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Traditional Chinese Medicine Prolongs Progression-Free Survival and Enhances Therapeutic Effects in Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) Treated Non-Small-Cell Lung Cancer (NSCLC) Patients Harboring EGFR Mutations

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Mo Tang
ABCDEFG 1 Shumei Wang
BCDF 1 Bin Zhao
BCDF 2 Wei Wang
BCD 3 Yuxi Zhu
BCF 4 Lingjing Hu
BF 5 Xianquan Zhang
BDF 6 Shaoquan Xiong

1 School of Traditional Chinese Medicine University, Chongqing, P.R. China
2 Department of Traditional Chinese Medicine, Chongqing Cancer Hospital, Chongqing University Cancer Hospital, Chongqing, P.R. China
3 Department of Oncology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China
4 Department of Oncology, Chongqing Traditional Chinese Medicine Hospital, Chongqing, P.R. China
5 Department of Oncology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China
6 Department of Oncology, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, P.R. China

Corresponding Author: Shumei Wang, e-mail: wangshumei@cqmu.edu.cn
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Background: Lung cancer is the most common cause of cancer-associated deaths worldwide. This study aimed to investigate the efficacy and safety of Traditional Chinese Medicine combining EGFR-TKIs in treatment of NSCLC patients harboring EGFR mutations.

Material/Methods: This study involved 153 advanced-stage NSCLC patients harboring EGFR mutations. Patients were divided into a Control group (administered EGFR-TKI, n=61) and an Experimental group (administered Traditional Chinese Medicine combining EGFR and TKI, n=92). Progression-free survival (PFS) was evaluated for exon 19 deletion and/or 21 deletion patients. Disease control rate (DCR) was assessed to observe therapeutic effects. Adverse effects, including rashes, diarrhea, ALT/AST increase, dental ulcers, and onychia lateralis, were also evaluated.

Results: TCM combining EGFR-TKI (90.11%) demonstrated no DCR improvement compared to single EGFR-TKI (83.33%) ($p>0.05$). Median PFS (mPFS) of TCM combining EGFR-TKI (13 months) was significantly longer compared to that in the single EGFR-TKI group (8.8 months) ($p=0.001$). For 19DEL mutant NSCLC, the mPFS (11 months) in TCM combining EGFR-TKI was significantly longer compared to single EGFR-TKI (8.5 months) ($p=0.007$). The mPFS of L858 mutant NSCLC patients in EGFR-TKI combining CTM (14 months) was significantly longer compared to single EGFR-TKI (9.5 months) ($p=0.015$). TCM combining EGFR-TKI was more inclined to prolong mPFS of NSCLC with exon 21 deletion. TCM combining EGFR-TKI illustrated no additional adverse effects in NSCLC patients ($p=0.956$).

Conclusions: Application of Traditional Chinese Medicine prolonged progression-free survival and enhanced therapeutic effect in NSCLC patients harboring EGFR mutations receiving EGFR-TKI treatment. Meanwhile, adjunctive Chinese medicine combining EGFR-TKI in NSCLC with EGFR mutations caused no adverse effects.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • Genetic Therapy • Lung Neoplasms • Medicine, Chinese Traditional

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Background

Lung cancer is the most common cause of cancer-associated death worldwide [1–3]. Clinically, lung cancer has the highest mortality and morbidity rates among all malignancies worldwide [4]. More than 75% of lung cancer patients, and especially non-small-cell lung cancer (NSCLC) patients, have advanced-stage disorder for the first diagnosis, followed by a poor prognosis [5]. Chemotherapy has been extensively applied for treating NSCLC; however, it only achieves a median survival of 8–10 months [5]. The 5-year survival rates for NSCLC for local-, regional-, and distant-stage cancers are 52%, 24%, and 4%, respectively [6]. Therefore, it is urgent to discover novel strategies for lung cancer treatment.

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), as a targeted therapy approach, have been extensively used for treating NSCLC patients harboring EGFR-activating mutations [7,8]. The incidence of lung cancer-associated EGFR mutations in whites and in Americans are 17% and 23%, respectively; however, the incidence in Chinese lung cancer patients is 51% [9]. Thus, it is critical for Chinese patients to test the EGFR mutations and administer appropriate interventions. EGFR-TKIs have been demonstrated to prolong progression-free survival (PFS) and delay cancer progression of NSCLC patients by more than 5 months compared with chemotherapy [10]. Only 15% of NSCLC patients are sensitive to treatment with TKIs [11] such as gefitinib and erlotinib, both of which have been approved by the US FDA. However, gefitinib and erlotinib cannot prolong the overall survival of NSCLC patients compared to chemotherapy [12] because of patient drug resistance [13].

Traditional Chinese Medicine (TCM) has been used for 5000 years and has a wealth of recorded treatment resources [14]. TCM mainly consists of acupuncture, Chinese herbal remedies, and manipulative treatments. TCM plays critical roles in alternative and complementary medicine practices, but might induce adverse effects when administered with cytotoxic chemotherapeutics for cancer patients [15]. In China TCM is the most common therapy for treating many disorders, including cancers, rheumatoid arthritis, diabetes, and stroke, by enhancing "vital energy", restoring "balance", boosting immunity, and detoxifying [16,17]. Moreover, the overall efficacy of TCM is rarely due to use of just one or a few herbal compounds; rather, it relies on the synergistic effects various small-effect, low-concentration compounds, together with a few active and enriched compounds. The molecular efficacy of TCM is based on the entire prescription, not just a few ingredients [18]. The toxicity of Chinese medicine compounds can be abated or offset using other herbs, but the overall effectiveness is significantly strengthened [19]. The advantage for applying TCM is associated with its functions on multiple molecular signaling pathways and molecular targets correlated with diseases [20].

In recent years, Chinese herbal medicine has been integrated with modern Western medicine to enhance the clinical benefits and alleviate the adverse effects [21]. Chinese herbal medicine can improve cancer therapy by triggering biological modification, enhancing the psycho-immunological function, and improving psycho-spiritual well-being [22]. Therefore, this study investigated the efficacy and safety of Traditional Chinese Medicine combining EGFR-TKIs therapy (EGFR-TKIs+TCM) in the treatment of late-stage lung cancer patients with EGFR mutations.

Material and Methods

Patients and diagnostic criteria

In this study, we enrolled 153 lung cancer patients diagnosed with NSCLC between July 2016 and January 2018 in the First Hospital Affiliated Hospital of Chongqing Medical University, Chongqing Traditional Chinese Medicine Hospital and Affiliated Hospital of Chengdu University of Traditional Chinese Medicine. This study was approved by the Ethics Committee of Chongqing Medical University, Chongqing, China. All of the patients signed written informed consent.

Western medicine diagnostic criteria include the TNM staging system for lung cancer of the Union for International Cancer Control (UICC) [23]. Meanwhile, according to the theory of Traditional Chinese Medicine, the patients were divided into 4 types: phlegm-dampness-stasis, deficiency for Qi and Yin, heat-toxic obstruction of lung, and lung-spleen deficiency.

Inclusion criteria: 1) Patients older than 18 years. 2) All patients were diagnosed as having NSCLC by the histology at stage IIIA, IIIB or IV. 3) EGFR mutations were determined to be *exon* 19 deletion and *exon* 21 deletion (also known as 19DEL and L858R, respectively) based on DNA direct sequencing.

Exclusion criteria: 1) Patients had serious complications, such as active infection, congestive heart failure, hepatic insufficiency, renal inadequacy, arrhythmia, and mental illness. 2) Some drugs caused adverse effects have not been recovered. 3) The patients were also participating in any other pharmaceutical research. 4) Patients administered Chinese medicine for less than 3 months or if the interval is prolonged to 1 week. 5) Patients lost to follow-up.

Trial grouping and drug administration

The 153 enrolled NSCLC patients were divided into 2 group according to patients treated with or without TCM (therefore, the sample sizes in both groups are incomparable), including Experimental group (n=90) and Control group (n=61). Patients in the Control group were orally administered

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gefitinib (250 mg/day) or erlotinib (150 mg/day). Patients in the Experimental group (TCM combining EGFR-TKI group, EGFR-TKIs-TCM group) were divided into 4 sub-groups: phlegm-dampness-stasis (n=47), deficiency for *Qi* and *Yin* (n=17), heat-toxic obstruction of lung (n=7), and lung-spleen deficiency (n=19).

The phlegm-dampness-stasis patients orally administrated Er Chen Tang plus San Ren Tang (combinations of herbs, for eliminating phlegm). One prescription mainly included ingredients of *Pinellia ternata* (15 g), Dried tangerine peel (10 g), *Poria cocos* (20 g), Licorice (10 g), *Agastache rugosus* (15 g), Apricot kernel (10 g), Talcum (15 g), White cardamom (10 g), Bamboo leaf (5 g), Coix seed (20 g), and *Mangnolia officinalis* (15 g). One prescription was decocted in water and administered 3 times a day for 2 weeks. The deficiency for *Qi* and *Yin* patients were orally administered Qian Jin Wei Jing Tang (a combination of herbs, for improving pulmonary functions). One prescription mainly included ingredients of Phragmites stem (30 g), Wax gourd seed (20 g), Peach seed (15 g), Coix seed (30 g), Honeysuckle (10 g), *Houttuynia cordata* thunb (20 g), Cortex Mori (15 g), and *Platycodon grandiflorum* (15 g). One prescription was decocted in water and administered 3 times a day for 2 weeks. The heat-toxic obstruction of lung patients orally administered Sheng Mai San plus Sha Shen Mai Dong Tang (a combination of herbs, for supplementing *Qi*). One prescription mainly included ingredients of *Radix pseudostellariae* (30 g), *Ophiopogon japonicus* (20 g), Schisandra seed (10 g), *Radix adenophora* (15 g), *Astragalus membranaceus* (60 g), *Rhizoma anemarrhenae* (10 g), *Ligustrum lucidum* (30 g), *Radix paeoniae alba* (20 g), *Rhizoma atractylodis macrocephalae* (15 g), and Donkey-hide gelatin (5 g). One prescription was decocted in water and administered 3 times a day for 2 weeks. The lung-spleen deficiency patients were orally administered Liu Ju Zi Tang (a combination of herbs, for decreasing vomiting or nausea and improving appetite). One prescription mainly included ingredients of Ginseng (20 g), *Rhizoma atractylodis macrocephalae* (15 g), *Poria cocos* (20 g), Licorice (10 g), *Astragalus membranaceus* (60 g), *Rhizoma pinellinae praeparata* (15 g), Dried tangerine peel (10 g), *Platycodon grandiflorum* (10 g), and Apricot kernel (10 g). One prescription was decocted in water and administered 3 times a day for 2 weeks. All of the above 4 types of patients are administered gefitinib (250 mg/day) or erlotinib (150 mg/day) together with the TCM treatment.

Follow-up

Follow-up was conducted at 2 months, prior to or after the therapy. Follow-up was performed at outpatient treatment, in the hospital, or by telephone. PFS was censored when NSCLC patients were alive at last follow-up. The last follow-up for PFS data analysis was July 2018.

Data evaluation

The primary endpoint was progression-free survival (PFS), which was defined as the survival period ranging from the start of enrollment to the first tumor progression or death of patients due to any reason. Tumor progression was assessed using the WHO evaluation criteria in solid tumors [24]. The secondary endpoint was disease control rate (DCR), which was defined as partial response (PR)+complete response (CR)+stable disease (SD). CR was defined as disappearance of all target lesions, confirmed at 4 weeks. PR was defined as ≥50% decrease, without new lesions, confirmed at 4 weeks. SD was defined as ≤50% decrease or ≤25% increase, without new lesions, confirmed at 4 weeks. Progressive disease (PD) was defined as ≥25% increase, no CR, PR, or SD documented before increased disease, with new lesions, ≥25% in a lesion. Moreover, the adverse effects, including rashes, diarrhea, ALT/AST increase, dental ulcer, and onychia lateralis, were also evaluated.

Statistical analysis

Data were analyzed using SPSS software (version: 22, SPSS, Inc., Chicago, IL, USA). Categorical variables are represented as median or percentage (%) and were analyzed using the chi-square test or the Fisher test. Continuous variables are represented as mean ±SD and were analyzed using the *t* test or by ANOVA. The *t* test was used to compare differences between 2 groups. Tukey's post hoc test validated by ANOVA was used to compare differences among multiple groups. PFS was calculated using Kaplan-Meier analysis and compared using the log-rank test. Statistical significance was defined at $p<0.05$.

Results

Basic characteristics of patients

Basic characteristics, including sex, age, TNM stage, EGFR mutation, targeted therapy, and Chinese medicine diagnosis, were calculated and compared between the Experimental group and the Control group (Table 1). Our results also showed that there were 53 19DEL and 37 L858 mutations in the Experimental group and 29 19DEL mutations and 32 L858R mutations in the Control group (Table 1), showing no significant differences ($p>0.05$). The statistical analysis results showed that there were no significant differences for the other parameters between the 2 groups (Table 1, $p>0.05$), which suggests the 2 groups were comparable. The median follow-up time was 10.5 months (range, 8–14.5 months).

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Table 1. Characteristics of patients [n(%)].

Characteristics	Experimental group (n=90)		Control group (n=61)		χ^2	*p*
Sex						
Male	46	(51.11)	28	(45.90)	0.395*F*	0.530Q
Female	44	(48.89)	33	(54.10)		
Age						
<60 years	45	(58.44)	32	(41.56)	0.088*F*	0.767
≥60 years	45	(60.81)	29	(39.19)		
Stage						
IIIA or IIIB	33	(67.35)	16	(32.65)	1.807*F*	0.179
IV	57	(55.88)	45	(44.12)		
Gene inspection						
Exon 19 deletion	53	(64.63)	29	(35.37)	1.887*F*	0.17
Exon 21 deletion	37	(53.62)	32	(46.38)		
Targeted therapy						
Gefitinib	62	(62.00)	38	(38.00)	/	0.073*
Erlotinib	23	(50.00)	23	(50.00)		
Gefitinib combined with Erlotinib	5	(100.0)	0	(0.00)		
Chinese medical diagnosis						
Phlegm-dampness-stasis	47	(60.26)	31	(39.74)	4.88*F*	0.181
Deficiency for Qi and Yin	17	(65.38)	9	(34.62)		
Heat-toxic obstruction of lung	7	(87.50)	1	(12.50)		
Lung-spleen deficiency	19	(48.72)	20	(51.28)		

* Represents the *p* value derived from the Fisher test; *F* Represents the χ^2 value for the chi-square test.

TCM combining EGFR-TKI demonstrated no improvement of DCR

The results indicated that the CR, PR, SD, PD, and DCR in the Experimental group were 0%, 66.3%, 28.7%, 6.2%, and 90.11%, respectively. The CR, PR, SD, PD, and DCR in the Control group were 0%, 52.7%, 30.5%, 16.3%, and 83.33%, respectively. Therefore, there were no significant differences in the DCR between the Experimental group and Control group (p=0.219).

TCM combining EGFR-TKI prolonged median PFS

The median PFS (mPFS) of EGFR-TKI administered in 90 patients who also received Chinese medicine treatment was 13 months (range, 10.5–15.5 months), which was significantly longer than the 8.8 months (range, 8.04–99.56 months) in 61 patients without Chinese medicine treatment (Figure 1, hazard ratio [HR]=0.59, 95% CI=0.33-0.75, p=0.001).

TCM combining EGFR-TKI prolonged mPFS in 19DEL mutant NSCLC patients

For the 19DEL mutant NSCLC patients, the mPFS was 11 months (range, 8.88–13.12 months) in the Experimental group and 8.5 months (range, 6.62–9.78 months) in the Control group (Figure 2A, HR=0.47, 95% CI=0.27-0.83). Therefore, the mPFS of the Experimental group was significantly longer than in the Control group (Figure 2A, p=0.007).

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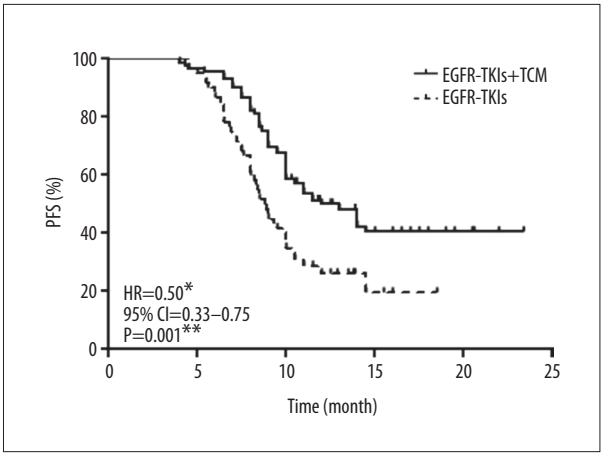

Figure 1. Comparison of mPFS between TCM combined with EGFR-TKI treatment and single EGFR-TKI treatment. *, ** Represents the *p* value comparing TCM combined with EGFR-TKI treatment and single EGFR-TKI treatment. ** Represents the *p* value derived from the log-rank test.

TCM combining EGFR-TKI prolonged mPFS in L858 mutant NSCLC patients

The mPFS of L858 mutant NSCLC patients in the Experimental group was 14 months (range, 13.71–17.81 months), which was significantly longer than the 9.5 months (range, 8.21–10.4 months) in the Control group (Figure 2B, HR=0.46, 95% CI=0.25–0.89, *p*=0.015).

TCM combining EGFR-TKI was more inclined to prolong mPFS of NSCLC patients harboring exon 21 deletion

The mPFS in NSCLC patients harboring *exon* 21 deletion was significantly higher compared to that in NSCLC patients harboring *exon* 19 deletion, in both TCM-EGFR-TKI (14 months *vs.* 11 months) and single EGFR-TKI treatments (9.5 months *vs.* 8.5 months). Therefore, we speculated that the TCM combining EGFR-TKI was more inclined to prolong mPFS of NSCLC patients harboring *exon* 21 deletion.

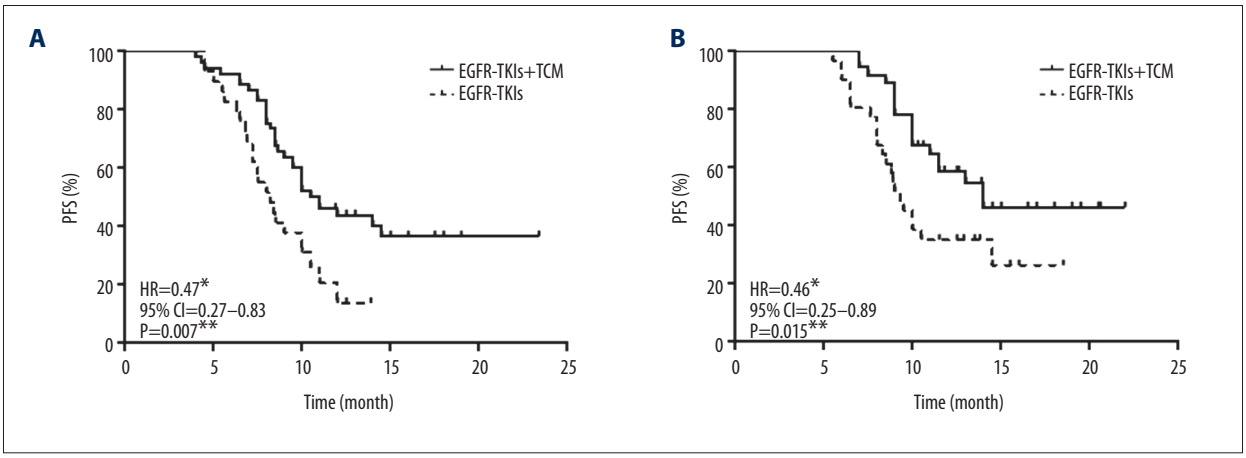

Figure 2. Comparison for the mPFS between TCM combined with EGFR-TKI treatment and single EGFR-TKI treatment in 19DEL (exon 19 deletion) and L858 (exon 21 deletion) mutant NSCLC patients. (**A**) Comparison for mPFS in 19DEL mutation. (**B**) Comparison of the mPFS in L858 mutation. *, ** Represents the *p* value comparing TCM combined with EGFR-TKI treatment and single EGFR-TKI treatment. ** Represents the *p* value derived from log-rank test.

Table 2. Comparison for the adverse effects between the experimental group and control group [n(%)].

Characteristics	Experimental group (n=90)		Control group (n=61)		χ^2	*p*
Adverse effects	69	(76.67)	47	(77.05)	0.003*F*	0.956
Rashes	38	(42.22)	17	(27.87)	3.235*F*	0.072
Diarrhea	16	(17.78)	12	(19.67)	0.086*F*	0.789
ALT/AST increasing	10	(10.31)	12	(19.67)	2.739*F*	0.098
Dental ulcer	5	(5.56)	7	(11.48)	/	0.227*
Onychia lateralis	0	(0.0)	2	(3.28)	/	0.162*

* Represents the *p* value derived from the Fisher test; *F* Represents the χ^2 value for the chi-square test.

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TCM combining EGFR-TKI administration illustrated no additional side effects for NSCLC patients

According to the statistical analysis data of adverse effects in the Experimental group and Control group, there were no significant differences in rashes, diarrhea, ALT/AST increase, dental ulcer, or onychia lateralis between the 2 groups (Table 2, all $p>0.05$). Adverse effects were observed in 69 patients (76.67%) in the Experimental group and in 47 patients (77.5%) in the Control group (Table 2). Although the incidence rate in the Experimental group was slightly lower than that in the Control group, there were no statistical differences (Table 2, $p=0.956$). Moreover, we did not observe the adverse effect of interstitial pneumonia in any patients in either group.

Discussion

In recent years, lung cancer therapy has become a cooperative and multi-strategy treatment, and Traditional Chinese Medicine has been applied in treating disorders for thousands of years in China. Exploring potential applications of TCM as adjuvant treatment is a critical topic in lung cancer therapy [25]. Therefore, in this study, we investigated efficacy and safety of Chinese herbal medicine together with modern Western medicine treatment for late-stage lung cancer patients with EGFR mutations.

EGFR is a kind of trans-membrane protein that is characterized by tyrosine kinase activity [26]. Activation of EGFR signaling pathways influence proliferation, differentiation, and signal transduction of cancer cells. A previous study [27] reported that EGFR mutation (exon 19 and 21 deletion are the most common mutations) is correlated with poor prognosis of lung cancer patients. EGFR-TKIs have become the first-line drug for treating lung cancer patients with EGFR mutations [28]. However, the targeted drug resistance has become a problem for clinical lung cancer therapy, especially for NSCLC. A previous study [29] showed that TCM can modulate multiple targets and alleviate drug resistance.

In this study, we collected clinical records from the First Hospital Affiliated Hospital of Chongqing Medical University, Chongqing Traditional Chinese Medicine Hospital and Affiliated Hospital of Chengdu University of Traditional Chinese Medicine to identify effects of Chinese medicine on EGFR-TKIs in improving PFS for NSCLC patients with EGFR mutations. Our results indicated that there were no significant differences in CR, PR, SD, PD and DCR between patients administered TCM combining EGFR-TKIs and patients treated with single EGFR-TKIs ($p=0.219$). However, the DCR of Chinese medicine combining EGFR-TKI (90.11%) was also slightly higher compared to that in single EGFR-TKI treatment (83.33%) ($p>0.05$), and demonstrated strengthened therapeutic effects. These results are consistent with a previous cohort study [30] investigating the CDR of patients undergoing TCM combined with EGFR-TKI and single EGFR-TKI treatment.

The PFS has been extensively considered to be a critical biomarker for evaluating late-stage anti-tumor effects [31,32]. For NSCLC patients harboring both mutations (exon 19 and 21 deletion), the mPFS was 13 months in the TCM combining EGFR-TKI group, which was significantly longer than in the single EGFR-TKI treatment group ($p=0.001$). For NSCLC patients harboring only exon 19 deletion mutation, the mPFS was 11 months in the TCM combining EGFR-TKI group, which was significantly longer than in the EGFR-TKI treatment group ($p=0.007$). For NSCLC patients harboring only exon 21 deletion mutation, the mPFS was 14 months in the TCM combining EGFR-TKI group, which was longer significantly than in the EGFR-TKI treatment group ($p=0.015$). Meanwhile, mPFS in NSCLC patients harboring exon 21 deletion was also significantly higher compared to that in NSCLC patients harboring exon 19 deletion, in both the TCM combining EGFR-TKI and single EGFR-TKI treatments. The above findings are consistent with previous studies [33,34] investigating treatment of NSCLC patients with mutated EGFR. However, our designed TCM combining EGFR-TK therapeutic strategy demonstrated greater efficacy and prolonged the mPFS for NSCLC patients harboring deletion mutations comparing to a previous Chinese cohort study [30]. The above results and the comparisons suggest that our applied Traditional Chinese Medicines together with the gefitinib or erlotinib are more effective for treating the NSCLC harboring deletion mutations. Moreover, compared with the previous studies of therapeutic strategies for NSCLC without TCM administration [15,35], TCM combining EGFR-TKIs administration is superior for inhibiting tumor progression, which suggests that patients with EGFR-activating mutations should receive TCM combining EGFR-TKI treatment.

Adverse effects of both TCM and TCM combining EGFR-TKI treatment have been reported in previous research [36,37], so we assessed the safety of TCM combining EGFR-TKI administration. We found that there were no significant differences in rashes, diarrhea, increased ALT/AST, dental ulcers, and onychia lateralis between the single EGFR-TKI group and the TCM combining EGFR-TKI group. Although the total number of adverse effects in the TCM combining EGFR-TKI group was slightly lower than that in the EGFR-TKI group, the difference was not significant. We found no cases of interstitial pneumonia, a common complication of lung cancer [38], in this study, possibly due to replacement of chemotherapy or radiotherapy or other therapeutic approaches with the present TCM combining EGFR-TKI treatment strategy for treating cancer patients [39]. Therefore, TCM combining EGFR-TKI treatment did not bring cause additional adverse effects and is safe for clinical use.

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There are a few limitations in the present study, Firstly, the anti-tumor signaling pathways affected by TCM are unclear and warrant further research. Secondarily, the synergy mechanism of TCM combining EGFR-TKI also needs to be explored. Thirdly, although the different TCMs were associated with the same outcomes, this study did not analyze the TCM-related clinical outcomes separately. Fourthly, this study may have had selection bias, such as the different numbers of patients in the 2 groups.

Conclusions

The present study demonstrated that the use of Chinese medicine can prolong the progression-free survival and enhanced therapeutic effect in NSCLC patients harboring EGFR mutations receiving EGFR-TKI treatment. The adjunctive Chinese Medicine combining the EGFR-TKI treatment in NSCLC patients with EGFR mutations did not show any adverse effects. Prospective controlled and randomized trials and mechanistic research are needed to confirm our results.

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Conflict of interest

None.

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