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Conventional Treatment Integrated with Chinese Herbal Medicine Improves the Survival of Patients with Advanced Non-Small Cell Lung Cancer

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Abstract

Background: There is a lack of research to evaluate the effectiveness of Chinese Herbal Medicine (CHM) as an adjunct therapy in patients with advanced Non-Small Cell Lung Cancer (NSCLC).

Objective: The main objective of this study was to assess whether the advanced NSCLC patients treated by Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs), when combined with CHM, can improve the five-year survival rate compared to those treated by EGFR-TKIs alone.

Methods: A nationwide population-based study of advanced NSCLC patients receiving EGRF-TKIs, combined with or without CHM treatment, was conducted in Taiwan. The study is based on information in the sub-dataset of the National Health Insurance Research Database (NHIRD) from 2000 to 2010, during which time a total of 14,244 patients were diagnosed with NSCLC. After selection of exclusion criteria and matching process, 2,616 NSCLC patients were included in the study. Statistical analysis was utilized to evaluate the differences in characteristic distribution, and to compare the survival rates between the CHM cohort and non-CHM cohort.

Results: Patients with advanced NSCLC using CHM as an adjunct therapy exhibited a significantly improved survival rate [hazard ration (HR) =0.8; 95% confidence interval (CI): 0.73-0.87, p value <0.001], compared with non-CHM users. Based on a survival analysis by Kaplan-Meier method, the 5-year survival rate of CHM users increased 4.9%, with the most notable difference being an increase of the 2-year survival rate by up to 12.75%. In addition to survival rate analysis, we provide the ten most used single herbs and herbal formulas prescribed for patients with advanced NSCLC.

Conclusion: This nationwide retrospective cohort study provides evidence supporting CHM as an effective adjunct modality to ameliorate the side effects of target therapy and prolong the five-year survival rate of patients with advanced NSCLC.

Keywords: Chinese herbal medicine; Non-small cell lung cancer; EGFR-TKIs; Retrospective cohort

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Introduction

Lung cancer is the leading cause of all cancer deaths in the world, whether in developed or developing countries. The diagnosis and treatment of lung cancer have made significant progress recently; however, the 5-year survival rate remains less than 15% [1,2]. According to a statistical analysis of cancer deaths in 2016 by the Ministry of Health and Welfare (MOHW) in Taiwan, the number of lung cancer deaths increased 5.7-foldover the prior three decades; meanwhile, lung cancer had the highest mortality rate for ten consecutive years, accounting for 25.4% of cancer deaths in 2016. It is generally believed that the particularly highly invasive nature of lung cancer cells is responsible for the high mortality rate of lung cancer, with nearly 90% of patients dying with metastasis [3]. Meanwhile, despite advances in treatment modalities, the overall 5-year survival rate of lung cancer patients has increased by only 4% (from 12% to 16%) over the past four decades [4]. Lung cancer may be subdivided into two categories: small cell lung cancer and Non-Small Cell Lung Cancer (NSCLC), accounting for approximately 13% and 87% of all lung cancers, respectively [5]. NSCLC can further be divided into three major cell types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, of which adenocarcinoma has the highest proportion, accounting for approximately 55% of incidence.

The development of Multi-Drug Resistance (MDR) to chemotherapy treatment has been cited as the primary cause of clinical failure in NSCLC treatment cases [6,7]. Gefitinib is the first generation of reversible Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI), which has become a standard first-line treatment for patients with EGFR mutations of NSCLC. In Taiwan, erlotinib has been used as the second generation of EGFR-targeted therapy since 2006. These EGFR-TKI drugs have demonstrated more effectiveness in treating patients with NSCLC than other targeted cancer therapies, and are consequently more commonly applied. The incidence rate of EGFR mutations are as high as 51.4% in patients with lung adenocarcinoma in Asia [8], where the application of EGFR-TKI drugs for the treatment of patients with advanced and metastatic NSCLC has exhibited therapeutic effects. Moreover, in comparison with platinum-based dual chemotherapy, gefitinib has shown Progression-Free Survival (PFS) in patients, and importantly, improved Quality of Life (QoL) [9,10]. However, many patients initially sensitive to gefitinib or erlotinib treatments have exhibited tendencies to develop drug resistance after six to twelve months [11]. Consequently, drug resistance and cytotoxicity are presently the two most significant therapeutic challenges facing targeted cancer therapies in clinical practice [12]; therefore, the discovery of effective drugs with limited toxicity remains a matter of urgency.

Chinese Herbal Medicine (CHM) is one of the most common complementary and alternative types of medicine used in the treatment of various ailments today. As such, CHM is gaining wider acceptance as an adjunct strategy for cancer treatment in particular. Traditional Chinese medicine has a long history of development, with roots tracing back thousands of years to China and other parts of East Asia, where it is commonly used in the treatment of cancer. It is applied to relieve clinical symptoms originating from cancer, and the related complications or side effects induced by chemotherapy or radiotherapy, having been shown to improve Quality of Life (QoL) and even prolong the five-year survival rate [13-15]. CHM can furthermore be used as an effective component of combined therapies to increase the efficacy of anti-cancer drugs [16-18]. With its long history of effective application in clinical practice, and reasonable cost, CHM is attracting the interest of scholars and researchers globally, further investigating its advantages in the treatment of cancer patients.

The National Health Insurance (NHI) system was launched in Taiwan in 1995, and the use of Traditional Chinese Medicine (TCM) as a treatment modality in itself, or as an adjunct therapy integrated with western medicine, has been reimbursed by the NHI since 1996. As of 2015, the NHI program covered 99.6% of the population of Taiwan [19]. The CHM granules supported by the NHI system in Taiwan, including single Chinese herbs and multi-herbal Chinese formulas, are produced by pharmaceutical companies in accordance with the Good Manufacturing Practice (GMP) certification mark. The purpose of this study is to analyze the NHI database from 2000 to 2010, to identify the frequency and prescription patterns of CHM as used in the treatment of NSCLC cancer patients, in combination with gefitinib or erlotinib treatment.

We herein conducted a population-based retrospective cohort study to evaluate and compare the cumulative five-year survival rates between CHM users and non-users in patients diagnosed with NSCLC; furthermore, this study explored the pharmacological prescription patterns of TCM practitioners.

Materials and Methods

Data source

The National Health Insurance (NHI) has provided affordable medical access to residents of Taiwan since 1995, currently registering over 99% of the population. The medical care data of the NHI are organized and released in the National Health Insurance Research Database (NHIRD) for medical research proposes after encryption of patient identification records. The Registry for Catastrophic Illness Patient Database (RCIPD) is a sub-dataset of the NHIRD, which contains the medical care data of patients with the catastrophic illnesses included therein. This study was approved by the Review Board and Ethics Committee of China Medical University Hospital, Taiwan (CMUH104-REC2-115(CR-2)).

Study population and covariates

This study investigated the usage patterns of CHM among patients with NSCLC. The lung cancer population was identified by the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) code 162 from the RCIPD. We further defined the NSCLC patients asthose lung cancer patients receiving erlotinib or gefitinib. The CHM users were defined as the population recorded as having a CHM clinical visit with code 162 after having been diagnosed with lung cancer. The non-CHM users were the lung cancer population without any CHM clinical visit recorded after being diagnosed with lung cancer. The various job types were classifiedunder the category of office worker, manual worker, or other. Any record of alcohol-related illness (ICD-9-CM: 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), cirrhosis (ICD-9-CM: 571 and A347), anemia (ICD-9-CM: 280-285), asthma (ICD-9-CM: 493), chronic obstructive pulmonary disease (COPD, ICD-9-CM: 491, 492, 493 and 496), diabetes mellitus (ICD-9-CM: 250 and A181), hypertension (ICD-9-CM: 401-405, A260 and A269), coronary artery disease (CAD, ICD-9-CM: 410-414), rheumatoid arthritis (RA, ICD-9-CM: 714), systemic lupus erythematosus (SLE, ICD-9-CM: 710.0), and stroke (ICD-9-CM: 430-438 and A29) before the diagnosis of lung cancer was considered as a comorbidity. Treatments of chemotherapy and/or radiotherapy were also included as covariates. Each CHM user was matched with one non-CHM user, according to the criteria of sex and age by frequency matching.

Statistical analysis

The Chi-square test and two-sample Student's t-test were utilized to evaluate the characteristic distribution differences between the CHM cohort and non-CHM cohort. The risk of mortality was displayed by Hazard Ratios (HRs). The HR was calculated by Cox proportional hazards regression with 95% Confidence Intervals (95%CIs). The variables of sex, age, job type, comorbidities, and treatments were considered in the multivariable Cox model. Network analysis was conducted by open-sourced freeware Node XL (http://nodexl.codeplex.com/) and utilized to analyze the relationship between two Chinese herbal products. The Kaplan-Meier method was used to compare the survival rate between CHM users and non-CHM users. Statistical analyses in this study were carried out by the statistical software package, SAS, version 9.4 (SAS Institute, Inc., Cary, NC) with significant level $\alpha = 0.05$.

Results

For initial application in the present study, there were 14,244 NSCLC patients recorded within the RCIPD (Figure 1). After selection

of exclusion criteria and matching process, 2,616 NSCLC patients were enrolled in this study. Those patients were classified into two groups, according to CHM using and non-using status. Among the CHM and non-CHM cohorts, approximately 53% of patients were male (Table 1), a majority of the individuals were older than 40 years of age, while approximately half of the NSCLC patients were manual workers. Of note, 96% and 70% of patients included in the study had received chemotherapy and radiotherapy, respectively. All covariates exhibited no significant differences between the two cohorts.

According to the Cox model analysis, the factors influencing mortality among NSCLC patients included usage of CHM, gender, age, job type, chemotherapy, and radiotherapy (Table 2). Compared to NSCLC patients without CHM use, NSCLC patients receiving CHM showed a 0.8 a HR (95%CI=0.73-0.87, p value <0.001). In addition, a higher mortality risk was noted in the male population (aHR=1.38, 95%CI=1.25-1.52, p value <0.001), and the manual worker population (aHR=1.24, 95%CI=1.1-1.4, p value <0.001); while older individuals showed a lower mortality risk than individuals 20 to 39 years of age. Additionally, patients having received chemotherapy or radiotherapy had the higher potential risk of mortality (aHR=1.48, 95%CI=1.1-2, p value <0.01; aHR=1.25, 95%CI=1.12-1.4, p value <0.01) compared to those without chemotherapy or radiotherapy treatment.

In terms of prescription behaviors by TCM practitioners, the ten single herbs in CHM most commonly prescribed for the treatment of patients with NSCLC are listed in Table 3. The most common of these ten herbs was *Hedyotidis Diffusae Herba*; with the second and third herbs being *Scutellaria, Barbatae, Herba* and *Fritillariae Cirrhosae Bulbus*, respectively. Of note, the average prescription duration was higher than ten days among the ten most common single herbs (Table 3). Furthermore, we herein list the ten most common formulas prescribed for the treatment of patients with NSCLC, as shown in Table 4. The top three formulas used were Xiang-Sha-Liu-Jun-Zi-Tang, Bai-He-Gu-Jin-Tang, and Qing-Zao-Jiu-Fei-Tang, respectively. The average daily doses among these ten formulas varied from 4.2 to 5.3 grams for patients with NSCLC; while the average duration for each prescription exceeded ten days (Table 4). Interestingly, the number of person-days of usage for the top ten single herbs was higher than most of the top ten formulas, while the total person-days of usage for *Hedyotidis Diffusae Herba* were more than double those of Xiang-Sha-Liu-Jun-Zi-Tang.

The analysis of CHM prescriptions for patients with NSCLC revealed that 30.86 percent of the prescriptions contained five or six Chinese herbal products in combination, while those containing seven or eight Chinese herbal products made of 27.71 percent of total prescriptions (Figure 2). The usage patterns and associations of the most common 50 herbs and formulas are illustrated in Figure 3. They demonstrate that *Hedyotidis Diffusae Herba*, *Scutellariae Barbatae Herba,* and *Fritillariae Cirrhosae Bulbus* were the three most frequent Chinese herbal products used in combination with one another; meanwhile, *Astragali Menbranacei Radix* and *Salviae Miltiorrhizae Radix*, in combination with *Hedyotidis Diffusae Herba* and *Scutellariae Barbatae Herba* were also notably used for treating patients with NSCLC. Bai-He-Gu-Jin-Tang and Qing-Zao-Jiu-Fei-Tang were the most commonly prescribed single herbs to be used in combination with other Chinese herbal products. The Kaplan-Meier method revealed a significant difference (p value <0.001) in the estimated five-year survival rate between the CHM cohort and non-CHM cohort (Figure 4), indicating that patients in the CHM cohort demonstrated a prolonged life span when compared to those in the non-CHM cohort.

Discussion

The importance of this study lies in the verification of whether CHM demonstrates a significant effect on advanced NSCLC patients. As such, the study reveals that the 5-year survival rate of NSCLC patients with both EGFR-TKI and CHM treatment increased by 4.9%, when compared to those patients without using CHM; furthermore, the most salient divergence in the 2-year survival rate exhibited as much as a 12.75% difference between the two cohorts. According to the NHI system, gefitinib and erlotinib are used primarily in patients with advanced and metastatic NSCLC, with the medical costs covered by the insurance system. It is important to note that if patients at the early-stage of NSCLC choose to use gefitinib or erlotinib, they are personally responsible for all costs, so the medical costs are relatively expensive. Consequently, the majority of gefitinib and erlotinib were prescribed for those patients with NSCLC at stage IIIB or IV, associated with the identification of EFGR mutation, and thus the NHI covers the EGFR-TKI treatment. Target therapy is therefore standard treatment in Taiwan for patients with advanced stage NSCLC. Although, it has been reported that the use of gefitinib or erlotinib can increase the incidence of Progression-Free Survival (PFS), but not the Overall Survival (OS) rate, in comparison with chemotherapy [20,21].

When comparing the differences between conventional western medical treatments and treatments with the integration of CHM, the results revealed a significant 0.8 difference in the Hazard Ratio (HR) of mortality, which is higher than the data of other studies [20-22]. The data indicates that CHM can not only increase the efficacy of treatment, but also reduce the side effects induced by target therapy, serving to improve the quality of life in patients with advanced NSCLC [23]. Both erlotinib and gefitinib have similar side effects, such as diarrhea, rash or acne, dry skin, pruritis, and interstitial lung disease, while between approximately 14% and 30% of patients undergoing target therapy treatment developed grade 3 or 4 adverse effects [9,21,24,25]. Due to such potentially harsh side effects induced by EGFR-TKI, it is likely that many patients will not be able to endure, and must consider stopping the treatment. Thus, we propose that CHM be combined with the EGFR-TKI treatment modality for advanced NSCLC to increase effectiveness, decrease toxicity, and prolong OS.

A study by Fidias *et al.* has shown that an effective dose of chemotherapy as associated with erlotinib and pemetrexed can delay NSCLC progression and extend the OS [26]. However, the side effects induced by such chemotherapy are more serious and unendurable than those induced by EGFR-TKIs in patients with NSCLC. The WHO has conducted a study of 26,957 NSCLC patients indicating that the performance status of patients is an independent prognostic factor for OS in NSCLC [27]. Therefore, how to maintain in dependent patient mobility, and the associated quality of life, are essential issues facing developers of NSCLC treatment strategies. To these ends, CHM can tonify Qi and nourish Blood to enhance physical strength, decrease the side effects induced by chemotherapy, and improve the quality of life [13,14]. Another factor which must be considered is cost. The expenses associated with target therapy and/or chemotherapy are significantly higher than that of CHM; as illustration, based on exchange rates at the time of this study, the cost of a CHM powder prescription is approximately US $1 per day in Taiwan. In terms of

therapeutic and economic benefits, CHM deserves consideration as an adjunct therapy in association with conventional medication.

A recent study has found that patients with lung cancer using CHM as an adjunct treatment demonstrated a 32% decrease in the all-cause mortality rate, and significant increases in survival rates of between 14% and 19% [28]. Our study arrives at similar results, showing that in patients with advanced NSCLC under treatment with EGFR-TKIs combined with CHM, the 5-year survival rate increased by 4.9%, while the 2-year survival rate improved by 12.75%. Since the resulting severity of advanced NSCLC is in itself greater than any other comorbidity, our study revealed no significant correlations with other comorbidities. Therefore, while the mortality rate in our study is less likely to be affected by any comorbidity, this also highlights the importance of CHM treatment in patients with advanced NSCLC. Both the abovementioned study and the present study indicate that patients who are older, male, or non-CHM patients, have a relatively higher mortality HR. Furthermore, in addition to the use of EGFR-TKIs, patients associated with chemotherapy or radiotherapy have higher HRs for mortality. Possible reasons could include the more severe condition of patients with NSCLC, or diminishing effectiveness due to the development of drug resistance under treatment with EGFR-TKIs. The present study indicates that the HR of patients between the ages of 20 and 39 years was higher; this could result from a bias due to too few samples, poor compliance for NSCLC, or an accelerated progression rate of advanced NSCLC among young Taiwanese patients. Our study further indicates that the HR of manual workers was 1.24 times more than that of office workers. Such a significant difference may be due to exposure to pollution sources. As illustration, Eckel *et al.* conducted a population-based cohort study of 352,053 lung cancer patients in California and found that the HRs of NO_2, PM10, and PM2.5 for all-cause mortality of lung cancer were 1.13, 1.11, and 1.16, respectively [29]; while the HR for adenocarcinoma was found to be significantly higher than that of small cell carcinoma [29]. Moreover, a study reported by Wei *et al.* on the exposure of NSCLC cell line A549 to PM2.5, found that the carcinogenetic mechanism of PM2.5 is associated with the induction of epithelial-mesenchymal transition and cancer stem cell activation [30]. This finding indirectly substantiates the notion that manual workers, as compared to office workers, will suffer more exposed to air pollution and increases the possibility of developing NSCLC.

The analytic results of our study revealed that most CHM formulas selected for the treatment of advanced NSCLC were those associated with strengthening of the Spleen Qi and nourishing the Lung Yin, according to TCM theory. The formulas prescribed for strengthening the Spleen Qi include Xiang-Sha-Liu-Jun-Zi-Tan, Bu-Zhong-Yi-Qi-Tang, Gui-Pi-Tang, and Liu-Jun-Zi-Tang. The formulas for nourishing the Lung Yin include Bai-He-Gu-Jin-Tang, Qing-Zao-Jiu-Fei-Tang, Sheng-Mai-San, Mai-Men-Dong-Tang, and Gan- Lu-Yin. The different formulas were applied according to the various symptoms associated with NSCLC patients. Under the management of target therapy, chemotherapy, and/or radiotherapy, the side effects developed are commonly associated with Spleen deficiency, Qi deficiency, or Yin deficiency, inducing various pathological effects. The use of CHM can strengthen the Spleen Qi and nourish the Lung Yin to reduce side effects and improve the quality of life. To this end, San-Zhong-Kui-Jian-Tang in association with *Hedyotidis Diffusae*, *Scutellariae Barbatae*, *Fritillariae Cirrhosae*, *Scutellaria baicalensis*, and *Houttyniae Cordatae* was commonly prescribed to treat patients with cancer. Furthermore, *Astragali Menbranacei Radix*, *Pinelliae Rhizoma*, and/or *Wolfiporia extensa* were prescribed to strengthen the Spleen Qi, as well as *Salviae Miltiorrhizae* or *Spatholobus suberectus* to invigorate Blood in order to alleviate blood stasis and improve poor circulation. Our results are in line with previous studies which indicate the importance of using CHM as an adjunct treatment to alleviate side effects and prevent cancer metastasis [14,31-33]. The possible anticancer biological effects and mechanisms of the most common single herbs and formulas are explained in supplementary Tables 1 and 2 [34-94].

CHM treatment emphasizes a holistic health care approach, and precise individual treatment based on four diagnostic examinations and syndrome differentiation. In Taiwan and other East Asian countries, CHM and acupuncture are commonly used as an adjuvant treatment for cancer patients. In this retrospective cohort study, the data was extracted from the NHIRD; therefore, there exist unavoidable limitations to this study. The NHI does not offer patient specifics, including laboratory data, images, pathology reports, and lifestyle details. Due to a lack of data, we could not assess if CHM influenced risk factors such as exposure to smoking and/or PM2.5, etc. Additionally, some cancer patients may intake supplements or medications from pharmacies instead of hospitals, the data of which were not recorded by the NHI. Finally, it must be noted that CHM is greatly complicated due to inherent variances of exact mixture concentrations of the various ingredients in each prescription. Although we identified the prescriptions, including single herbs and formulas, which were commonly used to treat patients with NSCLC, it is difficult to conclusively as certain the truly effective constituent compounds.

Conclusion

This nationwide retrospective cohort study provides evidence that CHM is an effective treatment modality to not only reduce the side effects, and improve quality of life, but also to prolong the five-year survival rate in patients with advanced NSCLC. However, it is necessary to further validate and investigate the therapeutic efficacy of CHM through well-designed prospective clinical trials in the future.

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