XiangShaLiuJunZi Decoction combined with S-1 in the maintenance treatment of Stage III and IV Gastric Cancer: a protocol for a randomized controlled trial

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Study protocol

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Abstract

Background The total effective rate of first-line chemotherapy based on fluorouracils and platinum for advanced gastric cancer is about 31%-64%, but most of Patients will develop worse after 3-8 months, while second-line chemotherapy is seems inefficient and prone to serious adverse chemotherapy reactions. The new oral fluorouracil chemotherapeutic drug, S-1, has been increasingly used in clinical maintenance after first-line chemotherapy for stage III and IV gastric cancer because of its its own advantages. In addition, the effects of XiangshaLiujunzi Decoction(XSLJZD) and other traditional Chinese medicines(TCM) on alleviating the side effects of chemotherapy and improving the quality of life of cancer patients have been gradually confirmed, no more reports about the maintenance treatment mode of combination of western medicine and TCM. We designed the trial of XSLJZD combined with S-1 in the maintenance treatment of Stage III and IV Gastric Cancer, hoped that this research program will go further and comprehensively evaluate its effectiveness, safety and superiority.

Methods/design This trial is an open, Single-center, randomized trial. Patients with stage III and stage IV gastric cancer will be randomized into group A (S-1), group B (S-1 combined with XSLJZD), and group C (symptomatic treatment/observation) for five year of corresponding treatment. Accordingly, the primary endpoint of this trial was progression-free survival (PFS), along with the secondary end point was Overall survival(OS) and Quality of Life Assessment (QOLA), the latter includes improvement in symptoms before and after treatment, Karnofsky Performance Status (KPS), and adverse events (AEs) assessment.

Discussion The results of this trial can uncover to some extent that S-1 or S-1 combined with XSLJZD on PFS, OS and QOLA in the maintenance period of stage III and IV gastric cancer, as well as provide a preliminary basis for the effectiveness of S-1 combined with XSLJZD in the maintenance period of stage III and IV gastric cancer.

Background

Gastric cancer is the fourth most common tumor in the world, and its incidence rate is increasing year by year. Now, early gastric cancer is mainly treated by surgery. Due to the occultity of the tumor, 40-50% of the patients are locally advanced or have distant metastasis during diagnosis[1], which cause them to lost the opportunity of radical surgery. Some studies have shown that Its 5-year survival rate is around 10% [2,3]. The principle of treatment for advanced gastric cancer is a comprehensive treatment model based on palliative chemotherapy recommended by the National Comprehensive Cancer Network(NCCN) guidelines. The total effective rate of first-line chemotherapy based on Fluorouracil, Platinum, and Docetaxel is about 31%-64%. However, most patients with advanced gastrointestinal cancer will develop their disease after 3-8 months, and the efficiency of second-line chemotherapy is seems low. The adverse events (AEs) of chemotherapy above grade 3/4 are very common, and the quality of life is seriously degraded, making it is difficult to survive and benefit from entering a platform for therapeutic efficacy.

There are few studies on maintenance therapy for advanced gastric cancer, a prospective trial evaluating the efficacy and safety of the chemotherapy drug capecitabine in the treatment of advanced gastric adenocarcinoma in China [4], After their condition was controlled by in the first-line XELOX regimen for 6 cycles of chemotherapy, 64 patients were treated with capecitabine and 222 patients were not treated with maintenance therapy. The median progression-free survival (PFS) was 11.4 months and 7.1 months, and the maintenance treatment of grade 3/4 adverse events and blood. Less toxicity occurs. Less happens. Palacio et al [5] combined with the targeted drug trastuzumab in the first-line chemotherapy for 7 patients with gastric cancer overexpressing HER2 gene, after partial remission or complete remission, trastuzumab maintenance treatment, the results showed median The PFS was 14.6 months and the median overall survival time trastuzumab maintenance treatment, the results showed median The PFS was 14.6 months and the median overall survival(OS) was 16.4 months. Eren et al [6] reported 11 patients with advanced gastric cancer treated with Capecitabine. The median PFS was 10.4 months and the median OS was 19.7 months. These studies suggest that maintenance therapy may benefit patients with advanced gastric cancer, but is still need more evidence-based medical evidence.

Regarding the choice of drugs for maintenance therapy, still insufficient evidence-based basis for the timing and duration of intervention. The principle of maintenance therapy is efficient, low-toxic and convenient to use. Capecitabine has been widely used as an oral fluorouracil chemotherapeutic drug in chemotherapy for gastric cancer, and the new oral fluorouracil chemotherapeutic drug S-1was developed by Japan. Studies have shown that it may be more suitable for Asians. It is a compound preparation whose main components are tegafur, oltipraz potassium, and gimeracil, converted to fluorouracil by oral absorption after oral absorption, while gemcitabine and oltipraz potassium act on the enzyme. The inhibitory effect of the former into a fluorouracil effective concentration for a longer time, and reduce the toxic effects of fluorouracil on the gastrointestinal tract [7,8]. Therefore, this trial used S-1 as a maintenance chemotherapy drug.

Chemotherapy belongs to the category of "explosive" in traditional Chinese medicines(TCM). "Drug poison" is the main external cause of adverse reactions after chemotherapy, resulting in impaired spleen and stomach function, liver and kidney deficiency, lack of blood and blood, and manifested as adverse reactions of various systems. Due to the loss of spleen and stomach, the kidney and kidney kidneys are depleted, the blood and blood are not supported by the end of the blood, the internal organs of the phlegm and dampness are blocked, and the meridians accumulate in the meridians, resulting in digestive tract reaction, impaired liver and kidney function, bone marrow suppression, and neurotoxicity. Wait for a series of adverse reactions. Now many studies have shown that the application of TCM can significantly reduce the adverse reactions caused by chemotherapy, improve postoperative maintenance, prevent recurrence and metastasis [9], increase white blood cells[10,11], improve the body's immune function[12], Reduce neurotoxicity [13], improve patient quality of life [14], and prolong survival. The use of TCM for tumor maintenance treatment is still inception, but it is gratifying that these preliminary exploratory studies have given some hope to this new clinical treatment model. Wu Xuan et al [15] used the chemotherapy drug Xeloda to treat 22 patients with advanced colon cancer, and 18 patients with advanced colon cancer treated with TCM. It was found that the average tumor progression time of the

Chinese medicine group was 1.24 months longer than that of the Xeloda group (4.91 months vs 3.67 months)."Sweet sand six gentlemen soup qi stagnation drink, vomiting is not stuffy, spleen and stomach are not harmonious, change the syndrome" [16], Xiangsha Liujunzi soup main function for qi and spleen, gasification, so this trial the use of XiangshaLiujunzi Decoction(XSLJZD) as a basic prescription for the maintenance treatment of gastric cancer is exactly the righteousness and evil spirits the theory of TCM. The evil spirits do not hurt the positive, the positive gas gradually recovers, and the poisonous evils such as wet poison and blood stasis gradually go away.

Although chemotherapy combined with targeted therapy has a good effect, it inevitably kills normal cells, toxic accumulation, and risk of drug resistance, and is limited to specific populations of genetic phenotypes, costly to maintain. The S-1 combined with TCM is convenient to take, combine strengthen the body with eliminate pathogens, less adverse reactions, only in outpatient treatment, no need for hospitalization, the price of TCM is relatively low, affordable costs for patients, follows the current economic conditions of most patients in China. Given above views, this model can become an ideal choice for maintenance treatment of advanced gastric cancer in our country.

In recent years, the maintenance treatment mode of lung cancer has become more mature, and still room for gastrointestinal tumors to develop. Specifically, no report on maintenance therapy mode of combination of Western medicine chemotherapeutic drugs or targeted drugs with TCM. Therefore, our group draws lessons from the preliminary results of small-scale exploratory trial on the maintenance treatment of gastric cancer with S-1 combined with XSLJZD. We hope to take this research program further and comprehensively evaluate its effectiveness, safety and superiority, so as to provide preliminary basis for the effectiveness of S-1 combined with XSLJZD in the maintenance treatment of stage III and IV gastric cancer.

Methods/design

Trial design

This trial is an open, Single-center, randomized trial, 180 patients with stage III and IV gastric cancer who met the inclusion criteria will be randomly assigned to three groups of ABC, receiving S-1, XSLJZD combined with S-1, Symptomatic treatment for 5 year. The flowchart of the trial is presented in Fig. 1.

This trial was to determine the efficacy and safety of S-1 combined with XSLJZD in the treatment of advanced gastric cancer, and the therapeutic advantages of this combination mode over single drug S-1. In addition, this trial also provides a scientific basis for exploring an ideal maintenance therapy for advanced gastric cancer.

The reporting of the protocol follows the Standard Protocol Items: Recommendations for Interventional Trials 2013(SPIRIT2013) guidelines[17,18]. Additional file 1 contains the SPIRIT 2013 checklist.

Ethics approval

The trial procedures and informed consent form have been approved by the independent Ethics Committee of the Affiliated Hospital of Guangdong Medical University in Guangdong province, China (YJ2016-010KT-01). Information on any AEs will be reported to the Ethics Committee until to reach a stable situation. Moreover, the Ethics Committee has the duty to periodically evaluate the progress of this trial.

Recruitment and diagnostic criteria

The trial was carried out at the Cancer Center of the Affiliated Hospital of Guangdong Medical University. The Cancer Center has obtained the qualification of "National Clinical Drug Testing Institute". The participants were all inpatients of cancer center of Affiliated Hospital of Guangdong Medical University, mainly recruited through Internet advertisements and hospital posters. The patients interested in participating in the trial will be evaluated by clinicians to determine their qualifications. The clinician will inform the patient of the detailed trial objectives, process, and potential benefits and risks. All participants will sign the informed consent before participating. The diagnostic criteria are as follows:

- Diagnostic criteria: According to the diagnostic criteria in the “Specifications for the Diagnosis and Treatment of Common Malignancies” prepared by the Medical Department of China, TNM and clinical staging refer to NCCN guidelines, stage III or IV gastric cancer diagnosed by pathology or cytology.
- Diagnostic criteria for maintenance stage of advanced gastric cancer: After a certain course of treatment, patients with stage III and IV gastric cancer reaches the maximum tumor control effect (in CR/PR/SD status by the Response Evaluation Criteria In Solid Tumors, RECIST 1.1)[19]and continue to receive drug treatment until the time of disease progression.

Inclusion criteria

The inclusion criteria are as follows:

- There must be an informed consent form signed by the patient himself or by the witness;
- Stage III or IV gastric cancer diagnosed by pathology or cytology;
- Controlled by chemically treated diseases (CR/PR/SD);
- Age 18 to 75 years old (≥18 years old, ≤75 years old); expected survival period is more than 3 months;
- Karnofsky Performance Status (KPS) [20,21]≥60;
- According to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1), at least one measurable lesion;
- Routine blood test: hemoglobin ≥ 90g/L; neutrophil count ≥ 1.5×10^9/L; platelet count ≥ 100×10^9/L;

- Biochemical examination: total bilirubin ≤ 1.5×upper limit of normal range (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2×ULN; if liver metastasis, ALT and AST ≤ 5×ULN Endogenous creatinine clearance rate ≥ 60ml/min;
- Cardiopulmonary function is basically normal.

Exclusion criteria

The exclusion criteria are as follows:

- Patients with severe heart, liver or kidney damage or abnormal bone marrow function;
- Past or concurrent with other malignant tumors, except for cured skin basal cell carcinoma and cervical carcinoma in situ;
- The general situation is poor, and those who cannot eat Chinese medicine;
- According to the judgment of the investigator, serious accompanying diseases that endanger the safety of the patient or affect the patient's completion of the trial;
- Pregnant or lactating women;
- Those known to be allergic to the therapeutic drugs used in the trial.

Randomization and blinding

The cancer center examines the participants into groups. After passing the examination, according to the random number generated by the computer, according to the order of the participants into groups, the drugs corresponding to the randomly assigned drug number are given. Participants who meet the eligibility criteria will be randomly assigned to the S-1 group, S-1 combined with XSLJZD, and the observation group in a 1:1:1 ratio. Clinicians, patients, data collectors, and outcome assessors will be blinded to the group assignment. The allocation will be unblended if a SAE occurs and when the final data analysis is complete.

Interventions

The participants were randomly divided into three groups of ABC in a 1:1:1 ratio, each group of 60 cases, the details of the intervention are as follows:

- **Group A(S-1 group)**: 80mg/m^2/d, divided into two orally, swallowed with water for half an hour after breakfast and dinner, used for two weeks, rest for one week, and 21 days for one cycle.
- **Group B(S-1 combined with XSLJZD group)**: S-1 80mg/ m^2/d, divided into two orally, swallowed with water for half an hour after breakfast and dinner, used for two weeks, rest for one week, 21 days for one cycle; According to the syndromes of the patients, XSLJZD was given combined treatment. Later physicians replaced ginseng with Codonopsis pilosula to give full play to its functions of warming and benefiting qi, invigorating the spleen and nourishing the stomach, the composition of XSLJZD:

Codonopsis 15g, Atractylodes 20g, Poria cocos 15g, tangerine peel 15g, 10g of Pinellia, 10g of woody, 10g of Amomum vulgaris, 10g of ginger, and 6g of licorice.

- **Group C(symptomatic treatment/observation group)**: clinical symptomatic treatment and supportive treatment, no Chinese medicine and anti-tumor drugs.

Outcome measurements

Primary endpoint

The primary endpoint is PFS at six months and one year, the time from randomization to disease progression(Evaluation of tumor progression about RECIST 1.1) or death. For participants who did not observe tumor progression or death, the PFS data were deleted on the last effective tumor evaluation day.

Secondary endpoints

- OS, time from randomization to death for any reason. The last follow-up time is usually calculated as the time of death for the participants who have lost the visit before death. The total survival time of the participants who survived in the last follow-up was deleted on the last contact day.
- Quality of Life Assessment (QOLA), including symptom improvement, KPS and AEs assessment before and after treatment, performed 1-3 days before each cycle of treatment, details are as follows:
- Symptom improvement, mainly observe the changes of common symptoms of gastric cancer and colorectal cancer (pain, diarrhea, fatigue, poor acceptance, sleep), refer to the "Guiding Principles for Clinical Research of New Chinese Medicine"[22,23]in the relevant TCM symptom integral quantification table(MDASI-TCM, Additional file 2), compared to the scores accumulated for each symptom, analyzed the difference before and after treatment.
- KPS, comparative analysis before and after the difference.
- Assessment of AEs (safety outcomes). Assessment and grading of AEs were based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0[24], AEs include nausea and vomiting, granulocytopenia, thrombocytopenia, anemia, impairment of liver and kidney function, diarrhea, peripheral neuritis, stomatitis, hand-foot syndrome and any other new symptoms or diseases related to or unrelated to intervention. SAEs refer to the events that must be hospitalized or prolonged, permanently and seriously disabled, life-threatening or death in clinical trials. SAEs will be reported to the chief researcher and the hospital ethics committee, and the experiment will be stopped within 24 hours.

Other measurements

Baseline was defined as pre chemotherapy (-7 to 0 days). During baseline examination, the patient's gender, age, marital status, education level, comorbidities, pathological gastric cancer, gastric cancer staging, radiotherapy and chemotherapy regimen, and medication records for the past 3 months will be recorded.

A detailed schedule of the trial is presented in Fig. 2(SPIRIT Figure).

Follow-up

This trial is expected to last for 5 years. After discontinuation of treatment, each patient will be followed until death or withdrawal from the trial. Follow up frequency: follow up every 28 ± 3 days before the end point of trial, and record the PFS; after the end point of trial, follow up every 3 months, and record the OS of 3-year and 5-year.

Case Elimination and withdrawal criteria

Elimination criteria

The elimination criteria are as follows:

- Case selection does not meet the inclusion criteria;
- Did not use the test drug;
- After the randomization, no data or major indicators missing, and the data is obviously incomplete;
- The drug prohibited by the test protocol was used, and the efficacy could not be evaluated.

Withdrawal criteria and solution

The withdrawal criteria are as follows:

- Participants voluntarily request to withdraw from the test;
- Severe adverse events(SAE) closely related to drugs occur, and toxicity intolerance makes the test impossible to continue.
- No reason for delaying treatment for more than 2 weeks;
- Can not be treated according to the program, poor compliance;
- Considering the interests of the Participants, the researchers believe that the best choice is to terminate the trial treatment.

Solution

Participants have the right to withdraw from the test at any time without any reason. Different follow-up solutions due to different reasons for participant withdrawal:

- If the participant does not appear as planned during the follow-up period, the researcher shall know the reason as much as possible, record the reason on the case report form(CRF), contact the participant as much as possible to ask the participant to conduct a final visit, record the last medication time, try to complete the effectiveness and safety inspection when withdrawing from the trial as specified in the scheme, and complete the safety follow-up period. AEs and outcomes were

fully recorded. According to the actual situation of the participants, researchers can suggest or provide new or alternative treatment methods to the participants.

- If the participant is asking for termination of the trial, researcher will retain the data and must follow up in the specific follow-up steps specified in the trial. If the participant refuses to visit further, he or she should continue to track his or her survival status unless the participant refuses to disclose further information or is contacted. In this case, no further research evaluations should be conducted and no further information should be collected. The trial sponsor may retain and continue to use all the information before the withdrawal of the participant's informed consent, unless the participant requests that the collected information be withdrawn.

Medication restriction

During the trial period, the use of any other anti-tumor drugs was prohibited except for trial drugs. When an adverse reaction occurs, it should be closely observed and actively treated. All drugs used simultaneously should be recorded on the CRF and stated.

Data collection

According to the original observation record of the trial, the researcher will fill in the CRF in time, complete, correct and clear and check it. After checking, the data manager will input the original case report form into the online database repeated, and the database is password protected. After importing the collected patient data into the database, the data administrator and the main researcher will perform a secondary check on the data, correct all the errors and save them properly. When the experimental data is collected, the person leading the data analysis will analyze the data.

Sample size estimate

The randomized controlled trial (RCT) is an advantage test that uses an appropriate formula to estimate the sample size. According to the small-sample trial completed in the previous trial group, the median PFS of the S-1 combined with XSLJZD Group, the S-1 Group and the observation group were 8.7 months, 8.1 months and 5.1 months, the Log-Rank test showed statistically significant differences between the two groups (P=0.0039<0.05), suggesting that S-1 maintenance treatment was significantly better than the observation group. The PFS of the S-1 combined with XSLJZD Group was longer than that of the S-1 group, but the Log-Rank test showed no significant difference between the two groups (P=0.3321>0.05), but a prolonged trend. It suggests that the combination of Chinese medicine may be more prolonged PFS, but need to the further clinical research. Previous capecitabine was reported as a maintenance therapy for 11 patients with advanced gastric cancer. The median PFS was 10.4 months and the median OS was 19.7 months. Based on the results of our preliminary observational trial and expert advice we assuming a significant level of $\alpha = 0.05$, test efficacy $(1-\beta) = 80\%$, Considering 10% dropout rate, the sample size of each group was 60, totaling 180 Participants.

Statistical analysis

- Primary endpoint PFS and secondary endpoint OS: The median of PFS and OS in each group was counted. Survival curves were plotted using Log-Rank test and Kaplam-meier survival analysis.
- symptom improvement assessment: behavioral status scores before and after chemotherapy (KPS), repeated measures analysis of variance before and after treatment in the group; TCM symptom scores before and after chemotherapy (MDASI-TCM), paired t test before and after treatment in the group the t test was used for comparison between groups.

Protocol monitoring

protocol contributors or relevant medical administrations have the right to inspect the clinical research to ensure the authenticity of the data recorded in the clinical research and to comply with the provisions of the clinical research program. In this trial, an Independent Response Evaluation Committee (IREC), which consists of two oncology imaging diagnostic and evaluation experts unrelated to this trial and one oncology clinical expert. Under the premise of blindness, the IREC carries out an independent third-party evaluation of the objective imaging data of all participants, with each participant the most successful. The final was based on the evaluation of IREC. The participants of the clinical trial will be informed that there will be relevant personnel to check during the trial, but the privacy and data of the patients will be strictly protected.

During the clinical trial, clinical inspectors will conduct regular on-site monitoring visits to ensure that all content of the research protocol is strictly observed and the original data is checked to ensure consistency with the CRF. The research team of this research group consists of a Interdisciplinary researcher with reasonable structure and different expertise (oncology, TCM, epidemiology). Most of the researchers have obtained the "GCP training certificate of the national drug clinical trial institution". Each participant has a designated work schedule to ensure the smooth implementation of the experiment.

Data confidentiality

All records relating to the identity of the participant are kept confidential and the information will not be disclosed to the public beyond the limits permitted by relevant laws and/or regulations. The name of the participant will not be provided to the sponsor. Only the abbreviation of participant number and name is recorded in the medical record report form. If the participant's name appears in any other document, it must be hidden before a copy of the document can be provided to the sponsor. Research reports stored by computer must comply with local laws on data protection. Patients will be informed in writing that representatives of the trial sponsor, ethics committee or drug administration may review their medical records to check the collected information, and all personal information involved in the review will be strictly confidential and comply with local data protection laws. If the results of the trial are published, the personal identity of the patient will remain confidential. The researchers will keep a list to check the patient's records.

Discussion

The treatment of advanced gastric cancer has always been a thorny problem. The first-line chemotherapy based on fluorouracils and platinum is still effective, but most patients will get worse after 3-8 months. The second-line chemotherapy is not effective and easy to cause serious adverse reactions. A new idea is urgently needed for the treatment of advanced gastric cancer.

At present, studies on maintenance therapy for advanced gastric cancer at home and abroad show that maintenance therapy may benefit the survival of patients with advanced gastric cancer. S-1, a new oral fluorouracil chemotherapeutic drug S-1, has been used more and more in clinic after first-line chemotherapy for stage III and IV gastric cancer because of its longer drug concentration and lower side effects. In addition, more and more reports have confirmed that TCM can alleviate adverse reactions caused by chemotherapy and improve the quality of life of patients. The maintenance treatment mode of combining western medicine with traditional Chinese medicine has gradually attracted the attention of researchers.

As described we designed the trial of XSLJZD combined with S-1 in the maintenance treatment of Stage III and IV Gastric Cancer, the purpose of this trial is to clarify the impact of S-1 or S-1 combined with XSLJZD on PFS, QOLA in patients with stage III and IV gastric cancer during maintenance period.
In addition, it can also prove to some extent the efficacy, safety and clinical application value of XSLJZD combined with S-1 in the maintenance treatment of stage III and IV gastric cancer, and provide a preliminary basis for the application of the combination model in the maintenance treatment of stage III and IV gastric cancer. We also hope that this trial will open a new direction for the treatment of patients with advanced gastric cancer.

Trial status The trial was initiated in July 1, 2016. Recruitment of participants is expected to be completed by December 2019.120 patients had been registered and randomized at the time of manuscript submission. The date and version identifier for this protocol is V2.0, March 8, 2016.

Abbreviations

AEs: Adverse events;

ALT: Alanine aminotransferase ;

AST: Aspartate aminotransferase ;

CR: Complete remission;

CRF: Case report form;

CTCAE: The Common Terminology Criteria for Adverse Events;

GCP: Good Clinical Practice, the qualification of National Clinical Drug Testing Institute;

IREC: Independent Response Evaluation Committee

KPS: Karnofsky Performance Status;

MDASI-TCM: MD Anderson Symptom Inventory for Traditional Chinese Medicine;

NCCN: National Comprehensive Cancer Network;

PFS: Progression-free survival;

PR: Partial remission;

QOLA: Quality of Life Assessment;

RCT: Randomized controlled trial;

RECIST: Response Evaluation Criteria In Solid Tumors;

SAEs: Severe Adverse Events;

SD: Stable disease;

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials;

TCM: Traditional Chinese Medicine;

ULN: Upper limit of normal range;

XSLJZD: XiangShaLiuJunZi Decoction;

Declarations

Ethics approval and consent to participate

Ethics approval has been sought from the Ethics Committee at the Affiliated Hospital of Guangdong Medical University (YJ2016-010KT-01). Written informed consent is obtained from the participants and their family members before screening.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QLL and XCH designed the trial and drafted the manuscript; XCH, QLL, XBL, KHH, HXY are responsible for the conduct of the trial.WTO and HJZ conceived and designed the trial, developed the statistical analysis plan, reviewed the manuscript. All authors approved the final version of the manuscript.

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Figures

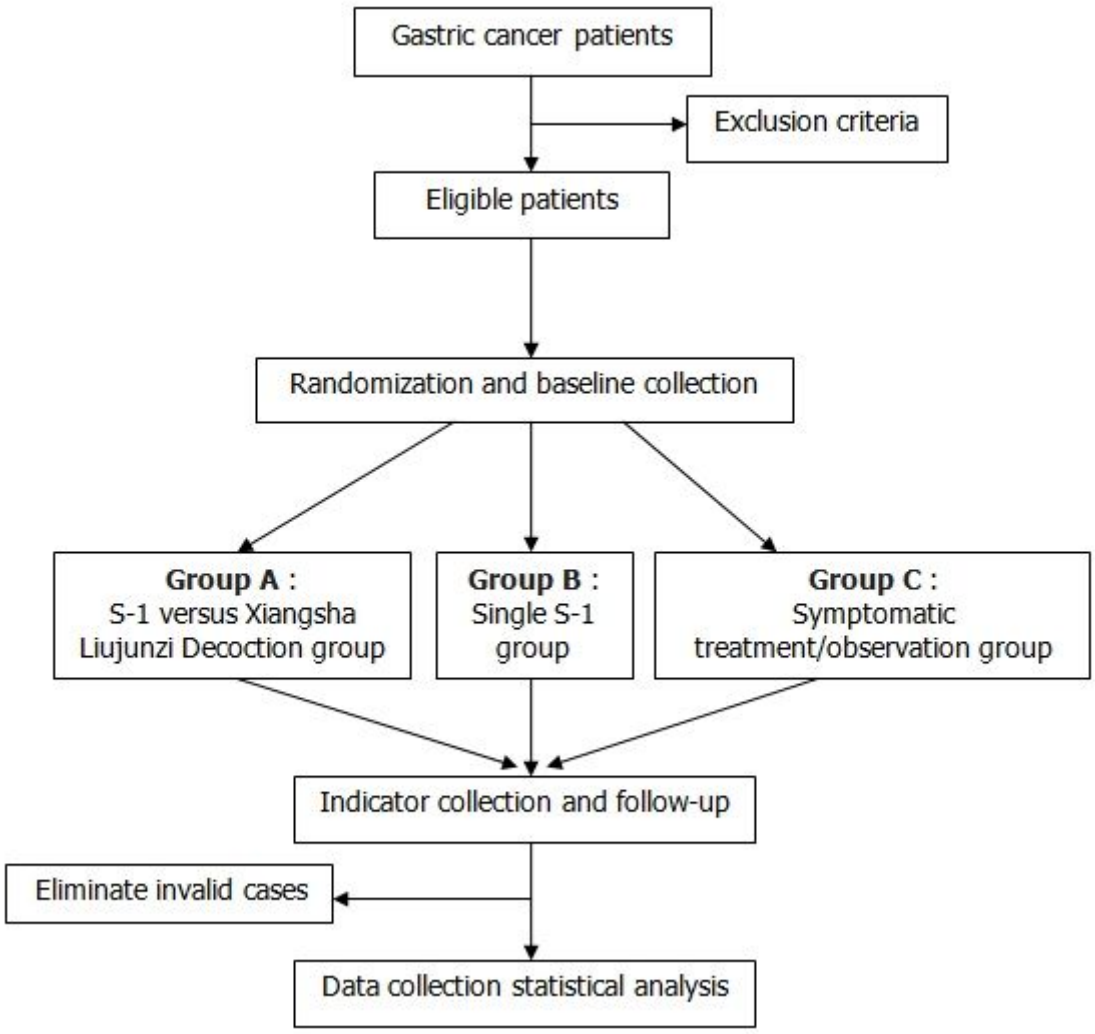

Figure 1

The flowchart of the trial

A detailed schedule of the trial

Time point	Screen	Follow-up												
	Base-line	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Day	Day-7~0	Day1	Day1×28±3	Day2×28±3	Day3×28±3	Day4×28±3	Day5×28±3	Day6×28±3	Day7×28±3	Day8×28±3	Day9×28±3	Day10×28±3	Day11×28±3	Day12×28±3
Sign informed consent	√													
Demographic data	√													
Medical history	√													
Enrolment/ Eliminate	√													
Withdraw / Suspension		√	√	√	√	√	√	√	√	√	√	√	√	√
Vital signs &physical examination	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Routine blood test	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Biochemical examination	√		√	√	√	√	√	√	√	√	√	√	√	√
Tumor markers	√		√	√	√	√	√	√	√	√	√	√	√	√
Electrocardiogram	√		√	√	√	√	√	√	√	√	√	√	√	√
KPS	√		√	√	√	√	√	√	√	√	√	√	√	√
Completion of chemotherapy			√	√	√	√	√	√	√	√	√	√	√	√
MDASI-TCM	√		√	√	√	√	√	√	√	√	√	√	√	√
Evaluation of tumor progression (RECIST 1.1)	√		√		√		√		√		√		√	
AEs/SAEs Assessment	√<·····>√													

Figure 2

A detailed schedule of the trial(SPIRIT Figure)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.doc
- Additionalfile2.doc