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Conventional treatment integrated with Chinese herbal medicine improves the survival rate of patients with advanced non-small cell lung cancer

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ABSTRACT

Objectives: The main objective of this study was to assess whether treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) combined with Chinese herbal medicine (CHM), can improve the five-year survival rate in patients suffering from advanced non-small cell lung cancer (NSCLC), compared to patients treated by EGFR-TKIs alone.

Interventions and main outcome measures: The study is based on information in the sub-dataset of the National Health Insurance Research Database (NHIRD) from years 2000 to 2010, during which time a total of 14,244 patients were diagnosed with NSCLC in Taiwan. After selection by 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 was 4.9% higher, with the most notable difference being an elevated 2-year survival rate of up to 12.75%. In addition to the survival rate analysis, we provide the ten most used single herbs and herbal formulas prescribed for patients with advanced NSCLC.

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

1. Introduction

Lung cancer is the primary cause of all cancer deaths in the world, both in developed and 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-fold over the prior three decades; meanwhile, lung cancer was responsible for the highest mortality rate for ten consecutive years, accounting for 25.4% of cancer deaths in 2016. This high mortality rate is generally believed to result from the highly invasive nature of lung

Abbreviations: CAD, coronary artery disease; CHM, Chinese herbal medicine; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; GMP, Good Manufacturing Practice; HR, hazard ratio; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; MDR, multi-drug resistance; MOHW, Ministry of Health and Welfare; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RA, rheumatoid arthritis; RCIPD, Registry for Catastrophic Illness Patient Database; SLE, systemic lupus erythematosus

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cancer cells, 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 accounts 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 the treatment of NSCLC cases.[6,7] Gefitinib was the first generation of reversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), and 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 is up to 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 indeed 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 alternative medicines used in the treatment of various ailments today. As such, CHM is gaining wider acceptance as an adjunct strategy for cancer treatment in particular. CHM 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 QoL and even prolong patients' five-year survival rate.[13–15] CHM can furthermore be used as an effective adjunct therapy 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, interested in further investigating its benefits as a cancer treatment.

The National Health Insurance (NHI) system was launched in Taiwan in 1995, and the use of CHM 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 Taiwanese population.[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 the years 2000 to 2010, in order 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 CHM practitioners.

2. Materials and methods

2.1. Data source

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 suffering from 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-3)).

2.2. 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, Clinical Modification (ICD-9-CM) code 162 from the RCIPD. We further defined the NSCLC patients as those lung cancer patients receiving erlotinib or gefitinib. The CHM users were defined as the population having recorded a CHM clinical visit with code 162 after having been diagnosed with lung cancer. The non-CHM users were the lung cancer population recording no CHM clinical visit after having been diagnosed with lung cancer. The various job types were classified under 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. The follow-up period started at the first recorded date of receiving CHM, and ended at mortality, withdrawal from NHI, or the end of 2011, whichever came first. For the non-CHM users, we assigned a dummy CHM receiving date to each subject to define the start of follow-up. The year of lung cancer diagnosis and CHM receiving date were considered as matching criteria, in order to ensure the lung cancer diagnosis and CHM receiving date were as close as possible between the two groups.

2.3. 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 (CIs). The variables of sex, age, job type, comorbidities, and treatments were considered in the multivariable Cox model. Network analysis was conducted by open-source freeware NodeXL (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 rates between the 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 $\alpha = 0.05$.