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The effectiveness of anticancer traditional Korean medicine treatment on the survival in patients with lung, breast, gastric, colorectal, hepatic, uterine, or ovarian cancer

A prospective cohort study protocol

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Abstract

Although anticancer traditional Korean medicine treatment (ACTKMT) is widely applied to patients with cancer together with, or in place of, conventional cancer treatment in Korea, the cohort evidence on its clinical effects is lacking. Therefore, this prospective cohort study is designed to evaluate the effect of ACTKMT on the survival and the clinical outcomes for patients being treated at an integrative oncology clinic.

This is a single center, prospective cohort study of patients within 1 year after the diagnosis of primary lung, breast, gastric, colorectal, hepatic, uterine, or ovarian cancer. The event-free survival, disease-free survival/progression-free survival, the overall survival, the results of blood tests, and telomere-length information will be compared between patients receiving and patients not receiving a key ACTKMT (HangAmDan-B1, Geonchil-jung, and/or cultivated wild ginseng pharmacopuncture), and the correlation between the use of the key ACTKMT and the prognosis will be identified considering other risk factors.

This study has received ethical approval from the Institutional Review Board, Dunsan Korean Medicine Hospital of Daejeon University (No. DJDSKH-16-BM-09). The results of this study will be published in a peer-reviewed journal.

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Abbreviations: ACTKMT = anticancer traditional Korean medicine treatment, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANOVA = analysis of variance, AST = aspartate aminotransferase, BDI-II = Beck Depression Inventory-II, BUN = blood urea nitrogen, CAM = complementary and alternative medicine, CRIS = Clinical Research Information Service, CRP = C-reactive protein, CTCAE = Common Terminology Criteria for Adverse Events, DFS = disease-free survival, ECOG PS = Eastern Cooperative Oncology Group Performance Status, eCRF = electronic case report form, EDTA = ethylenediaminetetraacetic acid, EFS = event-free survival, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, ESR = erythrocyte sedimentation rate, EWCC = East-West Cancer Center, HAD-B1 = HangAmDan-B1, HR = hazard ratio, ICTRP = International Clinical Trials Registry Platform, IRB = Institutional Review Board, MedDRA = Medical Dictionary for Regulatory Activities, NCCIH = National Center for Complementary and Integrative Health, OS = overall survival, PFS = progression-free survival, qPCR = quantitative real-time polymerase chain reaction, SEER = Surveillance, Epidemiology, and End Results, STAI-KYZ = Spielberger's State-Trait Anxiety Inventory-form Korean YZ, TKM = traditional Korean medicine, WHO = World Health Organization.

Keywords: anticancer traditional Korean medicine treatment, prospective cohort study, quality of life, survival, telomere length

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1. Introduction

In Korea, the mortality rate for patients with cancer has shown a decreasing trend over the last ten years.[1] Furthermore, the cancer death rate has decreased by about 1.5% annually during the last decade in the United States.[2] Despite remarkable advances in conventional cancer treatments, cancer is still the leading cause of death in Korea[3] and the second leading cause of death in the United States.[2] A meta-analysis demonstrated that 40% of cancer patients were using complementary and alternative medicine (CAM) and that 43% of cancer patients had used CAM at some time.[4] A questionnaire study conducted in Australia found that the popularity of CAM use among cancer patients might reflect the benefits experienced by those who use it.[5] A clinical practice guideline published in 2017 recommended the use of meditation, yoga, acupuncture and botanical agents to improve quality of life and relieve symptoms in patients with breast cancer.[6]

The US National Center for Complementary and Integrative Health (NCCIH) defined CAM as a nonmainstream practice used together with, or in place of, conventional medicine.[7] According to NCCIH, 2 broad subtypes of complementary health approaches are the use of natural products and the use of mind and body medicine. Traditional Korean medicine (TKM), which uses these approaches including herbal medicine, acupuncture, moxibustion, qi-gong and so on, has been applied for treating various diseases including cancer with a holistic and personalized approach.[8] Our integrative cancer center has implemented anticancer TKM treatment (ACTKMT) as an integrative holistic cancer care for the past 20 years and has reported its benefits of reducing side effects associated with conventional cancer therapy, improving quality of life, and preventing metastasis.[9,10] However, this cancer treatment modality has not been studied through prospective survival analysis in terms of clinical impact by its key component.

A prospective cohort study from 2005 to 2006 in Korea suggested that terminal cancer patients who used CAM or a subgroup of the alternative medical system showed longer median survival than patients who did not, but the differences were not statistically different (use of CAM, $P = .07$; use of alternative medical system, $P = .4$).[11] Another cohort study involving patients with advanced non-small-cell lung cancer showed longer survival for patients in the integrative medicine group compared to those in the conventional medicine group.[12] However, the subjects of these studies were relatively heterogeneous and terminally ill with advanced stages of cancer. Also, these studies reported neither the duration of CAM use nor the rate of compliance with CAM; neither were relevant analyses reported. The results of these studies led us to design a prospective cohort study that observes over a prolonged period of time patients within one year of their being diagnosed with cancer and that collects and analyzes sufficient data in order to evaluate the effec of ACTKMT on survival.

2. Objectives

2.1. Primary objective

The primary objective of this study is to evaluate the effect of a key ACTKMT on event-free survival (EFS) in patients being treated at an integrative oncology clinic. In this study, a key ACTKMT is defined as treatment with a multiherbal formula containing Panax Notoginseng Radix, Cordyceps militaris, Panax Ginseng C.A. Mey., and Boswellia carterii BIRDWOOD (HangAmDan-B1; HAD-B1); Rhus verniciflua Stoke extracts (Geonchil-jung); and/or cultivated wild ginseng pharmacopuncture.

2.2. Secondary objectives

1. To evaluate the clinical impacts of a key ACTKMT on disease-free survival (DFS)/progression-free survival (PFS), overall survival (OS), the quality of life, the results of blood tests, and the telomere length for patients being treated with ACTKMT.

2. To identify the correlation between the clinical variables (including the use of ACTKMT) and the survival outcomes in the constructed cancer-cohort.

3. Methods

3.1. Study setting and participants

This study is a prospective cohort study comparing cases with noncases for all patients in the cohort population based on the participants' exposure to a key ACTKMT. The study started in September 2016, is currently ongoing, and will finish in September 2020. In this study, cases are defined as recurrence, metastasis, progression, or death. Patients within one year after the diagnosis of primary lung, breast, gastric, colorectal, hepatic, uterine, or ovarian cancer will be enrolled from the East-West Cancer Center (EWCC), Dunsan Korean Medicine Hospital of Daejeon University. In order to avoid the possibility of encountering incomplete data, patients selected for this study must have medical records that include the exact date of diagnosis, the stage of the cancer, and the pathological results. Patients with cancer who visit the EWCC will be identified based on regular clinical examinations by all medical doctors trained in the study's protocol. Patients who meet the eligibility criteria, which are presented in Table 1, will be involved in the study. As an open cohort, eligible subjects who have agreed to participate in the study will be continually added to the cohort population based on the pre-established disease registry. Empirically considering the trends of patients visiting the EWCC, we estimated thath about 180 subjects will be enrolled (45 or more per year) and analysized at the end of study. As EWCC's routine treatment continues, follow-up visits will be scheduled every 6 months (± one month) until one year from the baseline and every year (± 1 month) after that. The maximum duration of follow-up will be 4 years. To ensure that patients adhere to the follow-up schedule, we will use phone calls or text messages to remind patients of their scheduled visits. The study flow is demonstrated in Figure 1.

3.2. Ethical issues

This study was registered at the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP): Clinical Research Information Service (CRIS) (Registration No. KCT0002160). The initial protocol of this study was approved by the Institutional Review Board (IRB), Dunsan Korean Medicine Hospital of Daejeon University, on September 19, 2016 (Study approval No. DJDSKH-16-BM-09). Because the study ends on September 30, 2020, a continuing review of research progress will be done every year from the start of the study. Informed research consent, human derivative research consent, human derivative donation consent, and genetic test consent will be obtained from all participants. A participant will be discontinued from the study if a severe adverse event occurs or

Table 1

Inclusion and exclusion criteria.

Inclusion criteria

1. Persons between 18 and 80 years old with primary lung, breast, gastric, colorectal, hepatic, uterine, or ovarian cancer;
2. Persons within one year after the diagnosis of the main cancer without recurrence or distant metastasis (code 7 based on SEER* summary staging; distant site(s)/node(s) involved) when screened;
3. Persons who have medical records that include the date of diagnosis, the stage of the cancer, and pathological results;
4. Persons who are receiving conventional cancer treatments, have finished conventional cancer treatments without any residual mass, or are receiving only traditional Korean medicine cancer treatments after having ceased, or having never received, conventional cancer treatments;
5. Whether or not having received traditional Korean medicine cancer treatments before, persons who agree to receive ACTKMT at the East-West Cancer Center, Dunsan Korean Medicine Hospital of Daejeon University;
6. Persons with an Eastern Cooperative Oncology Group Performance Status less than two;
7. Persons who voluntarily agree to participate in the study;
8. Persons who consent to provide personal information.

Exclusion criteria

1. Persons who visit the outpatient department at the East-West Cancer Center, to consult a Korean medicine doctor, but reject receiving traditional Korean medicine cancer treatments;
2. Persons with a life expectancy of less than 3 months or whose the Eastern Cooperative Oncology Group Performance Status is more than 3;
3. Persons who do not have medical records that include the date of diagnosis, the stage of the cancer, and pathological results;
4. Persons who cannot participate in the study due to other medical conditions or mental problems;
5. Persons who are judged improper to participate in the study according to the decision of the study physician.

* SEER = Surveillance, Epidemiology, and End Results.

the researchers, for any safety reason, judge the participant's continuation in the study not to be appropriate. In the case of discontinuation, the principal investigator will ask the IRB for permission to discontinue the participant from the study; the status of the participant as it pertains to this study will be in accordance with the decision of IRB.

3.3. Exposure and nonexposure

In this cohort study, no TKM treatments, such as herbal medicine and/or acupuncture, will be performed for the purpose of intervention. A participant will receive ACTKMT only as prescribed by his or her medical doctors according to the purpose of the treatment, which is established using both the status of the participant's disease and the participant's condition. This study will collect information on the participant's exposure to a key ACTKMT. That information will include the duration of treatment, the prescribed ACTKMT, and the rate of compliance with treatment between follow-up visits. A key ACTKMT is defined as treatment with HangAmDan-B1 (HAD-B1), *Rhus verniciflua Stoke* extracts (Geonchil-jung), and/or cultivated wild ginseng pharmacopuncture. The raw materials of HAD-B1 are *Panax Notoginseng, Radix Cordyceps militaris, Panax Ginseng C. A. Mey., and Boswellia carterii BIRDWOOD* in a ratio of 1.75: 1.3: 1.3: 1, and its fluid extract is dried in a powder form to be prescribed as a 486 mg capsule (3 times a day on average). Geonchil-jung contains 500 mg of *Rhus verniciflua Stoke* extract per capsule, and 2 capsules are administrated at a time (3 times a day on average). The cultivated wild ginseng pharmacopuncture contains an active ingredient panaxydol of 0.36 mg/20 mL or more and is prescribed as a maximum of 20 mL per day. Our research team reported liquid chromatography data on the 3 herbal medicines above in the previous studies.[13–15]

3.4. Data collection and management

The data collected in the cohort study contain demographic and clinical characteristics, cancer history, and status of the key ACTKMT. Demographic characteristics include information on gender, birth, age, height, weight, body mass index, residence, marital status, occupation, education, household income, and private insurance status. Clinical characteristics include information on the quality of life, depression, anxiety, past medical history, family history, smoking, drinking, menstruation, the use of contraceptives, history of hormone therapy, adverse events, blood test results, and the telomere length. As cancer history, the primary cancer site, date of diagnosis, metastasis, metastatic site, number and TNM stage at the first diagnosis, number and TNM stage at enrollment, disease status, prior surgery, chemo/immuno/hormonal therapy, radiotherapy, cancer treatment currently being received, and cancer-related symptoms will be collected. The information on the ACTKMT contains the days of treatment between follow-up visits, the prescribed ACTKMT, and the compliance rate. The data described above will be collected at every visit.

The research doctors will collect the predefined data on clinical characteristics and cancer history while certificated clinical research coordinators will collect other data face-to-face. Blood tests will include complete blood counts, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), natural killer cell activity test, and tumor markers. The average telomere length and the percentage of length distribution per age group will be collected as telomere-length information.

Participants will receive personal identification numbers, and data for the individuals will be entered anonymously onto an electronic case report form (eCRF). For analyzing the data, a third party will anonymously extract data saved on the eCRF forms.

3.5. Outcome measures

The primary outcome of the study is EFS, defined as the time from the date of diagnosis to the date of recurrence, metastasis, progression, or death from any cause. The secondary outcomes are DFS/PFS, OS, quality of life, blood test results, telomere-length information, and adverse events. DFS/PFS will be measured depending on whether the patient has residual mass at the time of enrollment. Participants will report their disease

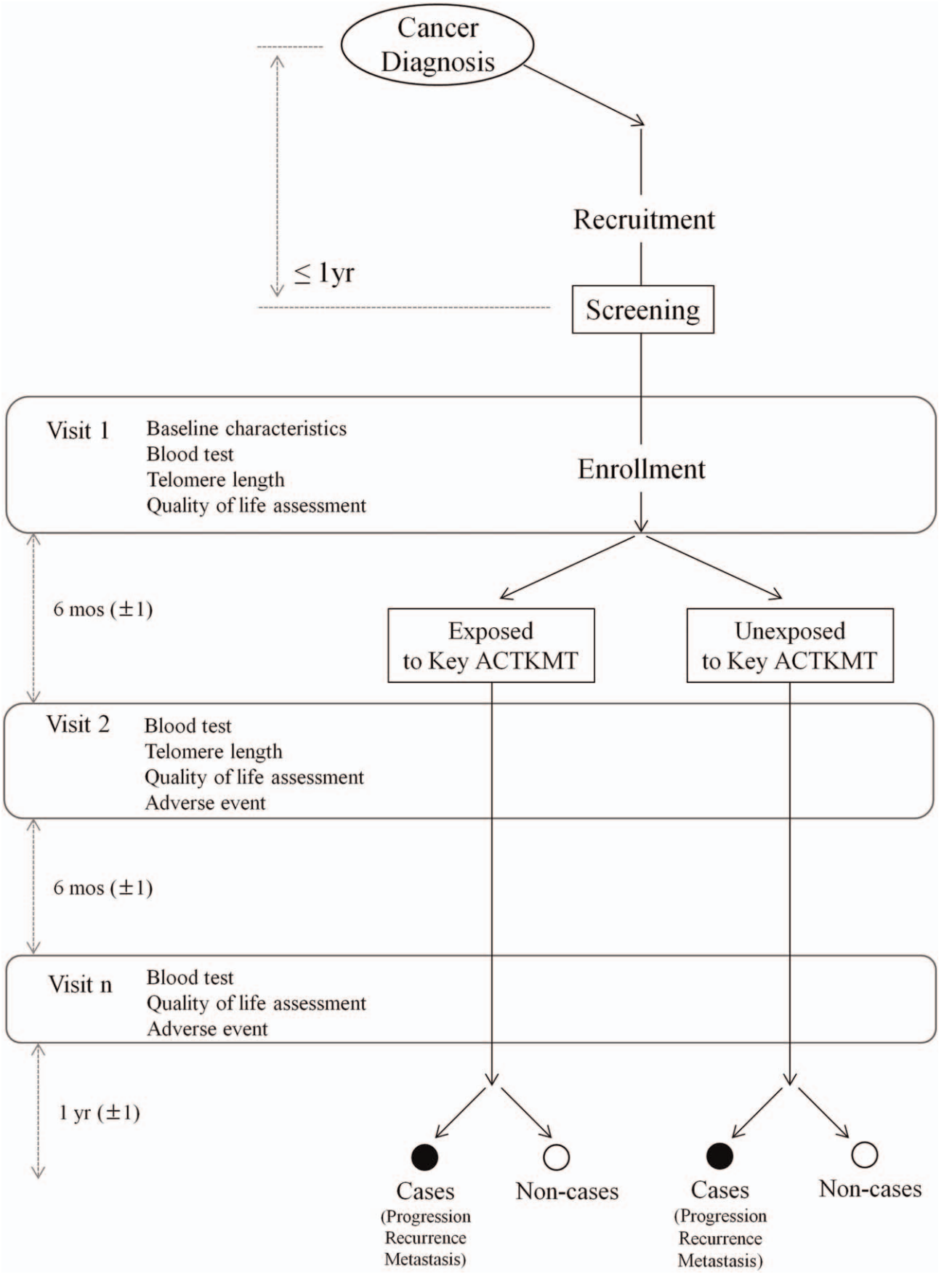

Figure 1. Study flow. ACTKMT = anticancer traditional Korean medicine treatment.

status, as well as cases such as recurrence, metastasis, and progression, at each follow-up visit. The quality of life will be assessed by using the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Beck Depression Inventory-II (BDI-II), and Spielberger's State-Trait Anxiety Inventory-form Korean YZ (STAI-KYZ). The ECOG PS, a 5-point scale, is widely used to assess the functional status of cancer patients.[16] This scale acts as a prognostic factor; patients with low ECOG PS have a better survival rate. The EORTC-QLQ-C30 is a reliable and valid measurement instrument for assessing the quality of life in patients with cancer.[17,18] This instrument contains 30 items, and global health status, functional scales, including physical, role, emotional, cognitive, and social functioning, and symptom scales, including fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties, are scored according to the scoring manual.[19] BDI-II[20] is a self-reporting 40-item questionnaire and is most commonly used in Korea to measure the severity of depression.[21] STAI-KYZ is a 20-item self-reporting questionnaire to evaluate state anxiety and trait anxiety. A previous case–control study found that patients with breast cancer tended to be unhappy compared to healthy subjects.[22]

The leukocyte telomere length in peripheral blood will be measured in this study. For the telomere length, 3 to 4 mL of blood will be drawn into an ethylenediaminetetraacetic acid (EDTA) tube and sent to Mediage Lab outside the hospital, where the telomere length will be determined by using the quantitative real-time polymerase chain reaction (qPCR).[23] At Mediage Lab, the percentage of length distribution per age group will be calculated using the Korean adult standard. For the blood bank, 8 mL of blood will be collected from participants who voluntarily complete the human derivative donation consent form for secondary research purposes. Plasma, buffy coat, and red blood cells separated by using a centrifugal separator, as well as a 4-mL EDTA bottle of whole blood, will be delivered to the human derivative bank and stored in a deep freezer.

3.6. Assessing adverse events

The medical term for an adverse event is defined according to the Medical Dictionary for Regulatory Activities (MedDRA), one of the international systems for classifying systems for adverse drug reactions. The grade of the adverse event will be established according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).[24] The relationship with ACTKMT will be assessed in accordance with the Korea Food and Drug Administration's Notification.

3.7. Data analysis

Descriptive analyses of the demographic and the clinical characteristics and the cancer history will be presented as means and standard deviations or frequencies. The statistical differences between the exposed and the unexposed will be assessed by using either the chi-squared test or Fisher's exact test for categorical variables and either the one-way analysis of variance (ANOVA) or the Kruskal–Wallis rank sum test for continuous variables. Participants flow during the study period will be reported. The survival outcomes will be compared between the exposed and the unexposed by using a Kaplan–Meier analysis with the log-rank test. Exploratory analyses of hazard ratios (HRs) will be performed through a Cox proportional hazard model, taking into account the clinical variables (including the use of ACTKMT), with 95% confidence interval and *P*-value. Statistical analyses will be conducted on the observed data without using any imputation of incomplete data.[25] Statistical analyses will be conducted by an independent statistician using IBM SPSS Statistics (version 23.0).[26]

4. Discussion

Recent reviews have suggested that adjunct CAM therapies, including acupuncture, pharmacopuncture, and herbs, have benificial effects on cancer-related symptoms, conventional treatment-associated side effects, and the response rate of the tumor.[27–34] However, limited cohort evidence has been published on its effects on survival and quality of life for patients being treated with TKM. The objective of this prospective cohort study is to evaluate both the effect of ACTKMT on EFS, DFS/PFS, OS, quality of life, blood test results, and telomere length and the adverse events associated with ACTKMT.

Prior to designing this prospective cohort study, a disease registry was established to store data prospectively collected from patients being treated with ACTKMT for lung, breast, gastric, colorectal, hepatic, uterine, or ovarian cancer at the EWCC, Dunsan Korean Medicine Hospital of Daejeon University. According to a descriptive analysis of a total of 785 patients who visited the EWCC in 2015, which was conducted internally in the beginning of 2016, the top nine cancers, according to numbers of patients diagnosed with diseases, were breast, gastric, lung, thyroid, uterine, ovarian, colorectal, pancreatic, and hepatic cancer. In 2014, the 5-year relative survival rates for patients with pancreatic cancer and thyroid cancer in Korea were 9.0% and 99.5%, respectively.[1] The 5-year survival rate for patients with pancreatic cancer, as reported by the American Cancer Journal for Clinicians in 2017, was 8%, the lowest for all carcinomas.[2] Because this study is based on long-term observation, pancreatic cancer was considered to be too difficult to follow-up and thyroid cancer was considered to be less important. Therefore, after extensive discussion among the researchers, the remaining 7 carcinomas, which accounted for about 82% of the patients seen at the EWCC in 2015, were selected for this study.

In this study, we defined a key ACTKMT as a multiherbal formula containing Panax Notoginseng Radix, Cordyceps militaris, Panax Ginseng C.A.Mey., and Boswellia carterii BIRDWOOD (HAD-B1); *Rhus verniciflua Stoke* extracts (Geonchil-jung); and/or cultivated wild ginseng pharmacopuncture. Previous studies demonstrated that HAD-B1 inhibited tumor growth and cell proliferation,[13] that Rhus verniciflua Stoke inhibited angiogenesis, tumor invasion, and cell cycle progression and induced apoptosis,[35,36] and that cultivated wild ginseng potentially inhibited inflammation and angiogenesis.[37–39]

Major strengths of this study are that data on demographic and clinical characteristics and on the status of the cancer can be accurately collected and that the detailed content of ACTKMT will be available, which should minimize bias in data analyses. On the other hand, one limitation is that the population at the end of the study is estimated to be small based on an empirical consideration of the trends in patients treated with ACTKMT at EWCC (an optional integrative oncolgy clinic). Moreover, this study might have selection bias because the cohort registry was established in a single center. However, we will continue the

observation for the participants in this cohort study with additional funding, and evaluate the effect of the ACTKMT on survival outcomes. Also, this is the first prospective cohort study to evaluate the effect of TKM on patients with any one of 7 carcinomas and is expected to provide valuable insights into ACTKMT.

Despite many efforts to find therapeutics for patients with cancer, the incidence rate of cancer and its mortality rate are still high. Large numbers of patients with cancer use CAM and TCM to relieve cancer-related symptoms and to improve the therapeutic effects of their treatment regimen. In addition, ACTKMT is expected to have a beneficial effect on the survival. This prospective cohort study will represent the current use of TKM in Korea and will be able to demonstrate the effect of ACTKMT on the survival of patients with any one of 7 carcinomas.

Author contributions

Kyeore Bae and Eunseok Kim are the co-first authors and contributed equally to the study design and the drafting of the manuscript. Hwa-Seung Yoo and Mi Kyung Kim conceived the concept of the study and are supervising its implementation. J.J. Choi helped establish a performance system for clinical chemistry. All of the authors have read and approved the final manuscript.

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