Randomized phase II study of erlotinib as first-line or second-line therapy for EGFR mutation-positive advanced lung adenocarcinoma patients.

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Abstract

Epidermal Growth Factor Receptor (EGFR) mutation in patients with Non-Small Cell Lung Cancer (NSCLC) in Asian population could benefit in survival to Tyrosine Kinase Inhibitor (TKI) treatment. Standard chemotherapy was the mainstay for advanced NSCLC. In this randomized, single center, phase 2 studies, we investigated erlotinib as first-line therapy plus docetaxel and cisplatin as second-line therapy compared to docetaxel and cisplatin as first-line therapy plus erlotinib as second-line therapy in treat naïve patients with advanced lung adenocarcinoma. 81 patients were randomized to receive erlotinib+chemotherapy (E+C group, n=43) and chemotherapy+erlotinib (C+E group, n=38). The primary objective was Overall Survival (OS) and secondary objective was objective response rate. The data showed the median OS in E+C group and C+E group were 23.7 months and 24.2 months, respectively (p=0.652). The objective response rate differed in the two groups (p<0.001). Our results indicated that sequential usage of erlotinib plus chemotherapy and chemotherapy plus erlotinib did not showed difference in OS.

Introduction

Lung cancer is the most commonly diagnosed cancer type and the leading cause of cancer-related deaths around the world [1]. Non-Small Cell Lung Cancer (NSCLC) accounts for the majority of lung cancers. Lung adenocarcinoma is a subtype of NSCLC and is often the main subject to Tyrosine Kinase Inhibitor (TKI) treatment of the Epidermal Growth Factor Receptor (EGFR) [2]. Several FDA-approved TKIs including Gefitinib, Erlotinib and Afatinib showed inspiring effects to patients with NSCLC and were recommended as the first-line or second-line treatment [3-8]. Patients with EGFR mutations are usually highly sensitive to EGFR Tyrosine Kinase Inhibitor (EGFR-TKI) therapy [9-13]. Sensitizing EGFR mutations were found in about 10% of Caucasian NSCLC patients, however, this proportion was up to about 50% in Asian population [14]. Therefore, Asian population with EGFR exon 19 deletions or exon 21 L858R mutations could benefit most from EGFR-TKIs theoretically.

Accumulating evidence has shown erlotinib could prolong the survival time of mutation-positive NSCLC [9,12,15,16], however, these studies did not investigated the comparison of sequential usage of TKI and standard chemotherapy. In the current randomized, phase II study, we explored the treatment regimen of erlotinib as first-line therapy plus docetaxel and cisplatin as second-line therapy compared to docetaxel and cisplatin as first-line therapy plus erlotinib as second-line

therapy in treatment of naïve EGFR mutation-positive lung adenocarcinoma patients with stage III or IV.

Materials and Methods

Eligibility

Patients with stages III-IV (AJCC 6th edition) lung adenocarcinoma who did not receive any treatment were considered for enrolment. Patients also had to be aged >18 years; have an Eastern Cooperative Oncology Group (ECOG) performance Status (PS) of 0-2; have measurable disease by the Response Evaluation Criteria (RECIST; version 1.1); have expected life expectancy of more than 12 weeks and have adequate organ function.

The exclusion criteria included previous treatment for NSCLC; patients with wild-type EGFR; HIV infection; with component of small cell lung cancer; pregnancy; had a myocardial infarction within 6 months. This trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

The Ethics Committees of the Chinese PLA General Hospital reviewed and approved the trial protocol. The trail was registered in www.clinicaltrials.gov (NCT01131429).

Study design and treatment

This was a randomized, single center; phase 2 study erlotinib as first-line therapy plus docetaxel and cisplatin as second-line therapy compared to docetaxel and cisplatin as first-line therapy plus erlotinib as second-line therapy in treat naïve patients with advanced lung adenocarcinoma. Eligible patients were randomized before induction therapy in a 1:1 ratio to receive treatment (Figure 1).

Treatment

Patients in the Erlotinib+chemotherapy (E+C) group received 150 mg of erlotinib daily (ROCHE) until disease progression. Then chemotherapy (docetaxel, 75 mg/m^2 i.v. combined cisplatin, 75 mg/m^2 i.v.) up to six cycles were administered. Patients in the chemotherapy+Erlotinib (C+E) group received chemotherapy (docetaxel, 75 mg/m^2 i.v. combined cisplatin, 75 mg/m^2 i.v.) up to six cycles and 150 mg of erlotinib daily (ROCHE) until disease progression.

Assessments

The primary objective was to assess OS in patients in each group. Secondary objectives included the radiographic objective response rate (ORR; evaluated every 2 cycles) according to RECIST (version 1.1).

Statistical analysis

The primary cut-off date for OS data was May 2015. OS were estimated by the Kaplan-Meier method. The difference between the two groups was assessed by means of log-rank tests. Chi-square tests were used to compare categorical data. The probability of OS was estimated using the Kaplan-Meier method, and survival curves were compared using a log-rank test. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) were calculated using a Cox proportional hazards analysis. Two-sided P values of<0.05 were considered as statistically significant.

All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA).

## Results

Patient characteristics

A total of 81 patients were randomized to receive either erlotinib and chemotherapy (43 patients) or chemotherapy and erlotinib (38 patients) at Chinese PLA General Hospital (Figure 1). The median follow-up was 11.7 months. The baseline characteristics including age, sex, ECOG PS, smoking history and EGFR mutations were well balanced between the two treatment arms (Table 1).

Efficacy

In the ITT population, the median OS in E+C group and C+E group were 23.7 months and 24.2 months, respectively. The

difference did not reach statistical significance (p=0.652) (Figure 2). The objective response rate after first or second line treatment evaluated by RECIST (version 1.1) was demonstrated in Table 2. In the E+C group, after erlotinib as first-line treatment, 55.8% of the patients had PR and 44.2% of the patients had SD, and after chemotherapy as second-line therapy, 17.9% of the patients had PR, 76.9% of the patients had SD and 5.1% of the patients had others.

In the C+E group, after chemotherapy as first-line therapy, 10.5% of the patients had PR, 57.9% of the patients had SD, 7.9% of the patients had PD and 23.7% of the patients had others and after erlotinib as second-line therapy, 63.3% of the patients had PR and 36.7% of the patients had SD.
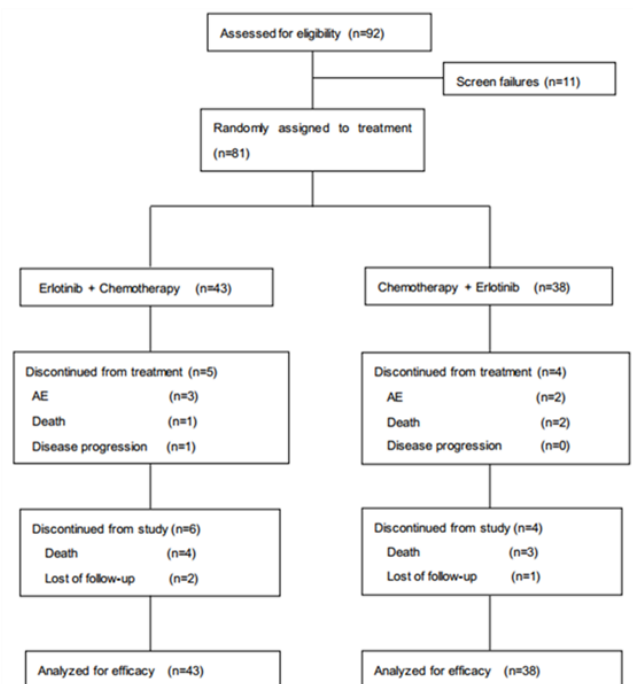
Figure 1. *Patient flow diagram. Forty-three patients in Erlotinib +chemotherapy (E+C) group received 150 mg of erlotinib daily (ROCHE) until disease progression. Then chemotherapy (docetaxel, 75 mg/m^2 i.v. combined cisplatin, 75 mg/m^2 i.v.) up to six cycles were administered. Thirty-eight patients in the chemotherapy+Erlotinib (C +E) group received chemotherapy (docetaxel, 75 mg/m^2 i.v. combined cisplatin, 75 mg/m^2 i.v.) up to six cycles and 150 mg of erlotinib daily (ROCHE) until disease progression.*

Table 1. *Baseline patient characteristics in both treatment groups.*

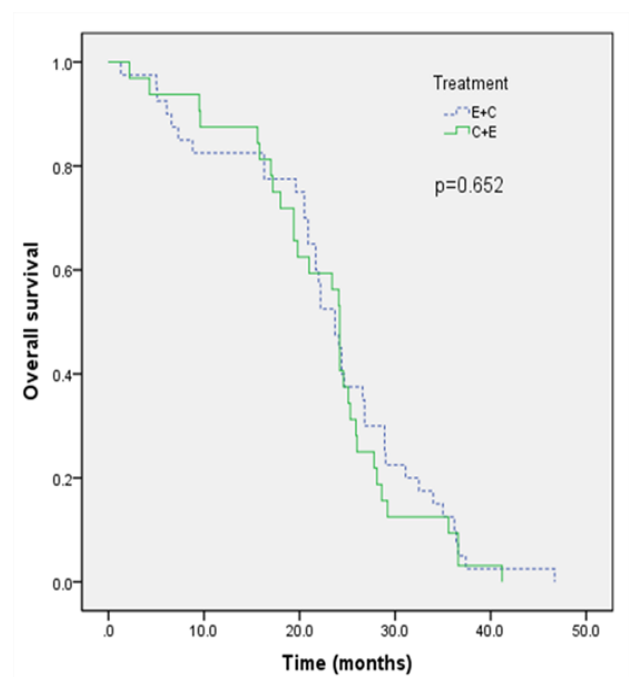| Characteristics	Erlotinib+ Chemotherapy (n=43)		Chemotherapy+ Erlotinib (n=38)	
	No.	%	No.	%
Gender				
Male	9	20.9	14	36.8
Female	34	79.1	24	63.2
Age, years				
Median	59		57	

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Range	35-78		34-75	
Smoking status				
Never smoker	38	88.4	30	78.9
Smoker	5	11.6	8	21.1
Family history of cancer				
No	31	72.1	26	68.4
Yes	12	27.9	12	31.6
Adenocarcinoma stage				
IIIB	1	2.3	2	5.3
IV	42	97.7	36	94.7
ECOG PS				
0	0	0	0	0
1	35	81.4	33	86.8
2	8	18.6	5	13.2
Differentiation				
Well	4	9.3	2	5.3
Moderate	6	14	10	26.3
Poor	11	25.6	16	42.1
Unknown	22	51.1	10	26.3
EGFR mutation				
Exon 19 deletion	24	55.8	23	60.5
Exon 21 L858R mutation	19	44.2	15	39.5

Table 2. Objective response rate for each treatment group.

Variable	Erlotinib + Chemotherapy (n=43)		Chemotherapy + Erlotinib (n=38)		P value
	No.	%	No.	%	
After 1st line treatment					
CR	0	0	0	0	
PR	24	55.8	4	10.5	
SD	19	44.2	22	57.9	<0.001
PD	0	0	3	7.9	
Others	0	0	9	23.7	
After 2nd line treatment	n=39		n=30		
CR	0	0	0	0	
PR	7	17.9	19	63.3	
SD	30	76.9	11	36.7	<0.001
PD	0	0	0	0	
Others	2	5.1	0	0	

Figure 2. Kaplan-Meier plot of overall survival. Green line represents the chemotherapy+Erlotinib (C+E) group and blue line represents Erlotinib+chemotherapy (E+C) group. P for Kaplan-Meier survival analysis was 0.652.

Discussion

EGFR mutation was an important biomarker in NSCLC with regard to responsiveness to EGFR TKIs [12,13,15-20]. To our knowledge, the current study was the first study to prospectively investigate erlotinib as first-line combined stand chemotherapy as second-line therapy versus chemotherapy as first-line therapy combined erlotinib as second-line therapy in Chinese population. Our results demonstrated that the two treatment regimen did not differ in OS (p=0.652). The objective response rate analyses showed that PR rate was higher in E+C group after first-line treatment, whereas, PR rate was higher in C+E group after second-line treatment. These data further confirm that the erlotinib regimen would be suitable for Asian patients with EGFR mutation.

Recently, ENSURE study investigated first-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer patients. Their results showed first-line erlotinib provides a statistically significant improvement in PFS versus GP [21]. The PFS benefit of erlotinib in EGFR mutation-positive patients was confirmed by OPTIMAL trail [22]. Our study did not investigated PFS as a monitored parameter because the patients recruited had III or IV disease. Notably, in ENSURE study, the data showed that OS was not significantly different between the two arms, which were in line with our results. Our data showed the objective response rate differed between the two treatment groups, which was possible due to the different treatment sequence.

There were several limitations in our study. First, the sample size was relatively small, which was due to limited resources and a difficult search for grant support. Second, the uses of the more traditional cisplatin/docetaxel regimen as a comparator instead of more novel combinations such as cisplatin/ pemetrexed are still needed.

In conclusion, the results of our study showed the sequential usage of erlotinib as first-line therapy plus docetaxel and cisplatin as second-line therapy compared to docetaxel and cisplatin as first-line therapy plus erlotinib as second-line therapy in treat naive patients with advanced lung adenocarcinoma did not show prolonged OS. In addition, the objective response rate varied between the two groups.

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Disclosure of Conflict of Interest

None.

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