Effect of early use of Chinese herbal products on mortality rate in patients with lung cancer

Hsuan-Shu Shen[a,b], Shu-Hui Wen[c,*]

[a] Department of Chinese Medicine, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[b] School of Post-Baccalaureate Chinese Medicine, Tzu Chi University, Hualien, Taiwan
[c] Department of Public Health, College of Medicine, Tzu Chi University, Hualien, Taiwan

ARTICLE INFO

ABSTRACT

Ethnopharmacological relevance: Patients with lung cancer are frequently treated with Western medical treatments. Recently, patients have begun to use Chinese medicine to strengthen the immune system and alleviate side effects.

Aim of the study: We aimed to evaluate the association between mortality rate and early use of Chinese herbal products (CHPs) among patients with lung cancer.

Materials and methods: We conducted a retrospective cohort study based on the National Health Insurance Research Database, Taiwan Cancer Registry, and Cause of Death Data. Patients with newly diagnosed lung cancer between 2002 and 2010 were classified as either the CHP ($n = 422$) or the non-CHP group ($n = 2828$) based on whether they used CHP within 3 months after first diagnosis of lung cancer. A robust Cox regression model was used to examine the hazard ratio (HR) of death for propensity score (PS) matching samples.

Results: After PS matching, average survival time of the CHP group was significantly longer than that of the non-CHP group. The adjusted HR (0.82; 95% CI: 0.73–0.92) in the CHP group was lower than the non-CHP group. Stratified by clinical cancer stages, CHP group had longer survival time in stage 3 subgroup. When the exposure period of CHP use was changed from 3 to 6 months, results remained similar (HR = 0.85; 95% CI: 0.76–0.95).

Conclusion: Results indicated that patients with lung cancer who used CHP within 3 months after first diagnosis had a lower hazard of death than non-CHP users, especially for stage 3 lung cancer. Further experimental studies are needed to examine the causal relationship.

1. Introduction

Lung cancer is well known to have a high mortality rate. According to previous surveys, lung cancer remains the leading cause of cancer death globally (Miller et al., 2016). In Taiwan, lung cancer has the lowest 5-year survival rate of all types of cancer (Chiang et al., 2016). From the Western medicine viewpoint, malignant tumors are associated with immune suppression and low oxygen levels in the living environment (Fyles et al., 1998; Whiteside, 2006). Cancer cells progress and fail to be recognized by the host cell due to dysfunction of the immune system. Moreover, they inhabit a poorly oxygenated area, decreasing the effect of radiotherapy and chemotherapy treatments. In addition to Western medical treatments, traditional Chinese medicine (TCM) can serve as a complementary treatment for patients with lung cancer. Increasing numbers of patients are receiving TCM as an alternative treatment for cancer (Horneber et al., 2012). TCM considers malignant tumors to be the consequence of *qi* (energy) deficiency and

blood stagnation. Insufficient energy and impaired blood circulation for long periods will result in abnormal growth of cancer cells.

As an alternative treatment for cancer, TCM can be beneficial in reducing side effects, improving immune function, and prolonging survival time (McQuade et al., 2012). Previous reports showed that TCM can alleviate nausea and vomiting and improve anemia and neutropenia in patients with lung cancer (Chen et al., 2010; Li et al., 2013). Further, a longitudinal study found that Pan-Asian medicine and vitamins combined with Western medical treatment improved survival time in patients with lung cancer compared with Western medicine treatment alone (McCulloch et al., 2011). However, Pan-Asian medical treatments included not only TCM but also dietary supplements. In this case, it was difficult to determine the impact of TCM alone. To date, several studies have suggested that compared with Western treatment alone, patients with end-stage lung cancer receiving Western medical treatments combined with Chinese herbal product (CHP) showed longer survival time. However, there is insufficient data regarding when to

---

begin adjunctive TCM therapy in patients with lung cancer (Guo et al., 2011; R. Liu et al., 2015). As few studies have focused on decreasing cancer-related mortality rates via the early use of adjunctive TCM therapy, we aimed to perform a large-scale study to evaluate the effect of early use of TCM on survival time in patients with lung cancer.

2. Materials and methods

2.1. Data sources

Data sources were the longitudinal health insurance database (LHID), Taiwan Cancer Registry (TCR), and Cause of Death Data (CDD) from 2000 to 2011. These datasets were provided by the Health and Welfare Statistics Application Center, Ministry of Health and Welfare, Taiwan. However, access to LHID is available only by application to the Health and Welfare Statistics Application Center, Ministry of Health and Welfare, Taiwan. All applications are reviewed for approval to get access to LHID. We completed the application of LHID in 2015 at which the time period of data release was up to 2011. The LHID comprises medical claim data from 2 million beneficiaries that were randomly sampled from the registry of all National Health Insurance (NHI) enrollees in 2000. The LHID contains information on demographic variables, outpatient or inpatient visits, drug prescriptions, and disease diagnoses based on the *International Classification of Disease-Clinical Modification*, 9th edition (*ICD-9-CM*). All related information, including cancer site, clinical stage, and anticancer treatment were recorded in TCR. Diagnosis codes for cancer types followed the *ICD for Oncology*, 3rd edition (*ICD-O-3*) from 2002. We used TCR to identify patients with lung cancer, as well as their treatment and clinical stage; LHID to identify CHP use; and CDD to identify the cause of death. This study was approved by the Research Ethics Committee of Buddhist Tzu Chi General Hospital, Hualien.

2.2. Study sample and exposure assessment

We conducted a retrospective cohort study to examine the association of early CHP use and mortality rate among patients with lung cancer. Eligible subjects were patients with lung cancer (*ICD-O-3*: C340–C349) identified from TCR in 2002–2010 and aged > 18 years. In Taiwan, lung cancer is among the top three cancers with the highest mortality rates, and patients often die within the weeks following diagnosis. Previous reports have indicated that a quarter of patients with lung cancer died within 3 months following diagnosis. Considering clinical practice for the treatment of lung cancer and loss of follow-up due to death, we defined 3 months as the exposure window for determination of early CHP use in patients with lung cancer. The definition of the exposure period involves a trade-off between survival time and lag time from first diagnosis of lung cancer to first CHP use. Further, this exposure window was assumed to be unaffected by immortal time bias; in other words, 3 months was chosen to avoid bias in which patients who lived longer would be more likely to receive more CHP. In this case, it is difficult to determine whether CHP use would lead to longer survival time. Finally, we classified eligible patients as either CHP non-users (non-CHP group) or CHP users (CHP group) based on whether or not they received CHP within 3 months following first diagnosis date of lung cancer. The CHP group was defined as patients with any CHP use during the exposure window. The non-CHP group was defined as patients without any use of CHP during the exposure window. We excluded subjects who had (1) prior diagnosis of malignancy or death before enrollment; (2) prior diagnosis of lung cancer before 2002; (3) death within 3 months of first lung cancer diagnosis, thereby avoiding incomplete duration for defining early CHP use or
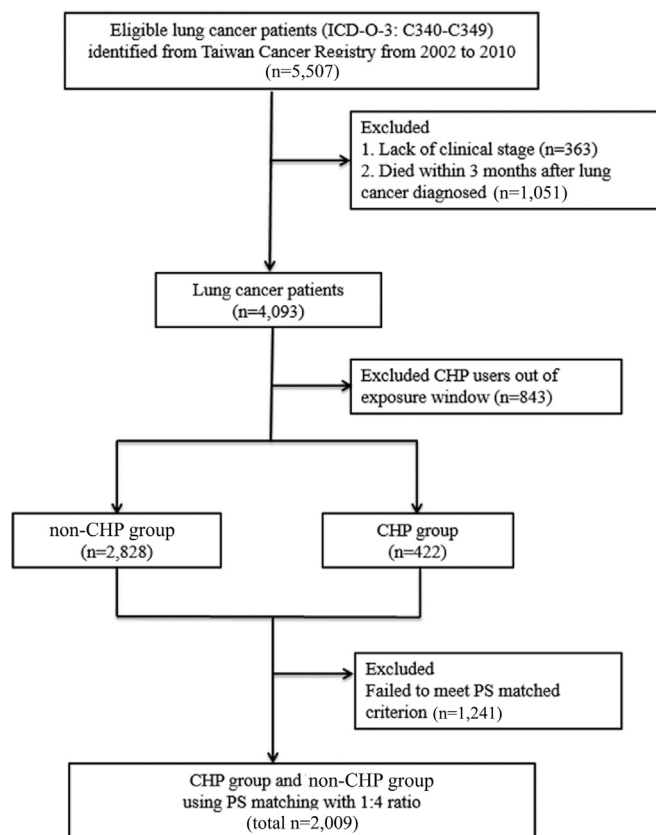

Fig. 1. Flowchart of study design.

because of not being able to be followed-up; (4) any CHP use after 3 months of first lung cancer diagnosis; or (5) lack of information regarding clinical stage. Finally, a total of 3250 patients were selected as the study cohort. To fairly compare CHP users and non-users, we adopted propensity score (PS) matching at a ratio of 1:4 of CHP to matched non-CHP patients (Fig. 1). PS (the predicted probability of CHP use) was calculated by logistic regression using gender, age, year of lung cancer diagnosis, and baseline comorbidities (described in more detail below) at enrollment. CHP users and non-users were matched by the greedy matching algorithm on the logit of the PS within a caliper of 0.2 of the standard deviation of the logit of the PS. Moreover, the exposure window of early use of CHP was crucial. A sensitivity analysis was implemented to examine if the results were robust to the definition of the exposure window. We extended the period of early CHP use to 6 months following the first diagnosis of lung cancer and evaluated the impact of longer exposure window on the mortality rate.

2.3. Outcome assessment and confounding variables

The primary outcome was lung cancer-specific death identified from CDD. The cause of death was classified according to ICD 10 (*ICD-10* C33-C34: Lung cancer). Patients were followed from the index date (i.e. 3 months after first lung cancer diagnosis), to date of death or December 31, 2011, whichever came first. Survival time was calculated in days from the first date of lung cancer diagnosis to either death or the end of study period. Potential confounding variables measured included demographic information (gender and age), baseline comorbidities, clinical stage of cancer, and treatment of lung cancer (year of lung cancer diagnosis, surgery, chemotherapy, radiation therapy). Baseline