations who received TKI treatment alone, 88.7% (47/53) had *EGFR* 19 del or L858R mutations and 11.3% (6/53) had an uncommon *EGFR* mutation. Among the 47 patients

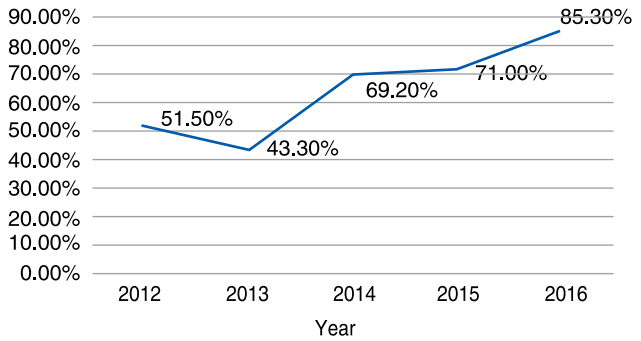

Fig. 1 *EGFR* gene testing rates from June 2012 to June 2016

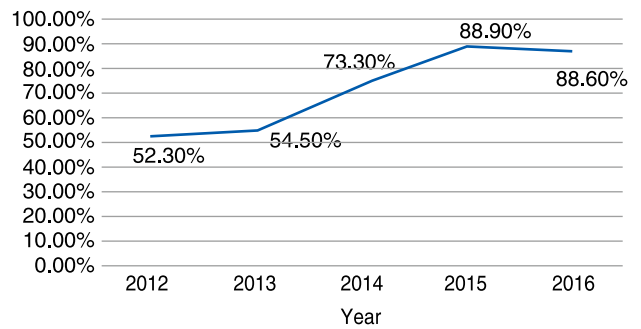

Fig. 2 First-line TKI treatment rates from June 2012 to June 2016

with *EGFR* mutations in exons 19 and 21, 11 had brain metastasis at diagnosis. A comparison of the remaining (36/47, 76.6%) patients without brain metastasis (Fig. 4) revealed an OS of 26.5 months and 30.0 months in those harboring 19 del or L858R mutations ($P = 0.096$). Patients harboring *EGFR* 19 del or L858R mutations without brain metastasis received first-generation TKI without chemotherapy during the entire disease process, although six patients received third-generation treatment after the first-generation TKI therapy failed.

Discussion

In this survey, we retrospectively analyzed the changing trends of *EGFR* testing and first-line TKI treatment rate in patients with stage IV lung adenocarcinoma living in the Ordos area of Inner Mongolia in the last 5 years. Both the *EGFR* testing rate and first-line TKI treatment rate increased sharply from June 2012 to June 2016. To some extent, this finding indicated the continuous advancement in clinical practice in accordance with the guidelines for the management of NSCLC patients harboring *EGFR* mutations in the minority areas of western China [3]. Nearly two-thirds of patients with stage IV lung adenocarcinoma had testing for *EGFR* aberration, and 52.90% of those tested had mutations. This *EGFR* mutation rate was similar to that (59.70%) observed in an

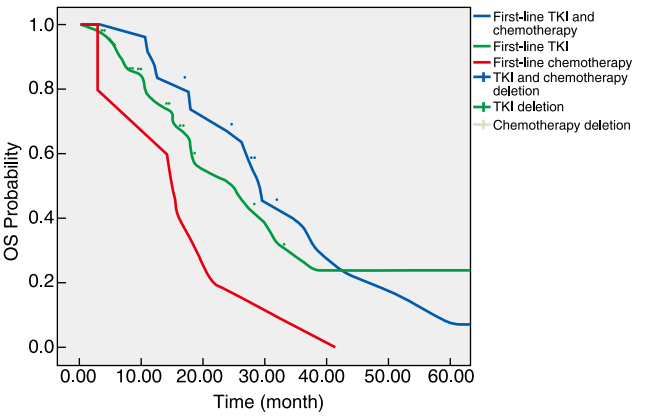

Fig. 3 OS comparison for patients who received different treatment strategies

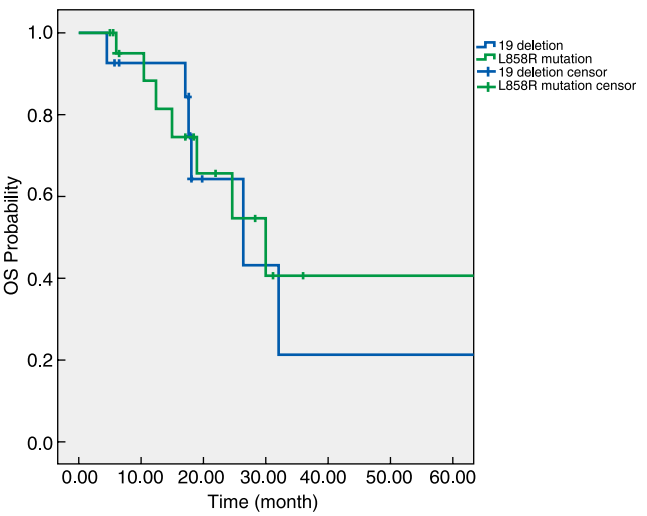

Fig. 4 OS comparison for patients *EGFR* 19 Del or L858R mutation

Asian population in the IPASS study [8].

Most of the patients (94.00%, 78/83) in our analysis with *EGFR* mutations received TKI treatment during the entire treatment period, and 63.86% (53/83) received first-line TKI for advanced NSCLC; this rate is clearly higher than that (48.68%) reported in the Guangdong Lung Cancer Institute and similar to that (66.30%) reported in the multicenter survey performed in the CTONG 1506 study [5–6]. These findings could be attributed to the fulfilment of clinical guidelines for managing EGFR mutation-positive NSCLC with the aid of medical insurance supporting TKI use in the Ordos area.

A previous meta-analysis showed that the *EGFR*-TKI therapy group of *EGFR* mutation-positive NSCLC patients had a significant improvement in progression-free survival (PFS) compared with the chemotherapy group, but the OS of the two groups did not differ significantly [9]. Most (94.00%) of the *EGFR* mutation-positive patients

in our study received TKI treatment, whereas only approximately one-third received both chemotherapy and TKI treatment during the entire process. In a previous study, *EGFR* mutation-positive patients who received first-line TKI and second-line chemotherapy achieved the highest OS of 30.39 months, compared with 20.67 months and 11.70 months for patients who received either TKI or chemotherapy alone, respectively, during the whole treatment period [10]. Our OS data supported these findings, with an average OS of 29.5 months for patients receiving both TKI and chemotherapy treatment, and were comparable to the results of phase III randomized, controlled clinical trials that reported OS times of 30.39 months and 27.7 months [10–11].

The treatment and survival data of our analysis represent the outcomes in real-world clinical practice because the patients' clinical characteristics in real-world practice differ from those in clinical studies, which have restrictive inclusion and exclusion criteria such as a required ECOG performance status (PS) of 0–2 and estimated life expectancy of at least 12 weeks and an absence of brain metastasis, history of cardiovascular disease, and uncontrolled pericardial or pleural effusion [10–11]. Our real-world population included patients with a range of conditions and only excluded those who could not tolerate or refused treatment.

Although the highest OS in our analysis (29.5 months) was not comparable with the 47.64 months obtained in patients with stage IV lung adenocarcinoma with *EGFR* mutations in the real-world study conducted by the Lung Cancer Mutation Consortium, which selected target treatments according to test results for 10 driver genes [12], it nevertheless represents an advancement in the TKI era. Moreover, the survival of female Asian stage IV lung adenocarcinoma patients in the Surveillance Epidemiology and End Results database was reported to increase from 8 months to 14 months from the pre-TKI era to the TKI era [13]. Additionally, patients treated with TKI in our database had notably longer OS times compared with that (13.9 months) of patients diagnosed with non-squamous NSCLC who received first-line pemetrexed maintenance treatment in the PARAMOUNT study [14]. This finding showed the importance of continuously improving *EGFR* testing and TKI treatment rates to prolong OS in *EGFR* mutation-positive patients (Fig. 1 and 2). Increased opportunities to administer TKI treatment may increase OS times for such patients.

As shown in Fig. 3, only around one-third of the patients in our database received both chemotherapy and TKI treatment, whereas 63.86% (53/83) received TKI treatment alone. This can be explained at least in part by the fact that first-line TKI therapy beyond progression is feasible but may delay salvage therapy for *EGFR* mutation-positive NSCLC, and is recommended as a basic strategy for cancer showing local progression or slow progression in the Chinese Society of Clinical Oncology guidelines [15–16]. Additionally, the TKI treatments gefitinib, erlotinib, and icotinib are provided by charitable organizations in mainland China. Therefore, patients with disease progression after first-line TKI treatment prefer to continuously apply for free TKI treatments rather than undergoing chemotherapy. Finally, the higher percentage of older patients and those with low PS status in real-world clinical practices compared with clinical trials contributes to the fact that most patients only receive TKI treatments.

Our OS of 26.5 months for patients who only received TKI treatment clearly exceeds the 20.67 months reported in the optimal study for similar patients [10]. This could be explained by the smaller sample sizes in our study. In several cases, the OS exceeded 60 months, which may explain why the Kaplan-Meier survival curves remain level after follow-up beyond 40 months in the TKI-only treatment group. In another study, encouraging PFS times were obtained for patients with T790M-positive advanced NSCLC who were pretreated with EGFR-TKI and received osimertinib, a third-generation TKI, after disease progression [17].

A previous pooled analysis of two multicenter, randomized clinical studies (Lux-lung 3 and Lux-lung 6) showed that *EGFR* 19 del and L858R mutations were considered as causative factors for two diseases that required different treatment strategies because of their distinct OS benefits with first-line TKI compared with first-line chemotherapy [18]. In this retrospective analysis, we compared the OS of 36 patients harboring *EGFR* 19 del or L858R mutations without brain metastasis at diagnosis who only received TKI treatment; however, the difference was not significant. Although our small sample size may have reduced the statistical power of the OS comparison, this is nevertheless in concordance with findings from Peking University Cancer Hospital [19]. In contrast, EGFR-TKIs provided a significant OS benefit to patients harboring 19 del compared with L858R mutations as reported in another study [20]. In our study, the OS of patients with L858R mutations was longer than that of patients with *EGFR* 19 del (26.5 months). One possible reason for this discrepancy is that more patients harboring L858R received third-generation TKI analogues after experiencing disease progression on first-line TKI treatment. To some degree, the different therapeutic effects of EGFR-tyrosine kinase inhibitors for 19 del and L858R mutations were more realistically reflected in this retrospective study because the patients in our analysis without brain metastasis at diagnosis who only received TKI had an OS level that was not affected by chemotherapy.

In conclusion, this retrospective study described

the results of a 5-year follow-up of stage IV lung adenocarcinoma *EGFR* mutation testing and treatment survival status in the Ordos area from a real-world viewpoint. Higher OS times were clearly attributed to the continuous improvements in *EGFR* testing and first-line TKI treatment rates. In the TKI era, the importance of chemotherapy in lengthening OS times should also be emphasized, because it did not only play an important role in whole process management but also showed a higher efficacy in managing TKI-resistant NSCLC when chemotherapy is given in combination with TKI [10, 21]. Differences in OS between patients harboring *EGFR* 19 del or L858R mutations should be analyzed further using a large data set.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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