

BMJ Open Single-arm, open-label, dose-escalation phase I study to evaluate the safety of a herbal medicine SH003 in patients with solid cancer: a study protocol

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ABSTRACT

Introduction Cancer is a major health problem worldwide and the leading cause of death in many countries. The number of patients with cancer and socioeconomic costs of cancer continues to increase. SH003 is a novel herbal medicine consisting of *Astragalus membranaceus*, *Angelica gigas* and *Trichosanthes Kirilowii Maximowicz*. Preclinical studies have shown that SH003 has therapeutic anticancer effects. The aim of this study is to determine the maximum tolerated dose of SH003 in patients with solid cancers.

Methods and analysis This study is an open-label, dose-escalation trial evaluating the safety and tolerability of SH003. The traditional 3+3 dose-escalation design will be implemented. Patients with solid cancers will be recruited. According to dose level, the patients will receive one to four tablets of SH003, three times a day for 3 weeks. Toxicity will be evaluated using common terminology criteria for adverse events (CTCAE). Dose-limiting toxicities are defined as grade 3 or higher adverse events based on CTCAE. The maximum tolerated dose will be determined by the highest dose at which no more than one of six patients experiences dose-limiting toxicity.

Ethics and dissemination This study has been approved by the institutional review board of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311). The results of this study will be disseminated through a scientific journal and a conference.

Trial registration number NCT03081819; Pre-results.

INTRODUCTION

Cancer, which is caused by an uncontrolled division of abnormal cells in a part of the body, is a leading cause of death globally, accounting for 8.8 million deaths in 2015.¹ Moreover, the economic cost of cancer is increasing. In 2010, the total economic cost of cancer was calculated at approximately US\$1.16 trillion.² In Korea, there were 1.46 million patients with cancer, and 9.57% of people aged 65 and older were patients with cancer.³ The Korea National Health Insurance Service reported that the socioeconomic cost of cancer was more than US\$12.1 billion in 2012, which

Strengths and limitations of this study

- This is the first human study to examine the safety and feasibility of administering SH003 to treat patients with solid cancers.
- The present study is the first phase I study to determine the maximum tolerated dose of a herbal medicine in Korea.
- Limitations of this study are that pharmacokinetic and pharmacodynamic studies could not be conducted due to the nature of the drug.

accounted for 43.2% of the socioeconomic costs of the five major causes of death.⁴

Although many investigations and development of several anticancer drugs have been conducted, the global market for cancer treatment is continuing to grow due to unmet needs. Therefore, many herbal medicines have received attention as potential new anticancer drugs.

SH003 is a mixed herbal extract containing Huang-Qi (*Astragalus membranaceus*), Dang-Gui (*Angelica gigas*), and Gua-Lou-Gen (*Trichosanthes Kirilowii Maximowicz*), which are traditionally used in Korean medicine. Huang-Qi has been reported to be effective in cancer treatment in many previous studies.⁵ Dang-Gui enhances chemosensitivity in ovarian cancer cells by inhibition of P-glycoprotein expression.⁶ Gua-Lou-Gen has shown antitumour activity in cancer cells.⁷ According to the theoretical framework of Korean medicine, Huang-Qi has the effect of tonifying qi, Dang-Gui has the function of tonifying blood and Gua-Lou-Gen has the effects of disperse swelling and expel pus.⁸ Therefore, the combination of those herbs is expected to be effective in the treatment of patients with cancer.

It has been reported that SH003 suppresses breast cancer growth and metastasis by

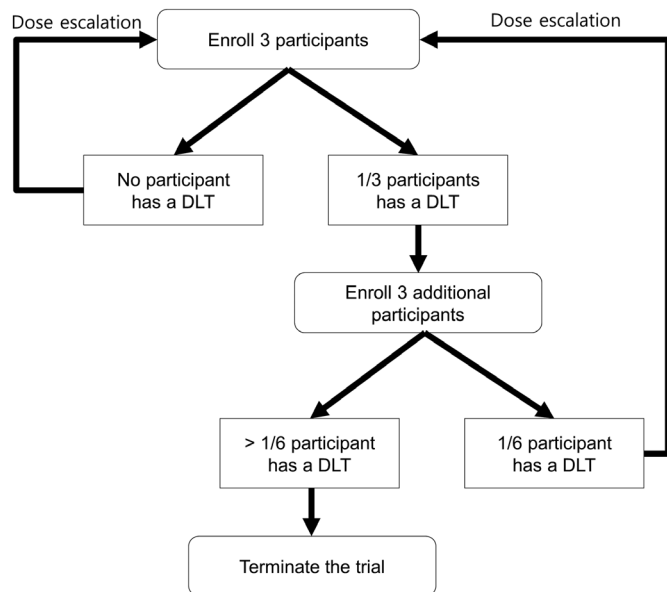


Figure 1 Study flow chart. DLT, dose-limiting toxicity.

inducing autophagy⁹ and inhibiting STAT3-IL-6 signaling.¹⁰ SH003 inhibits cell proliferation and induces apoptosis without an effect on normal cell viability.¹⁰ Moreover, it represses tumour angiogenesis by inhibiting vascular endothelial growth factor (VEGF)-induced VEGFR2 activation.¹¹ VEGF-induced phosphorylation of VEGFR2 is blocked by SH003 interrupting VEGF binding to VEGFR2. SH003 induces apoptosis of prostate cancer cells in a dose-dependent manner.¹² This is due to the intracellular mechanisms that SH003 inhibits extracellular signal-regulated kinase (ERK) 2-mediated signaling. In vivo xenograft studies have reported that SH003 inhibits tumour growth and metastasis,¹⁰ as well as VEGF-induced tumour angiogenesis¹¹ without detectable toxicity, and SH003 in combination with doxorubicin has shown a synergistic effect in treating triple-negative breast cancer (TNBC).¹³ The combinational treatment induces apoptotic cell death and suppresses tumour growth. Moreover, no toxicity was detected in the efficacy studies. In one toxicity test, hypertrophy of the liver was observed; however, it was deemed to be a reversible change with no toxicological significance.⁹ However, a herbology textbook has mentioned that components of SH003 should be used with caution in patients with diarrhoea.⁸

SH003 has never been tested in humans before; therefore, we have designed a phase I dose-escalation study to evaluate the maximum tolerated dose (MTD) of SH003 in patients with solid cancers.

METHODS

Study design

A phase I dose-escalation study will be conducted at the Ajou University Hospital in Suwon, Republic of Korea. Any participants fulfilling the eligibility criteria will be enrolled. The enrolled participants will be assigned to one of three groups receiving 1200 mg, 2400 mg and

4800 mg doses of SH003 per day. These doses represent the measurement of active ingredients found in a half of one tablet. The dose escalation will follow the modified Fibonacci sequence. The dose will be increased two times by 100% of the preceding dose. Each participant will be examined for signs and symptoms of any adverse events (AEs) during the study period. **Figure 1** shows the schematic flow of the present study. Protocol amendments are not expected; however, if they are essential, any changes in the study protocol will be provided to the all investigators via a conference. All modifications will be included in the final manuscript. The present study was begun in March 2017 and is currently in progress.

Recruitment

Subjects will be recruited as follows. Patients who visit the trial site and meet the inclusion criteria will be recommended to participate in the trial by the physician in charge of the study. Detailed information on the trial, including the study period, purpose of the study, inclusion and exclusion criteria, and interventions, will be provided by the investigators.

Participants

Inclusion criteria

Participants meeting the following criteria will be included: those 19 years of age and older; patients with histologically or cytologically confirmed solid cancers; metastatic or unresectable cancers for which standard curative measures do not exist or are no longer effective; those with ECOG performance status ≤ 2 ; life expectancy estimated to be at least 12 weeks; those who have not received chemotherapy or surgery within the last 4 weeks; those with recovery to haemoglobin ≥ 8 g/dL, platelets $\geq 75\,000/\mu\text{L}$ and absolute neutrophil count $\geq 1500/\mu\text{L}$; those patients with the ability to swallow tablets, as well as those with the ability to understand the study and who are willing to sign a written informed consent document.

Exclusion criteria

Patients with the following will be excluded: those with known hypersensitivity to any study drug component, including *A. membranaceus*, *A. gigas* and *T. Kirilowii Maximowicz*; patients with acute or chronic infections requiring treatment (active hepatitis A, B and C viruses, HIV, tuberculosis); estimated glomerular filtration rate < 60 mL/min, aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin ≥ 2.5 times the institutional upper limit of normal; patients with uncontrolled cardiovascular diseases (unstable angina, heart failure, myocardial infarction, hypertension that remains uncontrolled: 140/90 mm Hg or higher); patients with active cytomegalovirus infection within the past 4 weeks; patients who have experienced major surgery on cerebrovascular disease such as acute coronary syndrome, stroke, etc, within the past year; pregnant or lactating females and women with childbearing potential; patients who do not agree to either use effective means of contraception

or not to donate sperm during the trial and up to 1 month after final administration; patients who are taking anti-coagulants or anticonvulsants; those with any psychological, sociological or geographical conditions that could potentially interfere with their compliance to the study protocol, and finally, patients who have participated in other clinical trials of medicine or medical devices within the past month.

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study: those who receive other treatments for anticancer purposes; participants who withdraw their consent; those who experience serious AEs related to the investigational drug; those with significant protocol violations during the trial, including detection of eligibility violations; those patients who the investigator decides to terminate for their health. The participant who has been withdrawn regardless of the investigational product will be replaced by a new participant.

Sample size

The present study is a dose-escalation study that examines the MTD of SH003 for patients with solid cancers. The, dose-escalation rules for the traditional 3+3 design will be adopted.¹⁴ Three patients will be initially enrolled into a starting dose cohort. If there is no dose-limiting toxicity (DLT) observed in any of these participants, the study will proceed to enrol additional participants into the next higher dose cohort. If one participant develops a DLT at a specific dose, an additional three participants will be enrolled into the same dose cohort. Development of DLTs in more than one of six participants at a specific dose will suggest that the MTD has been exceeded, and further dose escalation will be stopped. The present study plans to conduct on three dose levels of SH003. Thus, at least 3 and up to 18 participants will be recruited for the study. Three to six participants will be allocated to each dose of SH003.

Allocation

The study participants who satisfy the eligibility criteria will be assigned to each cohort in the order they are recruited. After one cohort has been recruited, the participant enrolment will be suspended until the end of the study for that cohort to determine whether DLT has occurred. The recruitment and dose of the following cohort will depend on the outcome of the previous one.

Treatment protocol

The participants will receive SH003 for 3 weeks. They will orally take one to four tablets with water three times a day after meals for 3 weeks according to their dose level. It should be noted that no abnormal findings related to the investigational product were observed in either the single-dose toxicity study or the repeated-dose toxicity study. Therefore, the no observed adverse effect level of the investigational product was determined to be 2500 mg/kg for rats. According to the Food and Drug Administration

(FDA) guideline, the maximum recommended starting dose for adults is 2400 mg per day based on a safety factor of 10.¹⁵ Based on the toxicity and efficacy study results, the starting dose was determined to be 1200 mg per day for this study.¹⁰ The participants will be required to return unused investigational products for calculating their compliance. During the study, the participants will be prohibited from receiving other treatments for cancer, including chemotherapy and radiotherapy.

Interventions

The pharmaceutical company Hanpoong Pharm and Foods (Jeonju, Republic of Korea), produces the SH003 in accordance with Korea Good Manufacturing Practice standards. The SH003 used in the present study is a pale yellow-to-brown rectangular tablet. One tablet (total of 800 mg) includes 400 mg of solid extracts from *A. membranaceus*, *A. gigas*, *T. Kirilowii Maximowicz* (1:1:1) 30% ethanol extract.

Primary outcome measurement

The primary outcome in the present study will be determined by the number of grade 3 or higher AEs throughout the study period as measured by the National Cancer Institute (NCI; Bethesda, Maryland, USA) common terminology criteria for adverse events (CTCAE) V.4.03.¹⁶ CTCAE is a collection of AEs that commonly occur in oncology. Each AE listed has a grading scale indicating its severity. The AEs for this study will be measured by a trained investigator at every patient visit, in accordance with standard operating procedures (SOPs). The expected DLTs include diarrhoea, increases in ALT and/or AST, febrile neutropaenia and a decreased platelet count.

Secondary outcome measurement

Secondary outcome measurements include the AEs, regardless of grade, throughout the study period as measured by the NCI CTCAE V.4.03 as well as changes in tumour size as assessed by CT imaging. The study schedule is detailed in [table 1](#).

Safety outcomes


All variables related to the safety of participants, including vital signs, physical examination, haematologic, biochemical and urine tests, and AEs will be documented on the case report form at every visit. If an AE is severe and associated with the investigational product, the participant will be withdrawn from the study and appropriate therapy will be provided to them. Any loss caused by the present study will be reimbursed by insurance.

Outcomes analysis

Determination of MTD

MTD will be defined as the dose just below the lowest dose level at which more than one out of six patients exhibit DLT during the 4 weeks of the trial period. In the present study, the highest dose among the three dose groups (1200 mg, 2400 mg or 4800 mg per day) with one

Table 1 Study schedule of SH003 phase I study (4 weeks)

	Study period				
	Enrolment	Treatment period			Close-out
Time point	Day -7	Day 0	Day 8	Day 22	Day 29
Eligibility screen	X				
Informed consent	X				
Allocation		X			
SH003					
Demographic characteristic	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Laboratory test	X		X	X	X
Electrocardiography	X			X	
Pregnancy test	X				
Medical/drug use history	X				
Smoking and drinking history	X				
CT	X				X
Compliance calculation			X	X	
Concomitant medication	X	X	X	X	X
Adverse event			X	X	X

patient or less experiencing DLT will be determined as the MTD of SH003.

All analyses of data from the present study will be descriptive, as the study includes no inferential analysis and general hypothesis testing. The continuous variables will be displayed as the median and range, and the categorical variables will be displayed as the absolute and relative frequencies. After completion of each cohort's study period, an analysis will be conducted to determine the subsequent dose level.

Data and safety monitoring

To maintain the quality of the present study, monitoring will be conducted by the contract research organisation. The institution participating in the present study will be monitored while this trial is in progress through use of SOPs. For data quality improvement, double data entry and range checks for data values will be performed. Suspected and unexpected serious adverse reactions will be reported to the institutional review board (IRB) and regulatory authorities in the Republic of Korea within 24 hours.

Ethics and dissemination

The current protocol version is 1.1. The trial will be performed in compliance with the Declaration of Helsinki and according to Good Clinical Practice as described by the Korean Ministry of Food and Drug Safety (MFDS).

Confidentiality of patients' personal information will be protected. Each participant will be given a study identification number on enrolment. During the trial period, data will be dealt with by using study identification

numbers. During and after the study, all records will be kept in secure locked cabinets or in password-protected computer files. Only participating investigators will have the authority to access the data. The results of this study will be disseminated through an academic journal publication or a scientific conference.

Patient and public involvement

Patients or public were not involved to design the present study, and will not involve in the recruitment to and conduct of the study. So far, there is no established plan for announcement the results of the study to study participants.

DISCUSSION

The present study will investigate the tolerability and safety of administering SH003 to treat patients with solid cancers. Globally, there were 8.2 million reported deaths from cancer in 2012, and cancer is also the leading cause of mortality in Korea.^{17 18} Thus, development of anti-cancer drugs is active in Korea. Among a total of 628 cases of investigational new drug (IND) approvals in 2016, the number of anticancer drugs was the highest, at 202 cases.¹⁹ Nevertheless, there have been few IND approvals for new herbal medicines as anticancer drugs. In this situation, SH003 received IND approval from the Korean MFDS to begin a phase I trial testing it as anticancer drug.

In addition to the effect of tumour size reduction, SH003 has shown much potential as an anticancer agent in preclinical studies. The combination of SH003

and paclitaxel has been shown to enhance apoptotic cell death in paclitaxel-resistant breast cancer cells by inhibition of multidrug resistance protein 1 (MDR1) expression.²⁰ Decursin in Dang-Gui, one of the constituent herbs of SH003, has been shown to inhibit doxorubicin-resistant ovarian cancer cell proliferation and induce apoptosis.⁶ The combination of SH003 and doxorubicin has shown synergistic effects in TNBC treatment.¹³ Those studies suggest that SH003 could be used as an anti-MDR tumour agent and in combination with conventional chemotherapy drugs. SH003 has shown efficacy in treating various cancers, including breast, ovarian and prostate cancers. Thus, further clinical studies are necessary to evaluate its effectiveness in treating various cancers. The pharmacological action of SH003 has not yet been fully elucidated. Thus, preclinical studies for SH003 will also continue to be conducted and the results will be published.

The present study is particularly significant. First, it is the only phase I dose-escalation study conducted to date to determine the MTD for a new herbal medicine in Korea. While there have been several studies that investigated the anticancer effect of herbal medicine, most of these were preclinical studies or clinical trials to evaluate the effectiveness of established herbal medicine in treating patients with cancer.^{21–24} Second, the present study will investigate the effect of SH003 on changes in tumour size for planning further studies to evaluate its efficacy. Changes in tumour size, that is objective response, are not a common outcome measurement for phase I study, but have been included in the present study, expecting that the results would provide helpful information to plan further studies.

Limitations of the present study are that the number of dose levels is relatively small and the study does not include pharmacokinetics (PKs) and pharmacodynamics (PDs) research. Due to the nature of the formulation, a dose exceeding four tablets would be inconvenient and may reduce patient compliance, thus, the upper limit of dose level was determined as 4800 mg per day, the third dose level in this study. The effective dose estimated from preclinical studies was also considered.¹⁰ Most herbal medicines, including SH003, are composed of complex compounds, and thus, PK and PD studies are not easy.²⁵ Therefore, it is difficult to collect PK evidence on dose and frequency of administration of herbal medicines. Based on in vivo PK studies on SH003 currently being performed, further human studies will need to be conducted. One of the constituents of SH003, *A. gigas*, contains decursin and decursinol angelate, which are characterising compounds of *A. gigas* according to the Korean pharmacopoeia.²⁶ Decursin and decursinol angelate have been reported to have antitumour activities.²⁷ *A. membranaceus*, another constituent herb of SH003, contains calycosin and formononetin.^{28 29} Antitumour effect of calycosin and formononetin has also been reported.^{30 31} Therefore, it is reasonable to conduct

a PK studies on SH003 using decursin, calycosin and formononetin as marker compounds. Although it has not yet published, plasma concentrations monitoring of decursin, decursinol angelate, decursinol, calycosin and formononetin after the administration of SH003 in rat have conducted. In the study, decursin and decursinol angelate showed very low bioavailability, presumably because of the rapid conversion of decursin and decursinol angelate to decursinol in body,^{32 33} and decursinol showed a higher plasma concentration than the other components. Therefore, it suggest that decursinol could be used as a major marker compound in PK study of SH003. Based on these results, a clinical PK study of SH003 is being planned.

Although the present study has a few limitations, it serves as the first in-human trial to explore the use of SH003 to treat patients with cancer. Moreover, to the best of our knowledge, this is the first phase I study of a herbal medicine in Korea. We, therefore, expect that the present study could promote the overall development of new herbal medicines to treat cancer and other devastating diseases.

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Contributors CC, SK and YK wrote the first manuscript for this trial and contributed to monitoring this trial. MK, B-HJ and Y-CS edited the first manuscript. S-GK conducted all the procedures for this protocol. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The present study has been approved by the Institutional Review Board of the Ajou University Hospital (reference AJIRB-MED-CT1-16-311).

Provenance and peer review Not commissioned; externally peer reviewed.

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