



The use of Chinese herbal medicine as an adjuvant therapy to reduce incidence of chronic hepatitis in colon cancer patients: A Taiwanese population-based cohort study



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ABSTRACT

Ethnopharmacological relevance: There is a decided lack of in-depth studies to evaluate the effectiveness of Chinese Herbal Medicine (CHM) as an adjuvant therapy on the incidence of chronic hepatitis in patients with colon cancer.

Aim of the study: The aim of this study is to assess whether CHM treatment decreased the incidence of chronic hepatitis in colon cancer patients who received conventional Western medical treatment.

Materials and methods: A Taiwanese nationwide population-based study of colon cancer patients receiving Western medicine treatment in conjunction with CHM treatment, using data provided by the National Health Insurance (NHI) Research Database, was conducted. A total of 61676 patients were diagnosed with colon cancer in Taiwan within the defined study period, from 1997 to 2010. After randomly equal matching for age, sex, excluding patients younger than 18 years of age, chronic hepatitis before colon cancer diagnosis date, receiving acupuncture and/or moxibustion and taking CHM for less than 30 days, data from 155 patients were analyzed. Hazard ratios of incidence rate of chronic hepatitis were used to determine the influence of CHM and the therapeutic potential of herbal products in treating patients with colon cancer.

Results: CHM used for patients with colon cancer exhibited significantly decreased incidence rates of chronic hepatitis [hazard ratio (HR)=0.53; 95% confidence interval (CI):0.38–0.74], with multivariate adjustment, compared to those without CHM use. The protective effect of CHM treatment with statistical significance across the stratification of age, gender, co-morbidity and treatment modality was noted. The cumulative incidence of chronic hepatitis was also reduced in patients with colon cancer receiving CHM treatment during a five-year period. In this study, we provide the ten most used single herbs and herbal formulas that were prescribed for patients with colon cancer; moreover, we identify the eight single herbs and five formulas used in CHM treatment which significantly decreased incidence of chronic hepatitis among colon cancer patients.

Conclusions: This nationwide retrospective cohort study determined that therapy using CHM as an adjuvant modality may have a significant impact on liver protection in patients with colon cancer.

1. Introduction

In recent decades, cancer has emerged as a leading cause of death

globally, involving abnormal cell growth with the potential for metastasis to other parts of the body. Colon cancer is the third most commonly diagnosed cancer in males and the second in females, with

Abbreviations: CHM, Chinese Herbal Medicine; NHI, National Health Insurance; HR, hazard ratio; CI, confidence interval; 5-FU, 5-fluorouracil; GMP, Good Manufacturing Practice; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; P-gp, P-glycoprotein; LC3, microtubule-associated protein light chain 3S

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an estimated 1.4 million cases and 693,900 deaths occurring in 2012 (Torre et al., 2015). Currently, the 5-year overall survival rate remains at about 60% (Moghimi-Dehkordi and Safaei, 2012). While 25% of patients are diagnosed as having colorectal cancer with metastases initially, nearly 50% of patients will develop metastases, leading to the high rates of mortality (Van Cutsem et al., 2014). Conventional treatments of colorectal cancer include surgery, radiation, and chemotherapy. The favored treatment is complete surgical removal of localized tumor, in addition to chemotherapy in patients with nearby lymph node invasion or distal metastasis. Previous studies have demonstrated that the 12.5% of patients with unresectable colon cancer with liver metastasis are associated with an improved survival rate by liver surgery after chemotherapy (Adam et al., 2004; Lam et al., 2012). Most often, 5-fluorouracil (5-FU) has been used to treat advanced colon cancer since the 1990s (Laufman et al., 1987). The cytotoxic agents, such as oxaliplatin and irinotecan, were added on the standard regimens for chemotherapy: 5-FU/leucovorin/oxaliplatin or 5-FU/leucovorin/irinotecan (McWhirter et al., 2013). The combined regimens gave significantly higher treatment response rates, limitation of cancer progression, and longer survival periods (Douillard et al., 2000). Even for patients with metastatic colon cancer for whom 5-FU treatment failed, irinotecan could also have anticancer effects, including longer survival periods, fewer tumor-related symptoms, and a generally improved quality of life (Cunningham et al., 1998). While chemotherapy possesses benefits for advanced colon cancers, drug-induced hepatotoxicity has continued to be noted as a serious condition resulting from such treatment (McWhirter et al., 2013). For instance, 5-FU has been reported to increase hepatocyte steatosis via impaired β -oxidation and accumulation of fatty acids associated with increased post-operative infection. Irinotecan is often associated with steatohepatitis via mitochondrial impairment, leading to impaired β -oxidation and inflammation secondary to cytokine release. The patients with steatohepatitis had an increased risk of 90-day mortality rate after hepatic surgery compared to those without steatohepatitis (Vauthey et al., 2006). Meanwhile, oxaliplatin might cause sinusoidal dilatation or sinusoidal obstruction syndrome via generation of reactive oxygen species (ROS), or up-regulation of inflammation genes to induce hepatitis (McWhirter et al., 2013). Although the surviving patients have an association with improved liver function, the abnormal liver function induced by chemotherapy could interrupt and limit the treatment of patients with colon cancer (Sabbagh et al., 2015).

Traditional Chinese herbal medicine has been used to treat illnesses or symptoms of illness for thousands of years. Many studies of animal-liver injury models have proven that certain Chinese herbs or formulas, such as *Schisandra chinensis* (Wuweizi) (Hwang et al., 2013), curcumin (Girish and Pradhan, 2012), *Polygonum cuspidatum* (Zhang et al., 2012), *Gentiana asclepiadea* L. extracts (Mihailović et al., 2013), and *Rheum emodi* roots have protective effects for the liver (Akhtar et al., 2016). The Chinese herbal therapies demonstrated hepato-protective effectiveness via anti-inflammatory, antioxidant, anticancer, and immunomodulation effects (Wang et al., 2007). These defensive effects seem to reduce liver damage, even that resulting from chemotherapy. Furthermore, a recent cohort study demonstrated that the use of Chinese herbal medicine (CHM) may decrease the risk of death in patients with chronic hepatitis B receiving lamivudine treatment (Tsai et al., 2015).

In Taiwan, under the health insurance system, Western medicine combined with traditional Chinese medicine has been used to treat patients for many years, since CHM granules are supported by the National Health Insurance (NHI) system in Taiwan. The CHM is not only used to restore physical energy but also to reduce side effects resulting from radiotherapy and chemotherapy in patients suffering from cancer (Ye et al., 2015; Lin et al., 2013). These Chinese herbal products include single Chinese herbs and multi-herbal Chinese formulas. All of these CHM granules covered by the NHI program are manufactured by Good Manufacturing Practice (GMP)-certified

pharmaceutical companies. The daily clinical practices of actual CHM granules usage are recorded in the NHI database. The purpose of the present study is to determine whether using CHM as an adjuvant therapy for the treatment of advanced colon cancer with chemotherapy has liver-protective effects, or contrarily, acts to increase the burden placed on the liver. Herein, we conducted a population-based retrospective cohort study of the NHI database to evaluate and compare the cumulative incidence of chronic hepatitis between CHM users and non-users in patients diagnosed with colon cancer.

2. Materials and methods

2.1. Data source

This study used reimbursement claim data from the Taiwan National Health Insurance Program. An NHI program was implemented in March 1995, which consists of 22.6 million individuals from a total population of 23.0 million in Taiwan, who were enrolled in this insurance program. The NHI is an obligatory universal health insurance program, offering comprehensive medical care coverage to 99% of the entire Taiwanese population and contracted with 97% of the hospitals and clinics (<http://www.nhi.gov.tw/english/index.aspx>). The National Health Insurance Research Database (NHIRD) covered every medical record, including use of traditional Chinese medicine treatment by the NHI. The datasets of the study consisted of registry for beneficiaries, ambulatory and inpatient care claims, and Registry for Catastrophic Illness from NHIRD. We used ambulatory and inpatient care records for cancer patients linked with the registry for Catastrophic Illness patients, within the period of 2000–2010, identify the study subjects for follow-up until the completion of the 2011 calendar year. Ambulatory care claims contain the International Classification of Disease, Ninth Revision, and Clinical Modification (ICD-9-CM) codes for one major and/or two secondary diagnoses, associated with individual's gender, date of birth and visit date. Inpatient care claims contain ICD-9-CM codes for one principal diagnosis and/or four secondary diagnoses. The Registry for Catastrophic Illness database contains data from those insured who suffer from major diseases and are granted exemption from co-payment. The registration with ICD-9-CM codes is also used for diagnosis by Chinese medical physicians, as requested by the NHI program. Because the NHIRD offers data to be used for the purpose of academic research, the present study was waived from informed consent. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

2.2. Study cohort identification

Colon cancer is one of the 31 categories of serious illnesses or injuries that result in a patient being issued with a Catastrophic Illness Certificate. The colon cancer cohort was comprised of patients who were newly diagnosed with colon cancer of ICD-9-CM code 153.x from 1997 to 2010 (n=74,028). We excluded patients of less than 18 years of age (n=43), and those who had withdrawn from insurance or were diagnosed with chronic hepatitis before the first diagnosis date of colon cancer (n=12,309). The 61,676 patients diagnosed with colon cancer from 1997 to 2010 years were included (Fig. 1). Chronic hepatitis patients coded by ICD-9-CM 571.4, associated with ICD-9-CM 153.x to indicate colon cancer, were identified. All eligible patients were followed up from the index date to December 31, 2011.

Those patients with colon cancer receiving acupuncture, and orthopedics and traumatology of TCM were excluded from this study. Participants using CHM for a period of more than 30 days with a diagnosis of colon cancer were defined as CHM users; whereas those without CHM outpatient records were defined as the non-CHM cohort group. The CHM user cohort index was further defined from the first

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