Original Article

A Phase II Trial of Gefitinib as Maintenance Therapy after First-Line Chemotherapy for Advanced Non-Small Cell Lung Cancer in China

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ABSTRACT

Objective: To investigate the efficacy and safety of gefitinib as maintenance therapy for advanced non-small cell lung cancer (NSCLC) patients who obtained disease control (DC) after first-line chemotherapy in Chinese population.

Methods: Chinese patients with advanced NSCLC treated with standard chemotherapy and obtained DC were assigned to receive gefitinib as maintenance treatment. The primary end point was overall survival time (OS), the second end point was disease control rate (DCR) and progression-free survival time (PFS). DCR included complete response (CR) plus partial response (PR) and plus stable disease (SD). The impact of epidermal growth factor receptor (EGFR) mutation status on the treatment as exploratory point was also evaluated by denaturing high-performance liquid chromatography (DHPLC).

Results: Among 75 enrolled patients, the overall response rate was 37% and the DCR (CR + PR +SD) was 66%. The median PFS and OS were 17.13 months and 26.13 months respectively, with 1- and 2-year survival rates 89.3% and 34.7%. Patients harboring somatic EGFR mutations obtained a prolonged median PFS and OS compared with EGFR wide type (25.1 vs. 13.0 months, P=0.019 and 33.37 vs. 25.57 months, P=0.014, respectively). In COX regression model, only EGFR mutation status was the independently factor influencing both PFS and OS (P=0.029 and 0.017, respectively), however, rash status was the predictor in terms of PFS (P=0.027).

Conclusion: Gefitinib produced encouraging survival when delivered as maintenance therapy in Chinese patients obtaining DC after first-line chemotherapy, especially for patients carrying somatic EGFR mutations. EGFR mutation is an independently predictive factor of survival.

Key words: Gefitinib; Maintenance therapy; Non-small cell lung cancer

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% burden of lung cancer which is the leading cause of cancer-related death in the world[1]. The current treatment strategy for advanced NSCLC includes first-line chemotherapy using a platinum- based regimen, with the addition of the targeted agent bevacizumab for certain patients[2]. A number of chemotherapeutic agents, including gemcitabine, docetaxel, and paclitaxel, are active in first-line treatment as part of a platinum-based combination[3, 4]. Despite slight improvement in the survival rate, the effects reach

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a plateau impeding further efficacy. Recently, maintenance therapy as a novel strategy has drawn extensive attention. However, whether this kind of therapy could improve survival remained controversial.

Theoretically, patients who have obtained objective response or disease stabilization following initial chemotherapy would have a reduced tumor burden or reduced tumor growth. These tumors may benefit from early use of non-cross-resistance agents[5, 6]. A stimulating outcome currently reported by Ciuleanu et al.[7] seemed to verify the aforementioned theory and showed that pemetrexed as maintenance therapy provided survival improvement in selective patients with adenocarcinoma which also suggests that appropriate agents for appropriate patients may be a key factor for progression towards controlling cancer. With better understanding and exploitation of cancer biology, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) have been developed as validated targeted anticancer agents and approved for clinical use. Gefitinib and erlotinib are the representive agents both of which have demonstrated identical efficacy and lower toxicity compared with cellular toxicity agents and therefore have been used in clinical extensively[8–10]. Based on these theoretical and clinical evidences, we assumed that EGFR-TKI could provide further survival benefit as a maintenance treatment.

The aim of the present phase II trial we designed was to assess the efficacy and safety profiles of gefitinib as maintenance therapy for patients having achieved at least tumor stabilization after first-line chemotherapy. Additionally, an exploratory end point was to investigate the correlation of survival with EGFR mutation status.

PATIENTS AND METHODS

Trial Design

The trial is an open-label single-arm study of gefitinib delivered immediately as maintenance therapy in patients with advanced (inoperable stage III B or IV) NSCLC who obtained DC after standard first-line chemotherapy. Patients enrolled in the trial received gefitinib at least one month, and the tumor tissue samples were obtained immediately before starting gefitinib through core needle biopsy, bronchoscopic biopsy or surgical resection.

All patients provided written informed consent. The study was conducted in line with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, and applicable regulatory requirements.

Patients

Patients were eligible if they met the following criteria: more than 18 years; histologically or cytologically confirmed, unresectable, stage III B/IV NSCLC; Eastern Cooperative Oncology Group performance (ECOG) status 0–2; at least 2 courses of prior standard first-line chemotherapy, no longer than 2 m between the last chemotherapy and the initial dose of gefitinib; full recovery from toxicities due to prior therapy; adequate hematological, renal, and hepatic function; life expectancy longer than 3 m; negative pregnancy test for women of child-bearing potential.

Notable exclusion criteria were: evidence of unstable systemic disease; prior treatment with anti-EGFR agents; previous malignancies (last 5 years, other than successful treatment for cervical carcinoma/skin cancer); untreated brain metastases or spinal cord compression; significant ophthalmologic abnormalities (e.g., severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren syndrome, severe exposure keratitis).

Treatment Plan

All patients received standard first-line chemotherapy including platinum-based doublet regimens (cis/carboplatin plus gemcitabine, taxane or novelbine respectively). Total cycles number was no more than 6 cycles. Patients were then switched to receive gefitinib 250 mg orally per day if they completed 4–6 cycles of chemotherapy or underwent unacceptable chemotherapy associated toxicity. Gefitinib treatment continued until intolerable toxicity, disease progression or death, or withdrawal. Dose interruption/reduction was permitted for treatment-related adverse events.

Clinical Assessments

Tumor response was assessed using Response Evaluation Criteria in Solid Tumors, at least every 6 w during the period of chemotherapy and no more than 3 m in the gefitinib treatment phase. Responses were confirmed after 4 w. Overall survival (OS) and progression-free survival (PFS) were calculated from the date of starting first-line chemotherapy to the date of death/date of disease

progression or death, respectively. Clinical assessments were at baseline and then every 4 w.

The assessments of adverse events were recorded according to National Cancer Institute Common Toxicity Criteria3.0 (NCI-CTC3.0).

EGFR Mutation Detection

Paraffin-embedded tumor material was cut into 4 μm thick sections and placed onto glass slides, stained with H & E, and the presence of tumor was verified by a pathologist. Detailed methods were described in our prior paper[11].

Statistical Analysis

The primary endpoint of this study was OS. Previous prospective trials showed 1-year survival rate was 20%–46% (mean: 33%) in patients receiving chemotherapy with third generation agents (Gemicitabine, Paclitaxel, Docetaxel) in combination with platinum[3]. Based on the historical control benchmark, a relative improvement of 30% in 1-year survival rate for the patients receiving gefitinib as maintenance therapy after gained DC under front-line chemotherapy was considered sufficient evidence to move a regimen into a phase III study. So, 57 assessable patients were planed to be enrolled in our trial. Considering the difficult of obtaining sufficient tissue samples and censored cases, a planed assignment of more than 70 patients to our treatment regimen would provide a 90% statistical power to find an improvement of 30% in 1-year survival rate, with P=0.05 (two-sided) as significance level.

Survival analysis was conducted on all 75 patients, and there were 62 for whom EGFR mutation analysis could be successfully performed. The difference in mutation rate among groups categorized by smoking exposure was examined with χ^2 test.

The PFS and OS curves were plotted using the Kaplan-Meier method and survival curve comparisons were conducted with the log-rank test. Multivariate analysis of the impact of the factors, including EGFR mutation status and clinical characteristics were conducted using the Cox regression model. All analysis was determined to be statistically significant where the P-value was < 0.05. For statistical analyses, we used SPSS software for PC (version 13.0 for windows).

RESULTS

Patient Characteristics

The intent-to-treat population (n=75) comprised all registered patients from November 1, 2005 to April 1, 2009 with histologically or cytologically confirmed advanced NSCLC from two Chinese cancer center including Beijing Cancer Hospital and the Third Hospital of Peking University who received 250 mg/day gefitinib orally as maintenance treatment after disease controlled first-line chemotherapy. Table 1 summarizes the demographic and baseline clinical/tumor characteristics. The majority of the patients had performance status (PS) score of 0 or 1 and high percentage of patients had the characteristic of female, never smoking or adenocarcinoma compared to the opposite state. Thirty-one patients (41%) failed to complete 3 or more cycles of initial chemotherapy mainly due to intolerable toxicities or subjective refuse. At the date of April 1, 2009, 20 patients (27%) were still continuing gefitinib treatment and 43 patients (57%) had recorded death. The reasons of death were lung cancer-related with the exception of acute myocardial infarction for only 1 patient. The median interval of follow-up was 23.0 m (6.5–45.7 m).

Tolerability

Integrated safety data were collected during the gefitinib phase in all patients summarized in Table 2. The most common toxicities were skin rash and diarrhea, and most of the patients just experienced Grade 1/2 toxicities which relived gradually in the treatment period across the two groups. Grade 3/4 skin rash or diarrhea was observed in 4 patients (6%) and only 1 patient (2%) developed grade 3 hepatic damage, who restarted gefitinib treatment after recovery because of heap-protected medicine. No patients experienced pneumonitis, fibrosis, hematologic toxicities or any other grade 3 and 4 nonhematologic toxicities such as fatigue and nausea/vomiting in the present population. There was no gefitinib- related death.

Efficacy

Clinical information was not available for all patients. Tumor response was available for 73 of 75 patients (both no data). The overall response rate was 37% (27 of 73); 1 CR and 26 PRs. Twenty-nine percent (21 of 73) had SD. The disease control rate (CR + PR +SD) was 66%. Survival data were available for entire enrolled patients. Median PFS was 17.13 months [95% confidence interval (95%CI), 14.74–19.53]. Median OS was 26.13

months (95%CI, 22.77–29.49), 1 and 2-year survival rates were 89.3% and 34.7%, respectively (Figure 1A and 1B).

Correlations of Clinical Characteristics/EGFR Mutation Status with Survival

Histological samples were available from 62 patients for EGFR-mutation detection which showed EGFR mutations in 27 patients (44%) and wild type in 35 patients (56%). EGFR mutation rate seemed to be high in females, never-smokers and patients with adenocarcinoma or rash, but there was no significant statistical difference (Table 3).

Kaplan-Meier method indicated significantly longer median PFS only in patients harboring EGFR mutations (P=0.019). Moreover, patients who obtained tumor response (CR+PR) or carried EGFR mutation or underwent rash tended to improve the median OS significantly (Table 1, Figure 2A and 2B). Sequentially, multivariate analysis was conducted to identify factors contributing to survival. When all patients were analyzed considering of the clinical characteristics

Table 1. Demographics and relationship between clinical variables and survivals in all eligible patients

	No. of patients (%)	Median PFS	(95%CI)	P value*	Median OS	(95%CI)	P value*
All	75	17.13	(14.74–19.53)		26.13	(22.77–29.49)	
Gender				0.968			0.573
Male	27 (36)	16.73	12.42–21.04		24.40	22.86–29.94	
Female	48 (64)	17.27	14.50–20.03		24.33	18.43–30.23	
Age (median: 59 y)				0.755			0.534
≤ 65	40 (53)	15.37	9.77–20.97		26.13	20.12–32.15	
> 65	35 (47)	17.13	14.38–19.89		25.60	18.81–32.39	
ECOG PS				0.169			0.079
0–1	60 (80)	17.27	12.61–21.93		26.33	19.88–32.79	
2	15 (20)	16.73	9.65–23.81		22.20	17.62–26.78	
Smoke exposure				0.188			0.289
Never	63 (84)	17.50	14.87–20.13		26.33	22.67–30.00	
Ever	12 (16)	12.60	7.27–17.93		21.40	14.05–28.75	
Histology				0.829			0.946
Adenocarcinoma	62 (83)	17.13	14.40–19.87		26.13	23.04–29.23	
Others	13 (17)	16.73	12.34–21.13		26.20	18.36–28.66	
Prior chemotherapy cycle numbers				0.147			0.653
1–2	31 (41)	15.37	11.87–18.86		26.33	17.45–35.21	
3–6	44 (59)	17.50	9.70–25.30		25.60	23.18–28.02	
First-line response				0.254			0.018
CR plus PR	35 (47)	20.23	15.52–24.95		32.00	22.22–41.78	
SD	40 (53)	15.37	10.46–20.28		24.03	17.02–31.05	
Rash (n=66)				0.493			0.002
Never	30 (45)	14.23	7.99–20.47		19.77	17.68–21.85	
Ever	36 (55)	18.30	12.63–23.97		32.00	26.01–38.00	
EGFR gene status (n=62)				0.019			0.014
Wide type	27 (44)	13.00	8.61–17.39		25.57	21.26–29.88	
Mutation positive	35 (56)	25.10	17.21–32.99		33.37	28.75–37.99	
Exon 19 deletion	19 (54)	22.67	15.95–29.38		32.20	14.46–45.94	
Exon 21 (L858R)	10 (29)	33.67	14.47–52.86		40.43	22.64–58.23	
Double positive mutation	6 (17)	27.40	12.23–42.57		36.20	17.47–54.93	

ECOG: Eastern Clinical Oncology Group; PS: performance status; PR: partial response; SD: stable disease; PD: progressive disease; EGFR: epidermal growth factor receptor. *Kaplan-Meier method.

Table 2. Toxicity distribution of entire patients (N=75)

Toxicity	n	Percentage (%)	I / II	III / IV
Rash	36	48	33	3
Diarrhea	22	29	21	1
Nausea/vomiting	5	7	5	0
Liver damage	4	5	3	1
Fatigue	5	7	5	0

Table 3. EGFR mutation rates classified according to patient background (N=62)

Population	EGFR mutation		Mutation rate (%)	*P* value
	Wild type (n=27)	Mutation positive (n=35)		
Male (n=21)	11	10	47.6	0.166*
Female (n=41)	14	27	65.9	
Never smoker (n=53)	17	34	64.2	0.038**
Ever smoker (n=11)	8	3	27.3	
Adeno (n=52)	20	32	61.5	0.742**
Non-adeno (n=10)	5	5	50.0	
Rash (n=36)	14	22	61.1	0.395*
Non-rash (n=24)	12	12	50.0	

*Pearson chi-square; **Continuity corrected chi-square.

(gender, age, ECOG score, adenocarcinoma histology, smoking status, prior chemotherapy cycle numbers, first-line responses and rash), no factor was found to influence PFS and only rash status had impact on OS independently (Table 4). However, analysis based on both EGFR mutation status and clinical characteristics for the patients who provided tissue samples for the detection of EGFR mutation showed only EGFR gene mutation status rather than other clinical characteristics influenced PFS independently, and both rash and EGFR gene mutation status were the independent prognostic factors in terms of OS (Table 4).

Further analysis of EGFR mutation status was performed. Of the 35 EGFR mutations, 19 (54%) were exon 19 in-frame deletions, ten (29%) were exon 21-point mutations (L858R) and 6 (17%) were double positive mutations. Patients with exon 21-point mutation seemed to have greater PFS and OS compared with the exon 19 deletion mutation, however the difference failed to reach statistic significance (Figure 3A and 3B).

Table 4. Cox proportional hazard model for survival analysis in overall patients (n=75) and in patients whose EGFR mutation status has been detected (n=62)

Variables	For PFS		For OS		95%CI	*P* value
	HR	95%CI	*P* value	HR		
All patients (n=75)[a]						
First-line response				2.135	0.947–4.809	0.067
Rash status	0.927	0.489–1.758	0.816	0.420	0.193–0.915	0.029
Patients with EGFR mutation detection (n=62)[b]						
First-line response				1.653	0.687–3.974	0.262
Rash status	0.871	0.439–1.730	0.694	0.368	0.152–0.890	0.027
EGFR mutation	0.442	0.212–0.919	0.029	0.359	0.155–0.831	0.017

[a]Test variables: gender, ECOG score, age, adenocarcinoma histology, smoking status, prior chemotherapy cycle numbers, first-line responses and rash status; [b]Test variables: EGFR mutation and variables in ([a]).

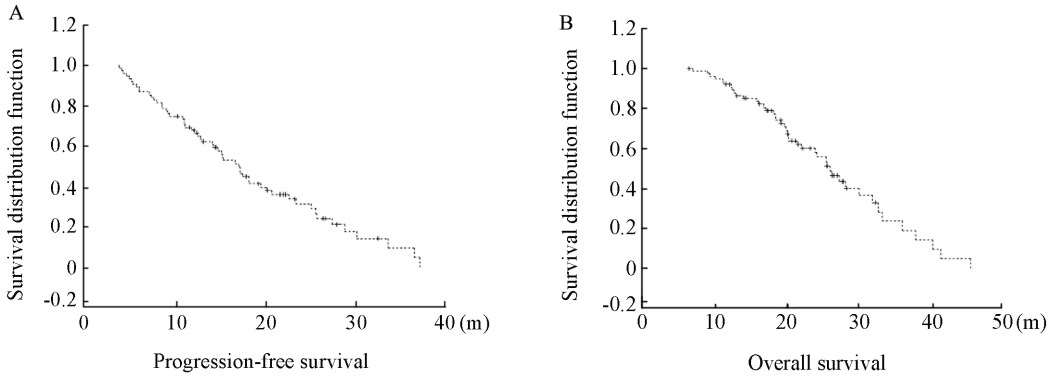

Figure 1. Kaplan-Meier curves of (A) PFS and (B) OS for the entire cohort classified according to EGFR gene mutation status.

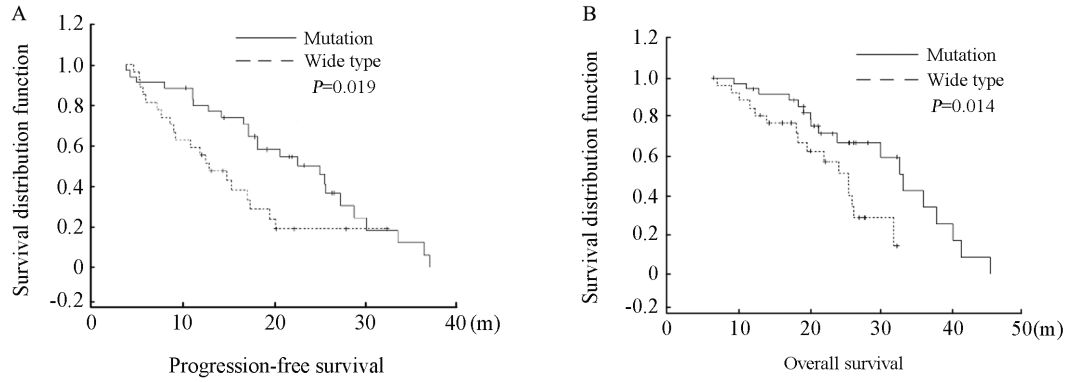

Figure 2. The median PFS (A) and the median OS (B) stratified by EGFR mutation status.

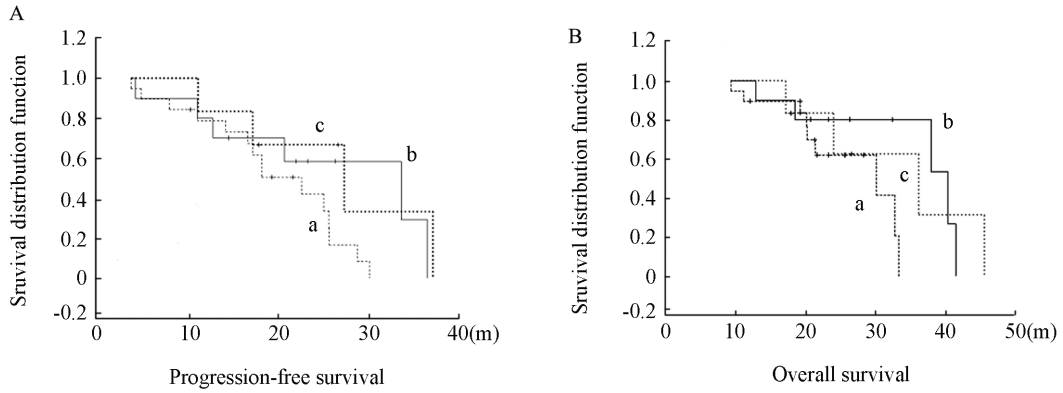

Figure 3. The median PFS (A) and the median OS (B) stratified by EGFR mutation status for patients harboring EGFR mutation.

DISCUSSION

Gefitinib has been recommended as one of the standard second-line agent for patients with refractory advanced NSCLC, due to similar therapeutic efficacy but less toxicities compared with other second line agents such as docetaxel[8]. So gefitinib delivered as maintenance use has a

theoretical basis. The present phase II trial was committed to investigate the efficacy and safety of gefitinib utilized as maintenance treatment for advanced NSCLC patients who achieved diseasestabilization after first-line chemotherapy, and simultaneously to exploit the appropriate population for gefitinib maintenance.

Previous studies have suggested a benefit of maintenance chemotherapy for patients with NSCLC following front-line chemotherapy[6, 7, 12–15]. In a phase III trial, Brodowicz et al.[13] compared maintenance gemcitabine with best supportive care in advanced stage NSCLC patients who achieved at least stable disease after front-line chemotherapy and found that patients with the maintenance treatment had a prolonged progression time but not OS, except in a subgroup of patients who had a Karnofsky performance score >80. In another study, Ciuleanu et al.[7] used pemetrexed in a sequential setting for patients with lung adenocarcinoma responded to a front-line chemotherapy and found a significantly improved PFS by 2.07 months and OS by 2.83 months. Hida et al.[15] recently reported that gefitinib used in a maintenance setting following induction chemotherapy improved PFS by 0.33 months (P<0.001) and OS by 1.09 months (P=0.03) compared with patients treat with continuous chemotherapy.

Majority of study had shown that the median PFS and OS for first-line chemotherapy were 6 months and 10 months respectively. However, in the present study, benefits from maintenance therapy seemed to be obtained, with confirmed prolonged survival. But, it should be acknowledged that patients included in the study were all Chinese and the ethnicity discrepancy might change the survival outcomes. Similarly, a trial from the neighboring ethnicity, Korea, reported by Park et al.[16] revealed that initial chemotherapy delivered for four or six cycles led to greater PFS compared to those from Caucasian. But even if compared to the survival time of aforementioned Korea study, our survival results were superior, suggesting that ethnicity difference was not predominately contributed to the survival improvement exhibited in our research. Furthermore, high frequency of female, never smoker and adenocarcinoma occurred in our data, which had been considered as positive predictors of gefitinib efficacy in some trials[17]. However, identified effects did not emerge in our study, with no clinical variables except for EGFR mutation status and rash status conferring the prolonged PFS and OS in Cox regression hazard model. There also have been several reports of clinical factors associated with EGFR mutations, which found high mutation frequencies in East Asian ethnicity, female, never-smoker and adenocarcinomas patients[18, 19]. Actually, EGFR mutation may be the real crucial factor hiding behind the superficial appearance. In our research it was manifested that patients carrying EGFR L858R or exon 19 deletions had prolonged PFS and OS compared with those with EGFR wide type. So, according to the present data, EGFR mutation is one predictive factor of survival time, which implied that selecting patients with EGFR mutations as candidate to receive gefitinib maintenance may be the pivotal step and gefitinib as maintenance therapy could do provide survival improvement through population selection including EGFR mutation screening. According to the present data, rash status is the other predictor in terms of OS but not PFS in the Cox hazard model. Considering the unrelatedness between rash and EGFR mutation status (P=0.395), rash status could be considered as an independently prognostic factor in terms of OS. Although significant statistical difference failed to be reached in PFS, patients with rash obtained longer PFS than those without rash. So, amplified samples might reach the trend significance.

A major selection bias we have to acknowledge is the study enrolled high percentage patients with the characteristics of female, never smoker or adenocarcinoma which might influence the outcomes, although there were no significant differences in PFS and OS in terms of the above characteristics according to our data. Moreover, only 59% patients completed more than 2 prior cycles of chemotherapy and the main reason was chemoagents associated toxicities. So we speculated that the survival time might be further prolonged if all patients had received 4 to 6 cycles of chemotherapy.

Incidentally, better survival seemed to be obtained in L858R cases in our study, which was inconsistent with some published reports[20, 21]. However, because statistically significant the outcome was not and other predictive bio-marks such as k-*ras* mutation were not included, final conclusion can not be drawn that exon 21 mutation is prior to exon 19 deletion in terms of survival and thus well-designed, large sample included trial need to be conducted to further differentiate which mutation type is better.

Previous studies have indicated that second-line gefitinib therapy for the advanced NSCLC patients who failed to first-line standard chemotherapy had less toxicities and resulted in better quality of life compared with second-line

chemotherapy[8, 15, 22]. This open-label single-arm study showed that Rash and diarrhea were the leading common toxicities, but grade three or four toxicities occurred rarely. No additional side effect was observed in the entire patient population. Overall, the safety feature is identical when gefitinib is used as maintenance or second-line therapy.

In conclusion, this study showed that gefitinib produced encouraging survival when delivered as maintenance therapy for Chinese patients obtaining DC after first-line chemotherapy, especially for the patients harboring somatic EGFR mutation. According to our data, EGFR mutation is an independent predictive factor of survival. So, once gefitinib maintenance is chosen as an alternative strategy, EGFR mutation detection should be recommended at first. This principle phase II study provides strong rationale to conduct randomized control-labeled phase III trial to further confirm our conclusions.

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