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Efficacy and long-term survival of advanced lung adenocarcinoma patients with uncommon EGFR mutations treated with 1st generation EGFR-TKIs compared with chemotherapy as first-line therapy

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ABSTRACT

Purpose: This study aims to understand the effects and long-term survival of 1st generation epithelial growth factor receptor tyrosine kinase inhibitors(EGFR-TKI)or platinum-based chemotherapy as first-line therapy in advanced lung adenocarcinoma patients with uncommon EGFR mutations.

Patients and Methods: Specimens from 4276 advanced (IIIB/IV) patients were diagnosed with lung adenocarcinoma and underwent EGFR gene detection at the Affiliated Cancer Hospital of Zhengzhou University. The clinic characteristics, survival outcomes data, treatment outcomes and data of subsequent therapies after first-line treatment were collected of patients with uncommon EGFR mutations. The results were compared with common EGFR mutations.

Results: For patients with uncommon EGFR mutations, EGFR-TKIs or platinum-based chemotherapy as first-line therapy, showed no difference in objective response rate (ORR 33% vs 27.1% P = 0.499) and disease control rate (DCR 76.5% vs 87.5%, P = 0.194). EGFR-TKIs showed a superior progression-free survival than chemotherapy (median PFS, 7.2 vs 4.9 mt, HR = 0.604; P = 0.0088). Interestingly, compared with chemotherapy, we found that overall survival (median OS, 14.3 vs 20.7 mts, HR = 1.759; P = 0.0336) was significantly worse in patients with EGFR-TKIs. Multivariate analysis showed that extra metastases (HR = 2.240, P = 0.001) and smoking history (HR = 2.048, P = 0.013) were independent prognostic factors for OS in lung adenocarcinoma patients with EGFR uncommon mutations.

Conclusions: Compared with chemotherapy, use of the 1st generation of EGFR-TKIs as first-line therapy can improve the short-term efficacy of patients with EGFR uncommon mutations advanced lung adenocarcinoma, but platinum-based chemotherapy showed a longer overall survival.

1. Introduction

Lung cancer is the most common malignant tumour worldwide. Cancer-related mortality has been ranked top one among all cancers, and the incidence of cancer is continuously increasing coupled with worsening prognoses, specifically among the younger population [1,2]. Approximately 80% of patients with primary lung cancers have non-small cell lung cancer (NSCLC). The development of molecular targeted therapy has significantly advanced in recent years, and the survival of patients with advanced NSCLC has been significantly prolonged. Studies have shown that EGFR gene mutation accounts for approximately 51.4% of all NSCLC in Asians. Among these patients, non-smokers account for about 60.7%, women are more, the most common type of lung cancer is adenocarcinoma, who more likely to benefit from EGFR-TKI [3–5]. EGFR-TKIs have shown higher efficacy than conventional chemotherapy, fewer side effects and longer progression-free survival (PFS) for patients with EGFR mutations in advanced lung adenocarcinomas. EGFR-TKIs are gradually becoming the first choice for first-line treatment.

However, EGFR mutations are diverse, and there are still many types of mutations that have not been clearly defined. Different types of EGFR mutations have different sensitivities to EGFR-TKIs.

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Approximately 85%–90% of sensitivity EGFR mutations occurred in exon 19 deletion mutations and exon 21 point mutations, and the objective response rate (ORR) and PFS of EGFR-TKI therapy in these patients were significantly prolonged to 70%–80% and 8.4–13.1 months, respectively [6,7]. In addition to the above two types of classical mutations, uncommon mutations, such as the primary drug resistance mutation T790 M, insertion mutations in exon 20, substitution mutations of L861Q, G719X, and S768I, and their coexisting mutations, less than 10% of all EGFR mutations [8]. Patients with uncommon EGFR mutations who received first-generation EGFR-TKI (gefitinib/erlotinib) treatment, it was reported that the ORR was approximately 40%–50%, and the median PFS was approximately 6–7.7 months [9]. However, most of clinical trials lack data on long-term survivors and have few comparison with chemotherapeutic drugs, furthermore, clinical experiments belong to a part of exploratory research and screening criteria are vastly strict that do not apply to all of patients in the real world. For uncommon EGFR mutations, the efficacy of EGFR-TKI remains poorly to understand. In this study, the activity and long-term survival of 1st generation EGFR-TKIs or platinum-based chemotherapy as first-line therapy were assessed for patients with uncommon EGFR mutations in advanced lung adenocarcinoma, and collected the data of subsequent therapies for those patients in disease progression after first-line treatment. We look forward to providing clinicians with useful data on real-world treatment modalities.

2. Materials and methods

2.1. Patients

A total of 4276 patients were diagnosed with lung adenocarcinoma from Affiliated Cancer Hospital of Zhengzhou University and received EGFR gene detection and started first-line therapy from January 2, 2012, to February 1, 2018. A total of 2043 patients with EGFR mutations and stage IIIB/IV were identified. Among them, 157 cases (7.7%) with uncommon EGFR mutations, excluding 58 patients (Fig. 1), and 99 patients with uncommon EGFR mutations were enrolled for the efficacy analyses. The study included some patients with uncommon EGFR mutations who already had brain metastases and did not have positive clinical symptoms when they were diagnosed or who progressed to brain metastases during treatment. The main clinical features included gender, age, smoking history, cancer cell pathological type, tumour stage, EGFR mutation type, Eastern Cooperative Oncology Group performance status (ECOG PS), metastatic sites, and responsiveness to treatment. A smoker was defined as a person who had smoked more than 100 cigarettes during his lifetime. Age, smoking status, ECOG PS and treatment methods were documented at the time of diagnosis.

2.2. EGFR gene analysis

In short, 99 cases DNA were derived from embedding tumours in paraffin blocks using a QIAmp DNA Mini Kit (Qiagen). 20 cases DNA were obtained from the second biopsy of fresh lung tissue using a QAAMP DNA Mini Kit (QIAGEN), 3 cases DNA was extracted from plasma ctDNA using a circulating DNA extraction kit (Shanghai Yunying Medical Technology Co., Ltd.). All samples were tested by an amplification refractory mutation system (ARMS), and mutational analyses were performed at the Department of Molecular Pathology, the Affiliated Cancer Hospital of Zhengzhou University, Henan. The ARMS was implemented using a ADx-ARMS kit (Amoy Diagnostics, Xiamen, China) according to the manufacturer's instructions.

2.3. Treatment

99 patients with uncommon EGFR mutations were enrolled for efficacy analyses, of whom 51 patients received EGFR-TKIs alone, and 48 patients received platinum-based chemotherapy as first-line therapy. In addition, we randomly selected 99 (Fig. 1) patients with common EGFR mutations (19Del/21L858R) in advanced lung adenocarcinoma as a cohort group from the Affiliated Cancer Hospital of Zhengzhou University and started first-line therapy between January 2012, and February 2015. Of whom 50 patients received EGFR-TKIs alone, and 49 patients received platinum-based chemotherapy as first-line therapy. All EGFR-TKIs were first-generation drugs, namely, gefitinib (250 mg qd po), erlotinib (150 mg qd po) and icotinib (125 mg tid po). All patients received at least 4 weeks of EGFR-TKI therapy. All chemotherapy drugs were third-generation drugs that were combined with platinum, namely, pemetrexed (500 mg/m2 d1), Taxol (200 mg/m2 d1), vinorelbine (25 mg/m2 d1, 8), or gemcitabine (1000 mg/m2 d 1, 8). Platinum-based chemotherapy was performed every 3 weeks as a treatment cycle.

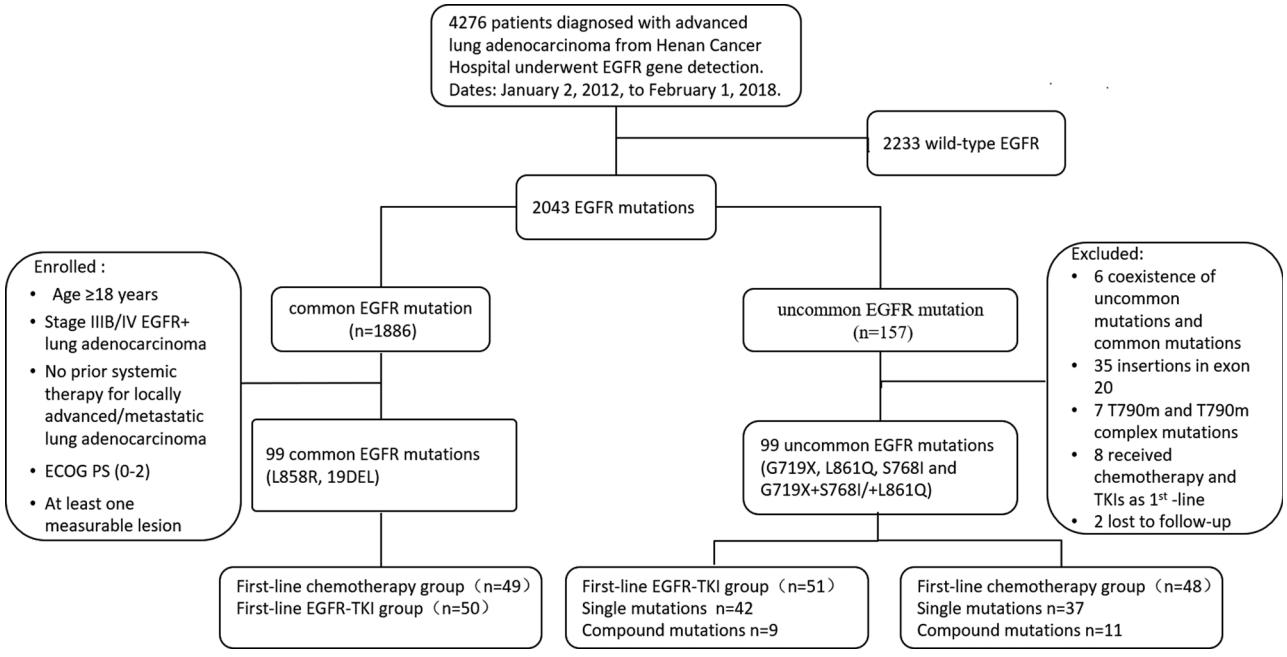

Fig. 1. Flowchart of the study.

2.4. Response evaluation

We performed baseline tumour assessments before the initiation of therapy and then evaluated the response of EGFR-TKI group every 2 months until disease progression. The response of platinum-based chemotherapy treatment was evaluated every 6 weeks until progressive disease or unacceptable toxic effects were identified by chest computed tomography scanning according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. The primary efficacy endpoint was overall survival (OS), as determined by investigator assessment. Secondary objectives included PFS, ORR, and disease control rate (DCR). Subgroup analysis included PFS and OS in patients carrying different uncommon EGFR mutation subtypes. Four types of tumour responses were assessed: partial response (PR), progressive disease, stable disease or complete response (CR). Original protocols were maintained for treatment until disease progression (PD) or unacceptable side effects. Regardless of the study design, patients who could to receive subsequent treatment (chemotherapy or other targeted drugs) after objective disease progression, according to investigator assessment. The duration of OS was defined as the time from the date of the first dose of first-line treatment until the date of death. The follow-up time was considered through October 15, 2018.

2.5. Statistical analysis

Categorical variables were compared using chi-square tests; data with an expected frequency of < 5 were analysed using Fisher's exact test when needed. Univariate survival analyses were plotted by the Kaplan-Meier method and compared using a two-sided log-rank test. A Cox regression model with a backward stepwise procedure was used for univariate and multivariate survival analyses to calculate the hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). A p-value less than 0.05 was considered statistically significant. All analyses were carried out using SPSS software, version 21.0 (SPSS Inc., Chicago), and GraphPad Prism 6.

3. Results

3.1. Characteristics of uncommon EGFR mutation patients

A total of 99 patients with uncommon EGFR mutations were enrolled in the efficacy analyses. The clinical characteristics of the study population are summarized in Table 1. 99 patients samples were obtained from paraffin blocks, including 96 samples from lung tissue, 2 samples from metastatic lymph nodes, and 1 sample from source liver metastases. Uncommon EGFR single mutations were detected in 79 (80.3%) of the tumours, and uncommon EGFR compound mutations were detected in 20 (19.7%). 23 patients underwent secondary biopsy. 1 patients had negative EGFR gene mutations, and 9 patients had T790 M positive mutations, including seven G719X + T790 M and two S768I + T790 M mutations. 1 case of plasma was positive for EGFR-T790 M mutation. The mean treatment time for PFS in the first-line EGFR-TKI treatment group was 8.67 months (median 7.2, range 2.53–28.93), and first-line platinum-based chemotherapy group was 6.46 months (median 4.9, range 1.37–29.53). The mean follow-up time for OS in the targeted treatment group was 15.36 months (median 14.3, range 1.4–39.27), and the chemotherapy group was 19.83 months (median 20.7, range 2.63–43.23).

First-line EGFR-TKI treatment failed in 51 patients, of whom, 38 (74.5%) continued to receive EGFR-TKIs (Including first and third generation TKI) as second-line therapy, 10 (19.6%) patients received platinum-based chemotherapy and 3 (6%) patients with chemotherapy combined with targeted therapy after the disease has progressed. (Table 2). The mean treatment time of PFS 2 in second-line EGFR-TKI treatment was 3.4 months (median 2.8, range 0.3–9.1), and second-line platinum-based chemotherapy was 2.6 months (median 2.4, range 1.1–4.3). Forty-eight patients received platinum-based chemotherapy as a first-line treatment, of whom, 25(52%) added EGFR-TKIs alone (Including first and third generation TKI) as a second-line treatment, 12 (25%) patients received platinum-based chemotherapy and 11 (23%) patients received chemotherapy combined with targeted therapy because of disease progression. (Table 2). The mean treatment time of PFS 2 in second-line EGFR-TKI treatment was 3.5 months (median 3.4, range 0.7–7.6), and second-line platinum-based chemotherapy was 2.6 months (median 2.6, range 0.7–4.2).

Table 1
Characteristics of the 99 patients with uncommon EGFR mutations.

	Uncommon EGFR mutations						
	All		EGFR-TKIs		Chemotherapy		P#
	n = 99	%	n = 51	%	n = 48	%	
Gender							0.171
Female	57	57.6	27	53	31	64.6	
Male	42	42.4	24	47	17	35.4	
Age							0.139
< 60 years	39	39.4	17	33.3	23	47.9	
≥60 years	60	60.6	34	66.7	25	52.1	
Status							0.640
IIIB	24	24.2	21	41.2	22	45.8	
IV	75	75.8	30	58.8	26	54.2	
Smoking history							0.036
Yes	22	22	7	32	15	68	
No	77	78	44	57	33	43	
Extra metastases							0.670
Yes	33	33.3	16	31.4	17	35.4	
No	66	66.7	35	68.6	31	64.4	
ECOG PS							0.880
0–2	91	87.9	48	94	48	100	
3–4	8	12.1	3 6		0 0		
Pathology							–
Adeno	99	100	51	100	48	100	
other	-	-	0 -		0 -		
Mutation subtypes							0.619
Compound mutation	20	19.7	9	17.6	11	22.9	
G719X/S768I			5		8		
G719X/L861Q			4		3		
Single mutation	79	80.3	42	82.4	37	77.1	
G719X			23		9		
S768I			4		15		
L861Q			15		13		

EGFR, epithelial growth factor receptor; TKI, tyrosine kinase inhibitor (gefitinib, erlotinib, icotinib); ECOG, Eastern Cooperative Oncology Group; PS, performance status; Adeno, adenocarcinoma; #, P-value based on the Chi-square test in patients with uncommon EGFR mutations treated with first-line EGFR-TKIs or platinum-based chemotherapy.

3.2. Effect of different therapeutic groups

Tumour responses in different therapeutic groups were listed in Supplemental Table 1. The ORR (33% vs 27.1%, P = 0.499) and DCR (76.5% vs 87.5%, P = 0.194) were similar in patients with uncommon EGFR mutations who received an EGFR-TKI alone or platinum-based chemotherapy as first-line treatment. Similarly, the ORR (31% vs 32%, P = 0.693) and DCR (71.4% vs 84%, P = 0.191) of the uncommon EGFR single-mutation subgroup. Both treatment methods of patients with uncommon EGFR compound mutations had the same DCR of 100%.

The first-line EGFR-TKI treatment showed superior PFS than platinum-based chemotherapy among all patients with uncommon EGFR mutations (median PFS, 7.2 vs 4.9 mts, P = 0.0088). Interestingly, compared with platinum-based chemotherapy, we found that the OS (median, 14.3 vs 20.7 mts, P = 0.0336) was significantly lower in patients treated with EGFR-TKIs (Fig. 2. A and B). The duration of PFS was

Table 2
Subsequent therapies of 99 patients with uncommon EGFR mutations.

Subsequent therapies (n = 99)			EGFR-TKI group n = 51		Chemotherapy group n = 48	
			NO.	%	NO.	%
	EGFR-TKI		51	51.5	–	
		Gefitinib	32	62.7	–	
		Erlotinib	6	11.8	–	
		Icotinib	13	25.5	–	
First-line treatment	Chemotherapy		–		48	48.5
		PP	–		29	60.4
		GP/GC	–		14	29.2
		TC	–		3	6.3
		VP/VC	–		2	4.1
	EGFR-TKI		38	74.5	25	52
		Gefitinib	9	23.7	14	56
		Erlotinib	3	7.9	4	16
		Icotinib	2	5.2	7	28
Second-line treatment		AZD9291/Osimertinib	24	63.2	0	–
	Chemotherapy		10	19.6	12	25
		PP	6	60	7	62
		GP/GC	3	30	5	38
		DC/DP	1	10	0	–
	Chemotherapy + TKI		3	6	11	23
		DC/DP + TKI	2	67	7	64
		GP/GC + TKI	1	33	4	36

PP, Pemetrexed plus cisplatin; GP/GC, Gemcitabine plus cisplatin or carboplatin; TC, Taxol and cisplatin; VP/VC, Vinorelbine plus cisplatin or carboplatin; DC/DP, Docetaxel plus cisplatin or carboplatin; TKI: Gefitinib, Erlotinib, Icotinib, Osimertinib.

significantly longer in the first-line EGFR-TKI group than the platinum-based chemotherapy group among patients with a common EGFR mutations (median, 8.7 vs 3.2 mts, P = 0.0001), but OS was similar in both groups (median, 26.3 vs 18.7 mts, P = 0.0741) (Fig. 2C and D). Moreover, we also found that the PFS (median, 8.7 vs 7.2 mts, P = 0.6538) was similar between patients with uncommon EGFR mutations and common EGFR mutations, but OS (median, 26.3 vs 14.3 mts, P = 0.0005) was significantly lower in uncommon EGFR mutations subgroup of patients who received EGFR-TKIs as first-line therapy (Supplemental Fig. 1.).

The OS was significantly longer in first-line platinum-based chemotherapy group than EGFR-TKI for patients with uncommon EGFR single mutations (median, 12.4 vs 20.3 mts, P = 0.0004), while PFS was similar between the two treatment groups (median, 7.0 vs 4.6 mts, P = 0.1368) (Fig. 3A and D). The PFS of patients who received EGFR-TKIs (median, 9.3 vs 5.3 mts, P = 0.0351) was significantly higher than patients who received platinum-based chemotherapy as first-line therapy, but the OS (median, 31.4 vs 16.8 mts, P = 0.0764) was similar in patients with uncommon EGFR compound mutations (Fig. 3. B and E). The patients who received EGFR-TKIs alone as first-line therapy with uncommon EGFR compound mutations showed similar PFS (median, 7.0 vs 9.3 mts, P = 0.4495) to people with uncommon EGFR single mutations but longer OS (median, 12.4 vs 31.4 mts, P = 0.004) (Fig. 3C and F).

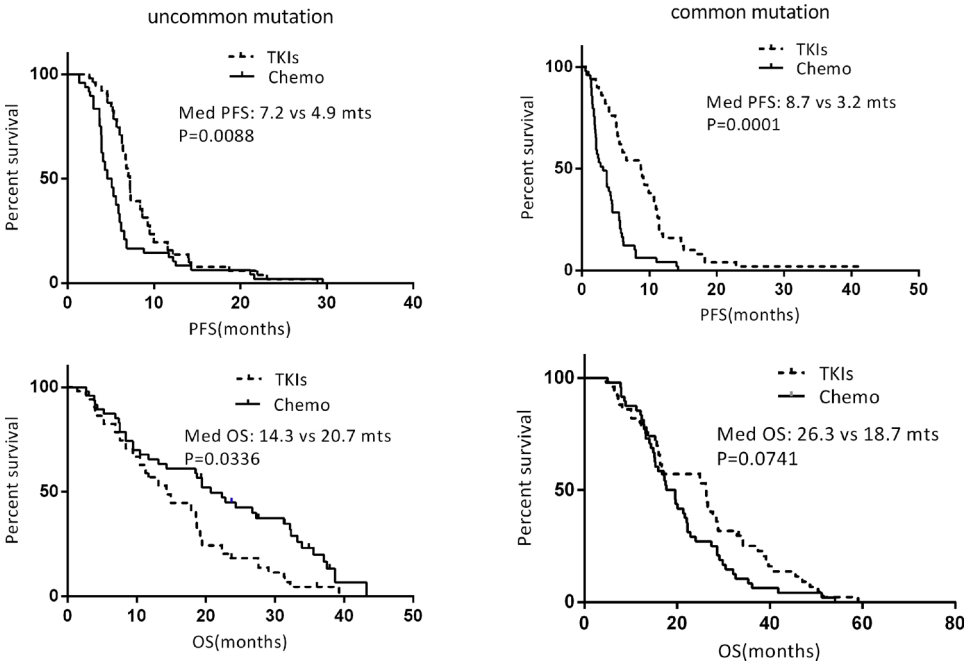

Fig. 2. Kaplan-Meier curves of PFS and OS, all patients in the study. The first-line use of EGFR-TKIs showed better PFS (A), but OS (B) was significantly higher for those patients who accepted platinum-based chemotherapy in advanced lung adenocarcinoma patients with uncommon EGFR mutations. First-line EGFR-TKIs were associated with superior PFS (C), but OS(D) was not significantly different from platinum-based chemotherapy in advanced lung adenocarcinoma patients with common EGFR mutations.

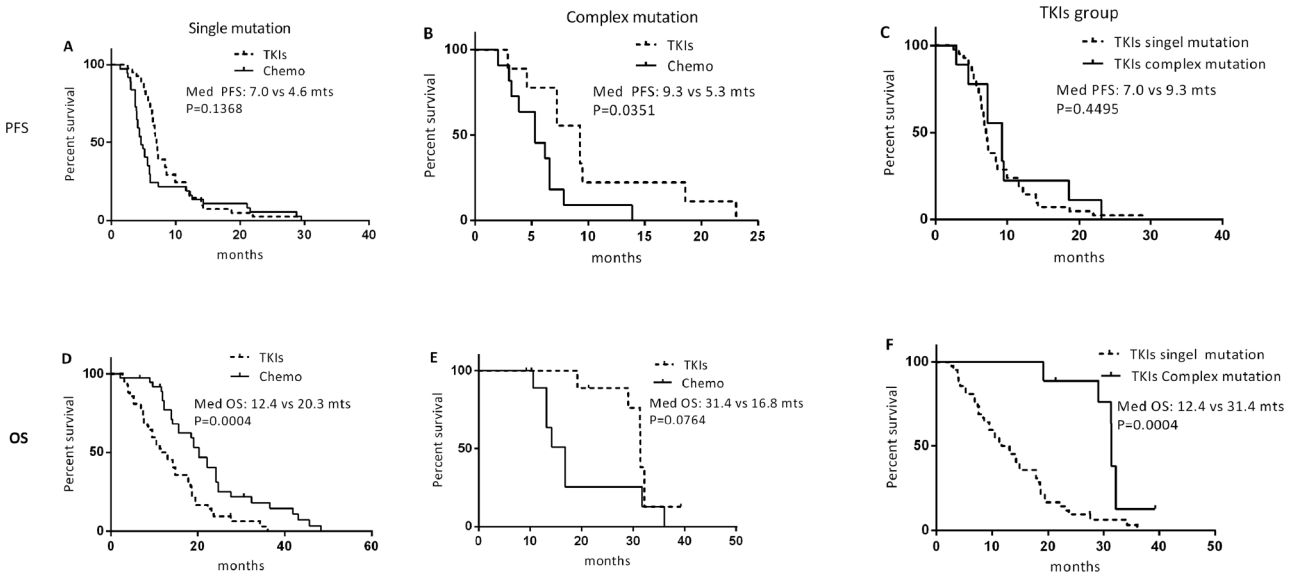

Fig. 3. Kaplan-Meier plots of PFS and OS according to subgroup. Effects of first-line EGFR-TKIs and platinum-based chemotherapy on PFS (A) and OS (D) in patients with uncommon EGFR single mutations. Effects of first-line EGFR-TKIs and platinum-based chemotherapy on PFS (B) and OS (E) in patients with uncommon EGFR complex mutations. The PFS (C) and OS (F) of patients with uncommon EGFR single mutations and uncommon complex mutations treated with first-line EGFR-TKIs.

Second-line TKI treatment showed similar PFS 2 (median, 2.8 vs 2.4 mts, P = 0.2365) than those accepted chemotherapy as second-line treatment in patients with disease progression after first-line EGFR-TKI therapy. Second-line TKI treatment showed longer PFS 2 (median, 3.4 vs 2.6 mts, P = 0.0479) than those accepted chemotherapy as second-line treatment in patients with disease progression after first-line platinum-based chemotherapy therapy. (Supplemental Fig. 2.)

3.3. Cox regression model in tumour survival

In the univariate analysis of 99 patients with uncommon EGFR mutations, smoking history (P = 0.013) and extra metastases (P = 0.001) were identified as predictors for OS. Multivariate analysis showed that patients without extra metastases had significantly better OS than those with extra metastases (HR = 2.240, 95% CI 1.402–3.577, P = 0.001), and OS was significantly longer in non-smokers than those with a history of smoking in Table 3 (HR = 2.048, 95% CI 1.160–3.617, P = 0.013).

3.4. Adverse events

In the EGFR-TKI group, the most commonly adverse events were diarrhea (in 26 patients [51%]), rash (in 15 [29%]), abnormal liver function (in 12 [24%]) and nausea (in 6 [7%]). The most commonly adverse events in the platinum-based chemotherapy were nausea (in 23 [47%]), appetite loss (in 16 [33%]), anemia (in 15 [31%]), and constipation (in 10 [21%]). Mostly patients adverse events of grade 1–2. Adverse events with a maximum grade of 4 were rash in 3 patients (6%) in the EGFR-TKI group, which were given to stop the drug until symptom relief and continued to use TKI until the disease progresses. Unbearable digestive tract reaction adverse events were developed in 1 patient (3%) in the chemotherapy group. The patient refused to receive chemotherapy and adjusted the treatment plan (oral gefitinib) according to the patient's own condition.

4. Discussion

In this study, we found that ORR and PFS were both better in advanced lung adenocarcinoma patients with uncommon EGFR mutations who received EGFR-TKIs alone as first-line therapy than platinum-based chemotherapy. It is worth mentioning that the OS (median, 14.3 vs 20.7 mts, P = 0.0336) of patients who received first-line EGFR-TKI therapy was inferior to those who received platinum-based chemotherapy. The latter group of patients exhibited significant OS benefits, and the risk ratio (RR) was less than 0.50 (P < 0.05). Interestingly, large-scale clinical trials, such as IPASS, NEJ002, and WJTOG3405, that performed head-to-head comparisons of first-line EGFR-TKI therapy versus platinum-based chemotherapy in patients with EGFR-positive NSCLC showed that there was significant differences in PFS between the EGFR-TKI and platinum-based chemotherapy groups but no significant differences in OS. In our study, patients with common EGFR mutations in lung adenocarcinoma who received EGFR-TKIs as the first-

Table 3
Univariate and multivariate analysis of overall survival.

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Gender (female/male)	1.218	0.786-1.887	0.378			
Age (< 60/≥60)	0.858	0.554-1.330	0.494			
Status (IIIB/IV)	1.010	0.619-1.939	0.970			
Smoking (never/smoking)	2.021	1.152-3.543	0.014	2.048	1.160-3.617	0.013*
Metastases (No/Yes)	2.008	1.275-3.163	0.003	2.240	1.402-3.577	0.001*
PS (0–2/ 3–4)	2.088	0.945-4.611	0.069			
Mutation abundance (< 10%/≥10%)	1.105	0.720-1.695	0.648			
Mutation subtypes (Single/Complex)	1.439	0.885-2.339	0.142	1.573	0.941-2.631	0.084

* Significant correlation at the 0.05 level, HR, hazard ratio; 95% CI, 95% confidence interval.

line therapy had longer PFS (P = 0.0001) but similar OS (P = 0.0741) to those who received platinum-based chemotherapy. These findings are consistent with previous reports.

Our results showed OS of patients with uncommon EGFR mutations who received platinum-based chemotherapy as the first-line treatment was significantly longer than patients who received EGFR-TKIs, which may be due to several factors. First, we chose a different subset of subjects than previous studies: All patients included in this study harboured uncommon EGFR mutations in lung adenocarcinoma, 95.4% of patients with a performance status score of PS 0–2 and all were advanced patients with stage IIIB-IV. Baseline characteristics were balanced between study arms. Whereas previous studies primarily focused on patients with common EGFR mutations in advanced NSCLC. Second, after first-line progression, differences in sequential treatment options and toxicity profiles result in differences in OS. TORCH [10] shown that first-line chemotherapy fails of patients with EGFR mutation in advanced NSCLC, second-line TKI is better than first-line TKI followed by second-Line chemotherapy. Isamu Okamoto [11], a Japanese researcher who suggested that patients with EGFR mutation in NSCLC who received first-line chemotherapy added to TKI as second-line treatment had a survival that did not inferior to second-line chemotherapy after failure of first-line EGFR-TKI. This is consistent with our findings that we found that second-line TKI showed a longer PFS 2 (median, 3.4 vs 2.6 mts, P = 0.0479) than second-line chemotherapy followed at progression by first-line chemotherapy. (Supplementary Fig. 2.). Studies [10,12] shown that second-line TKI was superior to second-line chemotherapy in terms of safety and improving the quality of life of patients, with fewer adverse reactions and better tolerance. Therefore, we believe that those patients received platinum-based chemotherapy as first-line treatment, after disease progression who received TKI as second-line treatment, OS was relatively elongated. Finally, TKI alone may not be beneficial than combined chemotherapy to OS of patients with uncommon EGFR mutations according to our data. After the first-line EGFR-TKI treatment failed, 38 patients received other EGFR-TKIs as the second-line treatment. Sixteen (42%) patients continued to receive targeted therapy as a follow-up treatment due to poor physical condition. Unfortunately, we did not get a three-line PFS until patients died. Among them, 6 patients changed their treatment plans. Those patients receiving 1 st generation EGFR-TKI as first-line therapy may depress overall OS compared with first-line platinum-based chemotherapy. Studies [13,14] shown that EGFR-TKI combined with chemotherapy significantly improved PFS and OS than TKI alone for patients with EGFR mutation in advanced NSCLC. Therefore, we believe that chemotherapy should be considered an important part of treatment for patients with uncommon EGFR mutations in lung adenocarcinoma.

The main highlight of our study is that we are the first to compare the OS in advanced lung adenocarcinoma patients with uncommon EGFR mutations who received 1 st generation EGFR-TKIs with chemotherapy as first-line treatment, and collected the data of subsequent therapies for those patients in disease progression after first-line treatment in real world. Our finding (median PFS, 7.2 vs 4.9 mts, P = 0.0088, ORR 31% vs 32%) is about in line with those of Caicun Zhou [15], who reported that PFS (median 7.1 vs 6.1 mts, p = 0.893) and the ORR (32.3% vs 27.5%) in NSCLC patients were similar between those with uncommon EGFR mutations who received EGFR-TKIs and platinum-based chemotherapy as first-line treatments, and we filled in their gaps in OS (median OS: 14.3 vs 20.7 mts, P = 0.0336). Zhou proposed that both EGFR-TKIs and platinum-based chemotherapy should be equally considered as first-line therapy for patients harbouring uncommon EGFR mutations. In addition, J.Y. Wu [16] reported that 62 patients with uncommon EGFR mutations who received first-line EGFR-TKI treatment had a PFS of 6 months, an OS of 15.7 months, and an ORR of 57.1%, consistent with our findings. Similarly, the outcomes of platinum-based chemotherapy (median PFS, 4.9 months, median OS, 20.7 months, ORR 27.1%, DCR 87.5%) as first-line therapy were broadly in line with those reported by Arrieta [17], who suggested that patients with uncommon EGFR mutations who received first-line platinum-based chemotherapy had a median PFS and OS of 3.9 months and 17.4 months, respectively. They claimed that EGFR-TKIs could be used as a second- or third-line therapy for patients with uncommon EGFR mutations, while platinum-based chemotherapy should be received as a first-line treatment. It is also consistent with Caicun Zhou [15], who advocated that people with uncommon EGFR mutations received platinum-based chemotherapy as first-line treatment had a median PFS of 6.1 months, an ORR of 23.3%, and a DCR of 82.5%. In a prospective study [18], Yang et al. indicated that advanced (stage III-IV) NSCLC patients (of all 25 cases) with uncommon EGFR mutations who received platinum-based chemotherapy as first-line therapy had a median OS (30.2 mts vs 19.4 mts) was significantly higher than patients received EFGR-TKIs as first-line treatment, which is consistent with our findings. The differences in us is that this study included patients were mainly Asian and Caucasians and second-generation EGFR-TKI, afatinib, was used.

Our results suggest that patients with uncommon EGFR mutations are also sensitive to EGFR-TKIs. In this study, first-line EGFR-TKI treatment group is consisted of 23(55%) with G719X mutations, 15(36%) with L861Q mutations, and 4 (9%) with S768I mutations. Preclinical studies [19–21] have found that uncommon EGFR mutations, such as G719X and L861Q, were sensitive to EGFR-TKIs. Several clinical [9,16,22] studies have shown that those median PFS can reach 7.7 months in advanced NSCLC patients with uncommon EGFR mutations receive EGFR-TKIs alone as first-line therapy. Consistent with these results, our study showed that median PFS of such patients who received EGFR-TKIs as first-line treatment was higher than patients received platinum-based chemotherapy (median, 7.2 vs. 4.9 mts P = 0.0088). Whether it is uncommon EGFR mutations or common EGFR mutations, we found that those patients received EGFR-TKIs as first-line therapy, there was no significant difference in PFS (median, 8.7 vs. 7.2 mts P = 0.6538). In spite of previous studies [9,23] have shown that patients with uncommon EGFR mutations (G719X and L861Q) may be less sensitive to EGFR-TKIs than people with common mutations (L858R, 19Del), we did not get similar results. We observed that OS (20.7 mts) of patients with uncommon EGFR mutations received platinum-based chemotherapy as first-line treatment was about to catch up with the OS (26.3 mts) of the current standard treatment regimen for sensitive EGFR mutations in NSCLC patients who receive EGFR-TKIs as first-line therapy. This supports our view that first-line platinum-based chemotherapy favours clinical benefits in OS in patients with uncommon EGFR mutations.

In the subgroup analysis, we found that patients in uncommon EGFR compound mutations group and uncommon EGFR single-mutation group who received EGFR-TKIs alone as the first-line therapy had the ORRs of 44% and 31% and the DCRs of 100% and 71.4%, respectively. The PFS of uncommon EGFR compound mutations group was slightly higher than that of uncommon EGFR single-mutation group, with no statistically significant difference (median 9.3 and 7.0 mts, P = 0.4495), OS of uncommon EGFR compound mutations group was significantly higher than people of uncommon EGFR single mutation group (median 31.4 versus 12.4 mts, P = 0.001). This is consistent with a study from Taiwan [9], which showed that PFS of uncommon EGFR compound mutation group was significantly higher than uncommon EGFR single-mutant group (median, 11.9 vs 6.5 mts, P = 0.010) among patients who received EGFR-TKIs alone as first-line therapy. In contrast to the study by Caicui Zhou [15], showed that the median PFS was only 4.2 months in people who with uncommon EGFR compound mutation received EGFR-TKIs as first-line therapy. The difference may be caused by that patients with 20 in. mutations, T790 M mutations or the coexistence of both common and uncommon EGFR mutations were excluded from our study.

We found that both PFS (median PFS, 9.3 vs 5.3 mts, P = 0.0351) and OS (median OS, 31.4 vs 16.8 mts, P = 0.0764) were significantly

higher in patients with uncommon EGFR compound mutations who received EGFR-TKIs as first-line therapy than people received platinum-based chemotherapy. Due to low incidence of uncommon EGFR compound mutations, our sample size was limited. Therefore, although there was no statistically significant difference in OS between two groups, we still considered EGFR-TKI treatment to be a better choice than chemotherapy in those patients. Unlike the uncommon EGFR compound mutations group, patients with uncommon EGFR single-mutation received first-line platinum-based chemotherapy had a significantly higher OS than EGRF-TKI treatment (P = 0.0004), and there is no difference in PFS between the two treatment regimens (P = 0.1368). For those patients, we believe that early intervention with chemotherapy is more beneficial for prognosis.

Multivariate analysis showed smoking history and extra metastases were independent influencing factors of OS. Surprisingly, we found that older age was a protective factor for OS (HR = 0.858, 95% CI 0.554–1.330, P = 0.494). On the one hand, we consider that it may be related to tumor heterogeneity, and younger patients have faster tumor progression. On the other hand, we believe that better efficacy and tolerability of side effects for EGFR-TKI to extend the life of older people. Certainly, this requires more theoretical research support in the future.

There are several limitations in our study. First, retrospective nature of this study inevitably caused a statistical bias. Second, the second biopsy is a traumatic examination, high risk, and tumor tissue is heterogeneous, which cannot represent the gene mutation status of tumor throughout all the time. So, feasibility of second biopsy is not high in actual clinical practice. Extraction of plasma ctDNA samples is highly feasible as a secondary gene test, but accuracy and sensitivity are lower than tissue biopsy, and is limited by economic conditions. Therefore, the number of matching samples is small. Third, Incidence of uncommon EGFR mutations is very low, there are few related reports, leading to a small sample size. Last, in recent years, it has been demonstrated [18] that the second-generation EGFR-TKI afatinib is more clinically beneficial for uncommon EGFR mutations. The activity of afatinib was superior to first-generation EGFR-TKIs as first-line treatment for patients with uncommon EGFR mutations, especially for patients with uncommon EGFR mutations of Gly719Xaa, Leu861Gln and Ser768Ile. However, considering the effectiveness and intolerable side effects of afatinib in patients with uncommon EGFR mutations treated in real clinical settings remains unclear, and treatment of uncommon EGFR mutations with afatinib was not authorized during the study period, and few patients use afatinib, we did not collect these data.

In conclusion, this study demonstrated that extra metastases (HR = 2.240, P = 0.001) and smoking history (HR = 2.048, P = 0.013) were independent prognostic factors for OS in lung adenocarcinoma patients with uncommon EGFR mutations. First-line chemotherapy have a better OS than EGFR-TKI therapy for those people, this conclusion still requires confirmation in a large-scale study. In the era of accurate treatment approaches using various targeted drugs, chemotherapy is still an irreplaceable treatment, even in lung adenocarcinoma patients with EGFR mutations.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent was obtained from all individual participants included in the study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.02.001.

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