


The Efficacy of Traditional Chinese Herbal Medicine in the Treatment of *EGFR* Mutated Stage IV Pulmonary Adenocarcinoma Patients Who Received First-Line *EGFR*-TKI Treatment

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Abstract

Background. Chinese herbal medicine (CHM) has been used for thousands of year in Eastern countries. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment is the standard treatment in stage IV pulmonary adenocarcinoma patients who had tumor *EGFR* mutations. This study was to find the efficacy of CHM on lung cancer treatment. **Materials and Methods.** We retrospectively reviewed chart records of our stage IV *EGFR*-mutated pulmonary adenocarcinoma patients who received first-line *EGFR*-TKI treatment from January 2010 to September 2014. **Results.** Total, 527 patients were studied. Among them, 34 patients received CHM treatment, including 24 patients who received CHM treatment from the beginning of first-line *EGFR*-TKI treatment and 10 patients who started to receive CHM treatment after their disease had progressed to *EGFR*-TKI treatment. Median progression-free survival (PFS) of first-line *EGFR*-TKI treatment was numerically better in patients who also received CHM than those who did not (12.1 months vs 10.5 months, $P = .7668$). Overall survival of those 24 patient who received CHM treatment together with *EGFR*-TKI was 30.63 months (95% CI = 11.7 to not reached), compared to 23.67 months in the remaining patients (95% CI = 21.37-26; hazard ratio = 0.75; $P = .399$). No increase of CHM-related toxicities was found during CHM treatment, compared with *EGFR*-TKI treatment alone ($P > .05$). **Conclusion.** Alternative CHM treatment during first-line *EGFR*-TKI treatment did no harm to the patients and PFS and overall survival was numerically better, although not significant, than those patients who did not receive CHM treatment.

Keywords

adenocarcinoma, Chinese herbal medicine, epidermal growth factor receptor, lung cancer, tyrosine kinase inhibitor

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Introduction

Lung cancer is the leading cause of cancer death throughout the world. More than 90% of lung cancers were non-small cell lung cancers in Taiwan, and adenocarcinoma accounted for the major histologic subtype of lung cancer.¹ Despite continuous improvement in the diagnosis and treatment of lung cancer, the 5-year survival rate is only 3.6% for stage IV patients in the United States,² and it is even lower in developing countries. The high proportion of disseminated disease in such patients has justified the numerous attempts to improve systemic treatment for more than 2 decades.

Herbs, which have an important role in complementary and alternative medicine (CAM) practices, may cause unfavorable

side-effects when used particularly with cytotoxic chemotherapeutics in cancer patients due to the substances they contain and due to the properties of some, which still cannot be clarified. Further compounding the challenges of cancer treatments,

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patients do not talk about these issues with their doctors, and physicians are unable to comprehend the properties of these herbs.³ It has been considered for years that traditional Chinese herbal medicine (CHM) may be integrated with modern Western medicine to improve cancer patient care. In CHM, herbs are used in combinations that enhance benefits while reducing side effects.⁴ Multiple low-dose pharmacological agents are being administered synergistically. The main purpose of CHM being used in cancer treatment is to reduce the side effects of anticancer drugs, but further research is required to determine their pharmacokinetic interactions with drugs and any potential adverse effects. CHM may improve cancer care through biological response modification, enhancement of psycho-immunological function, better symptom control, and improvement of psychospiritual well-being.⁵ However, the role of such medicine in modern molecular oncology is unknown, and majority of medical oncologists are hesitant of allowing their patients to receive CHM during the active treatment stage, such as lung cancer patients with *EGFR* mutations under epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment.

Taipei Veterans General Hospital has a Center for Traditional Medicine, and almost all doctors in this department have received modern medical doctor training in addition to Chinese medicine training. They can access patients' medical records in outpatient clinics of our hospital. Thus, CHM treatment could be administered according to patients' physical status and cancer treatment modality being received. The present retrospective study is designed to figure out the role of CHM in lung cancer patients with *EGFR* mutations who are undergoing EGFR-TKI treatment.

Patients and Methods

We retrospectively reviewed the chart records of lung cancer patients diagnosed and treated between January 2010 and September 2014 in our hospital. Patients who had stage IV adenocarcinoma (American Joint Committee for Cancer staging system, 7th edition) and a documented tumor *EGFR* mutation that received first-line EGFR-TKI therapy in our hospital were studied. Those who also received CHM treatment in the Center for Traditional Medicine of our hospital were also recorded. Clinical data including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history (nonsmokers [those who had smoked less than 100 cigarettes in their lifetime] or smokers), type of *EGFR* mutation, first-line EGFR-TKI used, progression-free survival (PFS) of first-line EGFR-TKI, and overall survival (OS) were recorded. The study was approved by the Institutional Ethical Review Board of Taipei Veterans General Hospital (VGHIRB No. 2014-05-008AC).

Chest computed tomography scans (including liver and adrenal glands) were performed within 3 weeks before

starting targeted therapy, and every 2 to 3 months thereafter, or when confirmation of treatment response or disease progression was required. The type of treatment response or disease progression was accessed on the chest computed tomography scan, using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).⁶ PFS of EGFR-TKI targeted therapy was defined as the duration from the date of initiating targeted therapy to the earliest sign of disease progression, as determined by RECIST criteria, or death from any cause. If disease progression had not occurred at the time of the last follow-up visit, PFS was considered to have been censored at that time. OS was defined as the period from the beginning of targeted therapy to the date of death. OS was censored when the patients were still alive at the time of the last follow-up. Last follow-up time for survival data analysis was the end of April 2015.

Tumor *EGFR* mutations were examined using 1 of 2 methods. Before the end of 2010, Sanger DNA sequencing was used. All the sequence variations were confirmed by multiple, independent polymerase chain reaction amplifications and repeated sequencing reactions. Since 2011, most specimens were tested using the Scorpion amplification refractory mutation system method.

The CHM was usually used in combination of at least 3 regimens. The majority of patients received Herba *Houttuyniae* (71%, for increasing immunity), Herba *Oldenlandiae* (71%, for increasing immunity), and qīng zào jiù fèi tāng (71%, combinations of herbs, for improving pulmonary function). Three patients received 3 regimens, and 21 patients received 2 regimens. Other CHM included sǎn zhōng kuì jiān tāng (58%, combinations of herbs, for decreasing inflammation and fluid retention), jiā wèi xiǎo yáo sǎn (50%, combinations of herbs, for decreasing anxiety and headache), and xiāng shā liù jūn zǐ tāng (50%, combinations of herbs, for improving appetite and decreasing nausea or vomiting). Additional herbal medicine was also allowed depending on the patient's clinical condition. Since CHM was a supplementary medicine, patients received CHM during EGFR-TKI treatment as long as they wished. Patients usually called the CHM outpatient clinic every 2 weeks, and all the herbal formulas used were prescribed by qualified doctors of Chinese traditional medicine, and all CHM was delivered by qualified pharmacists. Treatment-related toxicities (either EGFR-TKI or CHM) were evaluated in both CHM and our outpatient clinic according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

All categorical variables were analyzed with χ^2 tests. Two-sided *t* tests were used for continuous variables when comparing 2 groups. Median PFS and OS were calculated using the Kaplan-Meier method and compared by log-rank test. All statistical analyses were performed using SPSS software (version 19.0; SPSS Inc, Chicago, IL).

Table 1. Clinical Characteristics of 527 EGFR-Mutated Adenocarcinoma Patients Who Received First-Line EGFR-TKI.

Characteristics	All	No CHM	CHM From EGFR-TKI	CHM After TKI Failure	P
Male/female, n	223/304	210/283	9/15	4/6	.876
Age (years), mean (range)	66.2 (27-96)	66.7 (27-96)	60 (43-80)	59.6 (48-69)	.016
Performance status					.334
0	109	100	7	2	
1	317	296	13	8	
2	79	75	4	0	
3	18	18	0	0	
4	4	4	0	0	
Smoker					.356
No	384	356	19	9	
Yes	143	137	5	1	
EGFR mutation					.898
Exon 19del	229	217	10	2	
L858R	258	241	9	8	
T719X or L861Q	26	23	3	0	
T790M	2	1	1	0	
Exon 19del + L858R	7	6	1	0	
L858R + others	2	2	0	0	
Exon 19del + T790M	1	1	0	0	
L858R + T790M	2	2	0	0	

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CHM, Chinese herbal medicine.

Results

Between January 2010 and September 2014, 527 stage IV pulmonary adenocarcinoma patients who had tumor *EGFR* mutations were diagnosed and treated in our hospital. Female, nonsmoker, performance status of 1, and *EGFR* L858R mutation were the predominant clinical characteristics of all patients in the hospital. First-line EGFR-TKIs used were gefitinib in 416 patients, erlotinib in 92 patients, and afatinib in 19 patients. Patients made the choice to seek CHM treatment on their own, and there was no extra charge for CHM treatment because it was also covered by national health insurance in Taiwan. Among all *EGFR* mutated patients, 34 patients also received CHM treatment during their course of disease, including 24 patients who started CHM treatment from beginning of first-line EGFR-TKI treatment and 10 patients who started to receive CHM treatment after their disease had progressed to EGFR-TKI treatment. Mean number of visits to CHM outpatient clinic was 7.3, with a range of 1 to 39, during EGFR-TKI treatment. Median time of taking CHM was 19 weeks, with a range of 4 to 139 weeks. There were no statistically significant differences in clinical characteristics between those patients who received or did not receive CHM, except for age, which was lesser for patients who received CHM ($P = .016$). Among 527 patients who received EGFR-TKI treatment with or without CHM, there was no significant survival difference between patients <50 years and ≥ 50 years (median 26 months [$n = 60$, 95% confidence interval (CI) = 20.2-48.8]

vs 23.6 months [$n = 467$, 95% CI = 20.5-26.6], $P = .1902$), while there was significant survival difference when the line was drawn at 65 years (median 26.8 months [$n = 257$, 95% CI = 23.7-36.8] vs 18.6 months [$n = 270$, 95% CI = 15-23.7], $P = .0005$). Clinical characteristics of all subgroups of patients are shown in Table 1.

Median PFS of first-line EGFR-TKI treatment was numerically longer, although statistically nonsignificant, in patients who also received CHM treatment during EGFR-TKI treatment than those who did not receive CHM treatment. Median PFS of first-line EGFR-TKI treatment in 24 patients who also received CHM treatment was 12.10 months (95% CI = 4.8-15.17) compared to 10.53 months in 503 patients without CHM treatment (95% CI = 9.23-10.93; hazard ratio [HR] = 0.93; $P = .767$; see Figure 1). Overall survival of 24 patients who received CHM treatment together with EGFR-TKI was 30.63 months (95% CI = 11.7 to not reached), compared to 23.67 months in the remaining patients (95% CI = 21.37-26; HR = 0.75, $P = .399$; see Figure 2). Another 10 patients started their CHM treatment together with salvage chemotherapy after their disease progressed to EGFR-TKI treatment. Median overall survival of these 34 patients who ever received CHM treatment during their lung cancer disease course was 30.63 months (95% CI = 15.77 to not reached) compared to 23.5 months (95% CI = 21.03-25.7) in the remaining patients (HR = 0.64, $P = .118$; see Figure 3). OS was also nonsignificantly longer in patients who ever received CHM treatment. When considering the

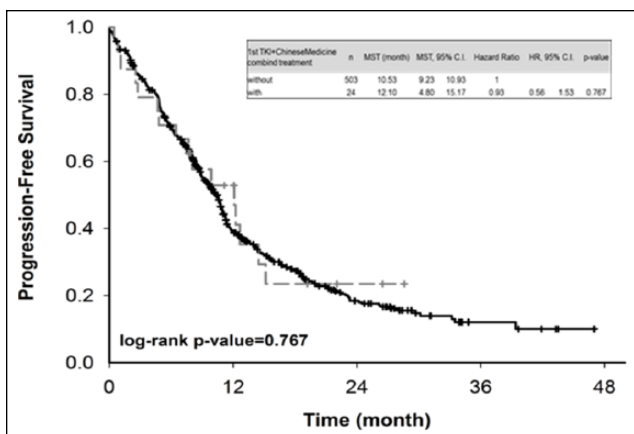


Figure 1. Progression-free survival (PFS) of 527 EGFR-mutated pulmonary adenocarcinoma patients who received first-line EGFR-TKI treatment with or without Chinese herbal medicine (CHM) treatment. Median PFS of 24 patients who also received CHM treatment was 12.10 months (95% CI = 4.8-15.17) compared to 10.53 months in 503 patients without CHM treatment (95% CI = 9.23-10.93; HR = 0.93, P = .767).

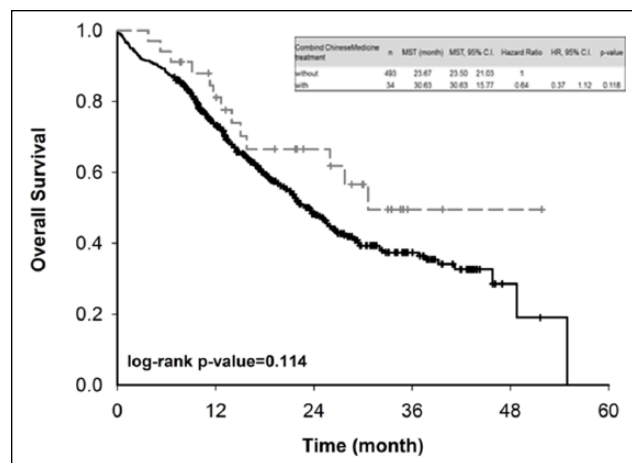


Figure 3. Overall survival of 527 EGFR-mutated pulmonary adenocarcinoma patients who ever or never received Chinese herbal medicine (CHM) treatment. Median overall survival of 34 patients who ever received CHM treatment during their lung cancer disease process was 30.63 months (95% CI = 15.77 to not reached) compared to 23.5 months (95% CI = 21.03-25.7) in the remaining 493 patients (HR = 0.64, P = .118).

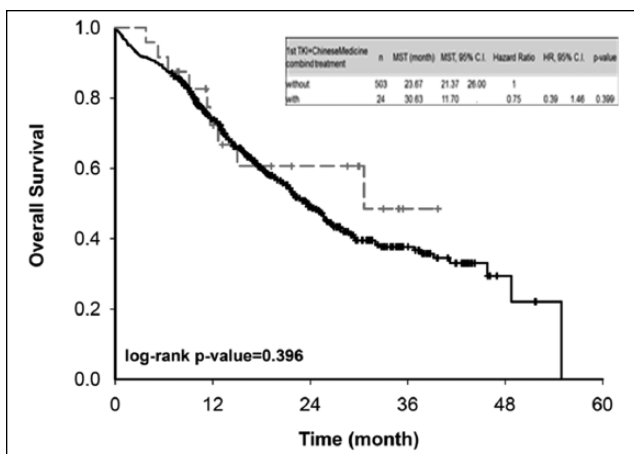


Figure 2. Overall survival of 527 EGFR-mutated pulmonary adenocarcinoma patients who received first-line EGFR-TKI treatment with or without Chinese herbal medicine (CHM) treatment. Overall survival in 24 patients who received CHM treatment together with EGFR-TKI was 30.63 months (95% CI = 11.7 to not reached), compared to 23.67 months in the remaining 503 patients (95% CI = 21.37-26; HR = 0.75, P = .399).

effect of CHM on different types of EGFR-TKI treatments, there was no statistical significance on PFS and overall survival on patients who received gefitinib treatment with or without CHM. The results were the same for patients who received erlotinib or afatinib treatment. There was also no statistically significant difference of the effect of CHM in PFS and OS in patients who were exon 19 deletions, nor exon 21 L858R (data not shown).

There were no specific expected toxicities related to CHM found in this present study. Regarding renal and hepatic toxicities, there was no significant statistical difference between patients who received both CHM and EGFR-TKI compared to patients treated with EGFR-TKI alone (see Table 2).

Discussion

Lung cancer treatment is now in an era of cooperative, multimodality treatments; and traditional CHM has been used in Asian countries for thousands of years. Thus, evaluation of the possibility of using CHM as adjuvant treatment for lung cancer patients is an important issue to address. The result of the study is promising, although modest and statistically nonsignificant. Since our physicians in the Center for Traditional Medicine can fully access patients' medical records in our outpatient clinic, CHM treatment could be given according to the patients' physical status and type of cancer treatment patients are receiving. This is important because if the patients call for CHM doctors outside of the hospital without adequate medical information, then adjuvant treatment will be less helpful, and even harmful. For example, herbal medicine with myelosuppressive function given to patients who are under cytotoxic chemotherapy will induce severe myelotoxicities.

Reasons for CAM (not limited to CHM) use and clinical characteristics associated with CAM use in cancer populations have been well documented and have been studied extensively in a systemic review article published in 2005.⁷

Table 2. Adverse Events of Special Interest in 527 EGFR-Mutated Adenocarcinoma Patients Who Received First-Line EGFR-TKI.

CTC Grade	EGFR-TKI + CHM, % (n = 24)				EGFR-TKI Alone, % (n = 503)				P
	1	2	3	4	1	2	3	4	
Increased serum creatine concentration ^a	4.2	0	0	0	6	3.2	4	0	.159
Increased serum total bilirubin concentration ^a	11.8	0	0	0	6.2	2.1	2.4	0.7	.597
Increased serum ALT concentration ^a	41.7	16.7	0	0	36.1	9.6	9.0	1.2	.551
Increased serum AST concentration ^a	41.7	4.2	0	0	28.8	4.7	3.0	0.4	.935

Abbreviations: CTC, common terminology criteria; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CHM, Chinese herbal medicine; ALT, alanine transaminase; AST, aspartate transaminase.

^aSerum chemistry changes: patients worsening from baseline to any grade or a specified grade.

It reported that a therapeutic response, wanting control, a strong belief in CAM, CAM as a last resort, and finding hope were the most commonly cited reasons for using CAM.⁷ Another systematic review of the literature about the use of herbal medicines used by cancer patients in the United Kingdom reported that declared motivations for using complementary and alternative therapies among cancer patients included the hope of a cure, remission or preventing disease spread, reducing treatment side effects, boosting the immune system, reducing stress/aiding relaxation, and improving quality of life.⁸ A recently published study examined current practices of 481 cancer patients and 100 health care providers as well as their interactions relating to complementary therapy use. Among the 224 participants who indicated their reasons for using complementary therapies, the 4 most prevalent reasons were to improve quality of life (64.7%), to improve the immune system (54.3%), to treat/be good to myself (40.8%), and to increase feelings of hope (35.1%). Forty-eight patients (21.6%) also reported that they were using complementary therapy to cure their cancer.⁹ As for Chinese patients, a comprehensive review of Chinese patients who received traditional CHM, including a total of 2964 reports (involving 253 434 cancer patients), was reported in 2013. However, the reasons for Chinese cancer patients receiving CHM were not reported in this review.¹⁰

There is preliminary evidence to encourage good-quality clinical trials to evaluate the efficacy of integrating CHM into modern cancer care. A scientific approach to introducing CHM into cancer care involves a systematic approach to phytochemical profiling, quality control, preclinical evaluation, safety evaluation, and phase I to III clinical trials. A *Cochrane Database Systemic Review* of CHM revealed only limited, weak evidence that some CHM improved leukopenia when used together with chemotherapy; and some CHM were of benefit for mitigating adverse effects in the digestive system caused by chemotherapy.¹¹ A double-blind placebo-controlled randomized study from Hong Kong with CHM as complementary therapy for reduction of chemotherapy-induced toxicity showed that CHM does not reduce the hematologic toxicity associated with chemotherapy. However, it has a

significant effect on nausea control.¹² The other randomized phase II trial of CHM (huachansu) combined with gemcitabine in patients with pancreatic adenocarcinomas showed no improvement in the outcome of patients with pancreatic cancer.¹³ There was also no symptom improvements or reductions of chemotherapy-induced toxicities found in this study. A meta-analysis of randomized trials of astragalus-based CHM showed that this CHM may increase effectiveness of platinum-based chemotherapy for advanced non-small cell lung cancer when combined with chemotherapy. However, these results still require confirmation with phase III randomized trials.¹⁴

Our patients who received CHM in our hospital were significantly younger than the remaining patients. A report of the American Cancer Society about the prevalence of complementary methods use by cancer survivors, who were surveyed 10 to 24 months after cancer diagnosis, showed that survivors more likely to use complementary methods were female, younger, white, higher income, and more educated.¹⁵ Another survey of the prevalence and predictors of complementary or alternative medicine use in patients at outpatient clinics of the University of Texas M.D. Anderson Cancer Center (Houston, TX) found that use was predicted ($P < .001$) by sex (female), younger age, indigent pay status, and surgery.¹⁶ Most of the similar studies showed that younger patients and females are more likely to seek CHM or alternative medicine, in addition to modern oncology treatment.¹⁷ It is important that oncologists are aware of what complementary medications, such as CHM, are being taken by their patients and have a basic understanding of the potential toxicities of these agents.¹⁸ Health care providers should be familiar with patients' CAM information sources, improve patient-provider communication, offer reliable information, and be able to discuss safety profiles and potential interactions with standard therapies.¹⁹

There were numerically longer PFS in patients treated with EGFR-TKI together with CHM in our study, although they were statistically nonsignificant. Overall survival was also nonsignificantly better in patients who also received CHM. Considering the absence of negative impact on survival status and no additional CHM induced toxicities,

further prospective clinical trial of lung cancer treatment with CHM as adjuvant therapy, and focusing on the improvement of patient's quality of life, mental status, symptom relief, and possible treatment efficacy involving survival status are required.

There are some limitations in our study. First, this was a retrospective study with an inevitable selection bias. For example, patients could call external Chinese medicine doctors or use CHM without informing our doctors. Second, not all patients called our CHM doctors regularly during EGFR-TKI or subsequent treatment. Third, only 24 of 527 patients received CHM and this ratio might lead to significantly statistical imbalance. Case-matching study is another way to evaluate the efficacy of CHM on EGFR-TKI treatment in lung cancer patients.

Conclusions

In conclusion, the use of CHM as adjuvant therapy for cancer patients is increasingly prevalent. Adjunctive CHM treatment during first-line EGFR-TKI treatment in EGFR-mutated stage IV non-small cell lung cancer patients at least does no harm to the patients, and their PFS and OS were numerically better than patients who did not receive CHM treatment. Further prospective study is warranted.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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