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Complementary Chinese herbal medicine therapy improves survival of patients with gastric cancer in Taiwan: A nationwide retrospective matched-cohort study

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ABSTRACT

Ethnopharmacological relevance: Many patients with gastric cancer seek traditional medicine consultations in Asian countries. This study aimed to investigate the prescription of Chinese herbal medicine (CHM) and its benefits for the patients with gastric cancer in Taiwan.

Methods: From the Registry for Catastrophic Illness Patients Database, we included all patients with gastric cancer whose age at diagnosis was ≥18 from 1997 to 2010 in Taiwan. We used 1:1 frequency matching by age, sex, Charlson comorbidity score, treatment and index year to compare the CHM users and non-CHM users. We used the Cox regression model to compare the hazard ratios (HR) for the risk of mortality and the Kaplan–Meier curve for the survival time.

Results: There was a total of 1333 patients in the CHM-cohort and 44786 patients in the non-CHM cohort. After matching, we compared 962 newly diagnosed CHM users and 962 non-CHM users. Adjusted HRs (aHR) were higher among patients of above 60-year-old group, with a Charlson Comorbidity Index score ≥2 before the index date, and those who need surgery combined with chemotherapy or radiotherapy. CHM users had a lower HR of mortality risk (adjusted HR: 0.55, 95% CI: 0.48–0.62). Compared to the non-CHM users, the aHR among CHM-users is 0.37 (95% CI:0.2–0.67) for those who used CHM more than 180 days annually. The Kaplan–Meier curve revealed that the survival probability was higher for complementary CHM-users. Bai-Hua-She-She-Cao (Herba Hedyotidis Diffusae) was the most commonly used single herb and Xiang-Sha-Liu-Jun-Zi-Tang was the most commonly used herbal formula among CHM prescriptions.

Conclusions: Complementary CHM improves the overall survival among patients with gastric cancer in Taiwan. Further ethnopharmacological investigations and clinical trials are required to validate the efficacy and safety.

Abbreviations: CAM, complementary and alternative medicine; CCI, Charlson Comorbidity Index; CHM, Chinese herbal medicine; CI, confidence interval; HR, hazard ratio; ICD-9-CM codes, International Classification of Diseases, Ninth Revision, Clinical Modification codes; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; RCIPD, Registry for Catastrophic Illness Patients Database; TCM, traditional Chinese medicine

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1. Introduction

Gastric cancer is one of the most common cancers in the world, especially in Asia (Shen et al., 2013). About eighty-five percent of them are adenocarcinomas, with other fifteen percent due to leiomyosarcomas, lymphomas, and gastrointestinal stromal tumors (Hartgrink et al., 2009; Waddell et al., 2014). Etiology of gastric cancer is associated with diet and infection of Helicobacter pylori. Conventional treatment includes surgery, radiotherapy, and chemotherapy. Surgical resection is taken as first-line therapy and adjuvant therapy such as chemotherapy or radiotherapy are often given in the advanced stage (Shah and Ajani, 2010; Van Cutsem et al., 2016). The 5-year survival for gastric cancer varied from 54% to 58% in Japan and South Korea to less than 40% in other countries (Allemani et al., 2015). Some patients also seek for complementary and alternative medicine (CAM) therapy for improving their quality of life (McCall et al., 2016) or relieving symptoms such as nausea, cramps, diarrhea and malnutrition (Chae et al., 2016; Lau et al., 2016).

In Taiwan, traditional Chinese medicine (TCM) is one of the mainstream CAM therapies for cancer patients (Fleischer et al., 2016a, 2016b; Yen et al., 2016). TCM consultation is given by qualified TCM doctors who usually received 7–8 year baccalaureate or 5-year post-baccalaureate medical education in Taiwan. TCM consultations include Chinese herbal medicine (CHM), acupuncture, and Chinese traumatology. Although some earlier studies have demonstrated the potential benefits of complementary herbal medicine treatment for patients with gastric cancer (Gunji et al., 2013; Taguchi et al., 2016; Takiguchi et al., 2013), large-scale clinical analysis of CHM usage in patients with gastric cancer is still absent.

In 1995, the National Health Insurance (NHI) program was implemented in Taiwan, which included Western medicine and TCM. Over 99% of 23-million people has enrolled in the program (NHIA, 2015). The computerized database of this NHI program, National Health Insurance Research Database (NHIRD), is maintained by the National Health Research Institutes and provided to scientists in Taiwan for research purposes. The NHIRD consists of registration files and original claim data for reimbursement, which avoids the selection bias and provides researchers a comprehensive understanding of the healthcare utilization, including Western medicine and TCM (Hsing and Ioannidis, 2015). For example, we have found that adjunctive CHM therapy improved the survival of patients with leukemia (Fleischer et al., 2016b, 2016c).

Hence, in order to fill the gap in existing research, we used NHIRD to address the following research question: How was the utilization of CHM in patients with gastric cancer in Taiwan?

2. Methods

2.1. Data source

All data were acquired from the NHIRD maintained by the National Health Research Institutes, Taiwan (http://nhird.nhri.org.tw/en/). The datasets included registry files as well as inpatient and outpatient claim data. The NHIRD has a Registry for Catastrophic Illness Patients Database (RCIPD), which enrolled every individual with catastrophic illness proven by the laboratory, pathological and clinical diagnoses and reviewed by specialists commissioned by the NHI Administration. All registered gastric cancer patients are issued catastrophic illness certificates and waived the copayments to visit TCM or Western medical doctors for cancer-related treatment. These datasets consisted of demographic characteristics, clinical visits, hospitalizations, diagnoses, assessments, procedures, prescriptions, and the medical costs for reimbursement. Diagnoses were in the format of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Ambulatory care recorded the three primary diagnosis codes, while inpatient care recorded one ICD-9-CM codes for principal diagnosis and four secondary diagnoses at most.

2.2. Study population

From the RCIPD, we identified every newly diagnosed gastric cancer patient (ICD-9-CM code: 151) whose age at diagnosis was ≥18 for the period from 1997 to 2010 and did not have past history of perforated peptic ulcer (ICD-9-CM code: 531.10, 531.11, 531.20, 531.21, 533.10, 533.11, 533.20, 533.21, 534.10, 534.11, 534.20 and 534.21) as the study cohort. We followed up the patients until December 31, 2011, or the patient's date of death. All of the gastric cancer patients were diagnosed by the gastroenterologists, oncologists or general surgeons. The NHIRD included all information of TCM and Western medicine consultations. To address the question of the utilization of CHM, we excluded patients who came to TCM outpatient service only for acupuncture or tuina/traumatology. Patients who had TCM outpatient records after the date of diagnosis and took CHM for more than 30 days were defined as CHM users. Patients who never visited TCM doctors or who didn't continue TCM consultation after 30 days are categorized as non-CHM users. There was a total of 1333 patients in the CHM cohort and 44,786 patients in the non-CHM cohort. We matched 962 newly diagnosed gastric cancer patients who received CHM with the same number from comparison cohort by using one to one frequency matching (Fig. 1).

2.3. Study variables

The index date was the date of diagnosis of gastric cancer. Endpoint of this study was defined as the time from the index date until death, withdrawal of the database or December 31, 2011. The survival

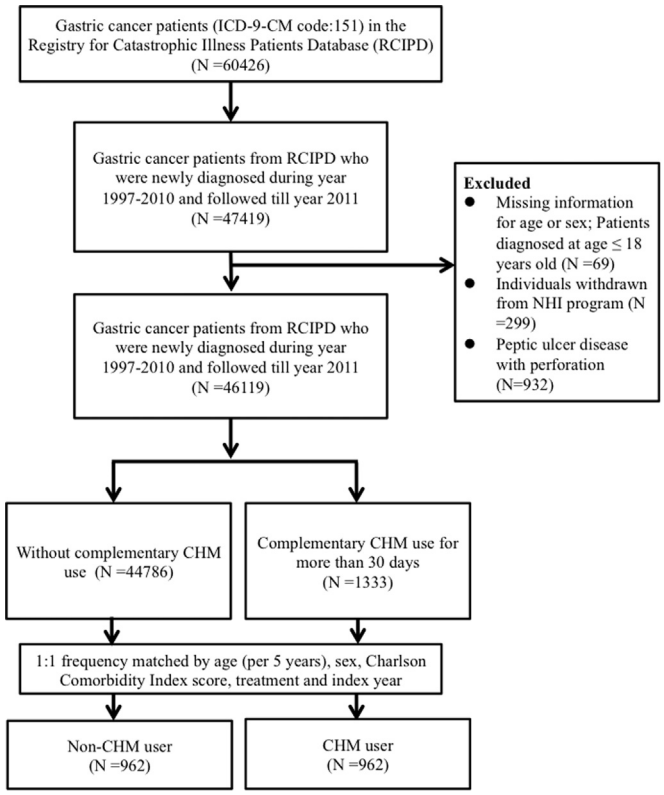

Fig. 1. Flow recruitment chart of patients with gastric cancer from the Registry for Catastrophic Illness Patients Database (RCIPD) of the National Health Insurance Research Database (NHIRD) during the year 1997–2000 in Taiwan. After exclusion of patients not fitting the inclusion criteria and after matching 1:1 by age, sex, Charlson Comorbidity Index score, treatment and index year, both Chinese herbal medicine (CHM) and non-CHM groups contained 962 patients.