Efficacy and safety of Sanzi-huangshi pill as an adjuvant therapy in lower-risk myelodysplastic syndrome: study protocol for a multi-center randomized controlled trial

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Study protocol

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Abstract

Background: Lower-risk myelodysplastic syndrome (MDS) is characterized by the presence of dysplasia, low bone marrow blast percentage, low number and depth of cytopenia(s), and relatively good-risk karyotypic and molecular abnormalities. Lower-risk MDS patients have primarily received supportive care, immunomodulators, and immunosuppressants. New effective regimens or drugs are urgently needed for treatment of lower-risk MDS due to the unsatisfactory clinical efficacy. Sanzi-huangshi pill is an arsenic-containing Chinese medicine as a promising drug used for MDS for decades whose efficacy is not yet proven by high-quality clinical trial.

Methods: SPIRIT guidelines were followed in drafting this protocol for a randomized controlled multicenter trial. Ninety-two adults with lower-risk MDS are randomly assigned in a 1:1 ratio to Sanzi-huangshi pill group or control group, and all participants are required to receive 6 months of intervention and 18 months of observation. The primary outcome is Overall Response Rate defined as the sum of complete remission, partial remission, cytogenetic complete remission and hematologic improvement accounting for the proportion of total evaluable cases.

Discussion: This is the first randomized controlled trial to evaluate the efficacy and safety of arsenic-containing Chinese medicine as an adjuvant therapy in lower-risk MDS with serum erythropoietin (sEPO) >500 IU/ml. The purpose of this study is to correctly evaluate the position of traditional Chinese medicine in the treatment plan of MDS and to formulate an effective regimen of integrated Traditional Chinese and Western Medicine to provide preliminary clinical evidence.


Introduction

Background and rationale {6a}

Myelodysplastic syndrome (MDS) are myeloid neoplasms characterized by clonal proliferation of hematopoietic stem cells, recurrent genetic abnormalities, myelodysplasia, ineffective hematopoiesis, peripheral-blood cytopenia, and a high risk of evolution to acute myeloid leukemia (AML) [1]. The annual age-adjusted incidence of MDS in the United States is approximately 4.0/100,000 persons, and the incidence substantially rises with age [2]. The average annual incidence of newly diagnosed MDS during 2004–2007 in 236 adult patients in Shanghai, China was 1.51/10^5 in which incidence of adult male was 1.48/10^5 and that of adult female was 1.54/10^5 [3]. In the past 10 years, there has been a lack of epidemiological studies on the incidence of MDS in China and continued advances in molecular diagnostic techniques may help detect more MDS in China. In fact, there are some differences in the incidence of different countries, the reasons may include ethnic differences and environment, ethnic differences and environment and the use of different diagnostic criteria and classification [3]. The true
incidence is likely to be higher because of incomplete case assessment and underreporting of MDS in cancer registries, and it may be close to 75 per 100,000 among persons over the age of 70 years[4]. In 1997, a collaborative group developed the International Prognostic Scoring System (IPSS) for MDS[5]. IPSS stratifies patients into four risk groups based on cytogenetic features, number of cytopenias, and blast percentage, and Low and Intermediate-1 risks are considered lower-risk MDS (LR-MDS), and Intermediate-2 and High risks are considered higher-risk MDS[5]. According to the European MDS statistics, lower-risk MDS accounts for approximately 70% of the entire MDS population[6].

LR-MDS are characterized by the presence of dysplasia, low bone marrow blast percentage, low number and depth of cytopenia(s), and relatively good-risk karyotpic and molecular abnormalities[7]. Supportive care measures have traditionally been the mainstay of LR-MDS therapy, including RBC and platelet transfusions, erythropoiesis stimulating agents, hematopoietic growth factors and iron chelation therapy[8]. Immunomodulators (thalidomide and lenalidomide) and immunosuppressants (antithymocyte globulin and cyclosporine A) are also recommended as treatment options for some LR-MDS[8,9]. The main therapeutic goals of LR-MDS include improving bone marrow hematopoiesis, improving quality of life, avoiding disease progression to higher-risk types or even AML, and prolonging survival[9]. Thalidomide and its derivatives have been used in the treatment of MDS because of their anti-angiogenic and immunomodulatory effects[10]. LR-MDS patients have a notably longer survival compared with high-risks MDS, and the deliberate selection and sequencing of therapies will lead to an optimal risk/benefit ratio[10]. For LR-MDS patients with sEPO >500 IU/ml who are not eligible for IST or demethylation drugs, there is no treatment option other than participating in clinical trials[8]. Therefore, the development of new effective drugs and treatment options carries great significance, among which the research results from alternative and traditional medicine for hematological diseases are gradually attracting people's interest.

Some clinical evidence confirmed the efficacy and safety of Traditional Chinese medicine (TCM) as a major adjuvant therapy in MDS. A clinical observation with a sample size of 124 of MDS treated with Qinghuang Powder in China found that the total effective rate is increased by 23.71% (77.55% vs 53.84%, P<0.01) by Western medicine plus Chinese herbal medicine compared to Western medicine alone[11]. Arsenic dispensing powder (ADP) has been used in treating MDS for decades and a study shown that ADP is a promising drug to promote erythropoiesis in MDS via downregulation of HIF1A and upregulation of GATA factors[12]. Increasing scientific evidence suggests that TCM may exert therapeutic effects by regulating DNA methylation, which is one of the key pathological mechanisms of MDS[13].

Since the 1950s, after more than 70 years of clinical practice and exploration, our team proposed that the TCM pathogenesis of MDS be "loss of the spleen and kidney, evil poison in the bone marrow, and endogenous phlegm and blood stasis"[14]. Based on the above understanding of pathogenesis, we developed Sanzi-huangshi pill (SHP) consisting of realgar, radix pseudostellariae, semen cuscutae and ligustrum lucidum, which is an arsenic-containing Chinese medicine for MDS[14]. Our preliminary study[14] showed that SHP as adjuvant therapy can improve erythrocytopenia, thrombocytopenia, and poor quality of life in LR-MDS possibly by regulating apoptosis and histone acetylation. However, there is no evidence
based on randomized controlled trials (RCTs) to support the efficacy and safety of SHP in MDS. Therefore, we will conduct the first RCT to determine the efficacy of SHP as adjuvant therapy in LR-MDS.

**Objectives (7)**

To make clear that the efficacy and safety of SHP as adjuvant therapy in LR-MDS.

**Trial design (8)**

This study was designed as a multicenter randomized controlled trial. Eligible participants will be randomly divided into two groups at a 1:1 ratio: SHP group and control group. All enrolled patients will receive 6 months of intervention and 18 months of observation (as shown in Fig.1). The data will be collected to determine the efficacy and safety of SHP as an adjuvant therapy in LR-MDS.

**Methods: Participants, Interventions, And Outcomes**

**Study setting (9)**

This trial will be conducted in Shanghai municipal Hospital of Traditional Chinese Medicine, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Sixth People's Hospital, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine and Yueyang integrated traditional Chinese and Western Medicine Hospital Affiliated to Shanghai University of traditional Chinese Medicine. Prior to the trial, all personnel are trained to ensure that the physicians and staff participating in the trial at every center fully understand all aspects of the trial.

**Eligibility criteria (10)**

Male and female patients with LR-MDS with serum erythropoietin (sEPO) >500 IU/ml aged 18–75 years are eligible for study participations. The diagnostic criteria for LR-MDS referred to Guidelines for the diagnosis and treatment of myelodysplastic syndromes in China (2019 edition)[9].

**Inclusion criteria**

*The inclusion criteria are as follows:*

1. Meet the diagnostic criteria of Western medicine for MDS, and the risk is classified as lower risk;
2. Age between 18 and 75 years old;
3. Serum erythropoietin (sEPO) >500 IU/ml;
4. Bone marrow blasts <5%;
5. All drugs used to treat MDS were discontinued for more than 2 weeks;
6. Voluntarily signed the informed consent.

**Exclusion criteria**
The exclusion criteria are as follows:

1. Secondary MDS;
2. MDS with 5q deletion;
3. Transplant patients and peri-transplant patients;
4. The risk is classified as higher risk;
5. Applicable to immunosuppressant (IST) patients (age ≤ 60 years with bone marrow blasts ≤ 5%, or bone marrow hypoplasia, HLA-DR 15 positive, PNH clone positive, or cytotoxic T cell clone with STAT-3 mutation);
6. Patients with other hematologic or non-hematologic tumors;
7. Combined with severe cardiovascular and cerebrovascular, liver, kidney and other organic diseases and peripheral neuropathy;
8. pregnant or breastfeeding women;
9. Patients with mental illness who cannot cooperate with treatment;
10. Patients with infectious diseases such as viral hepatitis.
11. Patients who are participating in other clinical trials;
12. History of hypersensitivity to test drug components
13. patients with poor compliance.

Informed consent (26a)

A doctor will confirm if the patients satisfy the criteria after consent being given. Subsequently, the medical officers of the trial team in every center will communicate with the patients and their families to inform the possible benefits and risks of participating in this study. Participants need to sign a written informed consent form.

Interventions

Explanation for the choice of comparators, Intervention description (6b, 11a)

Both groups will be treated with routine supportive care including supportive care and thalidomide. The active arm is orally administered SHP plus routine supportive care. The pharmaceutical dosage form used in this trial is traditional pills, and there is currently no suitable placebo as a control group. The SHP group received SHP three times a day, 12 pills each time after meals for 6 months. Whole ingredients of SHP formula include Realgar 0.2g, Radix pseudostellariae 20g, Semen cuscutae 20g and Ligustrum lucidum 20g. The above-mentioned medicines were prepared into pills by Shanghai municipal Hospital of Traditional Chinese Medicine.

Criteria for discontinuing or modifying allocated interventions (11b)

Use of study drug will be halted or modified if any of the following criteria develop:
1. Severe gastrointestinal symptoms prevented oral administration of the trial drug;
2. Disease progression to higher-risk MDS;
3. Patients with severe complications requiring hospitalization;
4. Patients with severe liver and kidney damage from any cause;
5. Any other symptom or sign which, in the investigators' judgment, requires withdrawal of the subject from the study warrants halting the oral administration.

**Strategies to improve adherence to interventions** {11c}

It is the responsibility of the study physician to fully inform patients of the benefits of the drug and the possible costs of discontinuation. Patients will be asked to complete a daily medication diary to improve compliance.

**Relevant concomitant care permitted or prohibited during the trial** {11d}

In case of co-infection, sensitive antibiotics, intravenous gamma globulin, etc. must be used. If combined with bleeding, hemostatic drugs must be used; if platelets are less than $20 \times 10^9 / L$ and severe bleeding occurs, apheresis platelet suspension should be transfused. If combined with severe anemia, hemoglobin <60g/L or combined with patient tolerance, red blood cell suspension should be transfused. Severe agranulocytosis or thrombocytopenia should be treated with cytokines such as G-CSF or TPO, and iron-free therapy.

**Outcomes Measurements** {12}

**Primary outcome**

The primary outcome is overall response rate (ORR) defined as the sum of complete remission (CR), partial remission (PR), cytogenetic complete remission (mCR), and hematologic improvement (HI) accounting for the proportion of total available cases. The criteria for determining the response to treatment refer to the efficacy criteria established by the International Working Group (IWG) on MDS$^{[8,9]}$.

**Secondary outcomes**

Secondary outcomes are the following:

1. the changes in TCM symptom scores: to evaluate the improvement of SHP on MDS clinical symptom scores;
2. Progression-free survival (PFS): the time interval from receiving treatment to disease progression (PD) or death due to MDS;
3. Progression rate: The number of cases with PD or death due to MDS by the end of treatment as a proportion of total cases;
4. Overall survival (OS): the time interval from receiving treatment to death from any cause;
5. Survival rate: The proportion of the total number of cases surviving to the end of treatment;
6. RBC/Platelet Transfusion Frequency and RBC/Platelet Transfusion Independence: Efficacy Analysis of Collecting Clinical Transfusion Cases for Transfusion;
7. Infection rate: the proportion of co-infection cases in the total;
8. Infection-related mortality: the proportion of the total number of cases that died due to co-infection;
9. The physical condition was assessed by KPS scale, before treatment and once every 2 weeks after enrollment;
10. The quality of life was assessed by the Quality-of-Life Questionnaire (EORTC) before treatment and once every 2 weeks after enrollment.

**Participant timeline and Recruitment (13, 15)**

Participants will be recruited from 5 research centers, which included the main MDS population in Shanghai, China. The timeline of participant interventions and assessments is shown in Table 1.

Table 1. Schedule of enrollment, interventions, and assessments
Sample size (14)

Sample size calculations are based on the primary endpoint (ORR). At the 5% significance level, a total of 92 patients per group is required to achieve 90% power and to determine an increase of 35% in the ORR between SHP group and the control group, assuming that the ORR of the control group receiving routine supportive care is about 35%.

Assignment of interventions: allocation

Sequence generation (16a), Concealment (16b) and Implementation (16c)
Allocation process of participants will follow Good Clinical Practice (2020) issued by China National Medical Products Administration[15]. All patients will be randomly assigned according to stratified block randomization method. The random sequence will be generated by Research Center for Drug Safety Evaluation, Shanghai University of Traditional Chinese Medicine via the PRCO PLAN function of the analysis system of SAS software (SAS, Cary, NC, USA). The randomization sequence will be hidden in a closed envelope and kept by the independent statistician. Independent drug administrators will be responsible for assign numbered packs of the trial drug in order by randomization list[16].

Assignment of interventions: blinding

Who will be blinded after assignment to interventions? {17a}

Not the investigators and subjects but the outcome assessors will be blinded. Because realgar in SHP requires dose adjustment based on blood levels, investigators and subjects cannot be blinded.

Data collection methods

Plans for assessment and collection of outcomes {18a}

Treatment response needs to be comprehensively judged based on the results of routine blood tests, chromosomal testing, and bone marrow aspirate, which requires the collection of bone marrow and peripheral blood samples. Training sessions on outcome evaluation and data collection will be held for investigators from all centers prior to the start of the study. In addition to laboratory testing, patients will be assessed for clinical symptoms and quality of life through the KPS score, EORTC and TCM symptom scales at each visit.

Plans to promote participant retention and complete follow-up {18b}

The investigators must inform the patients of the importance of the treatment course and follow-up evaluation and data collection, which brings more clinical benefits, provide high-quality data and an effective treatment option for others. The researchers will provide financial subsidies for transportation and nutrition to improve participant retention for all patients.

Data management {19}

An independent Steering Committee is responsible for review and supervise the original CRFs. A team led by an independent statistical expert is responsible for data management on the EDC platform, which has been always technically supported and maintained by the Shanghai Shenkang Hospital Development Center in China.

Statistical methods

Statistical methods for analyzing primary and secondary outcomes {20a}
The clinical data will be analyzed by the independent statisticians in accordance with the statistical analysis plan. The Research Center for Drug Safety Evaluation of Shanghai University of Traditional Chinese Medicine will use SAS (SAS Institute, Cary, NC, USA) for statistical analysis. Appropriate statistical method will be selected depends on the following three things: aim and objective of the study, type and distribution of the data used, and nature of the observations (paired/unpaired)\textsuperscript{[17]}. Cochran-Mantel-Haenszel (CMH) test will be used compare the between-group difference in ORR, progression rate, overall survival rate, infection rate and infection-related mortality. The Kaplan-Meier method will be used to estimate time-to-event end points. Log-rank tests are used for progression-free survival and overall survival, and stratified Cox regression models will be applied to estimate hazard ratios. The change from baseline in continuous end points such as TCM symptom scores and patient-reported outcomes were analyzed by a mixed-effects model with repeated measures. For safety analysis, the prevalence of adverse events in the two groups will be compared using the Pearson $\chi^2$ test, as well as listing and describing the events that occur during the trial\textsuperscript{[16]}. According to the CONSORT statement, baseline demographic and clinical characteristics for each group will be presented in the trial report, and significance testing of baseline differences will not be performed\textsuperscript{[18]}.  

**Definition of analysis population relating to protocol nonadherence\textsuperscript{[20c]}**

Efficacy analyses will be conducted for the modified intent to-treat (mITT) population. This is defined as all patients randomized who received at least one dose of SHP and one time efficacy evaluation at any timepoint. The per-protocol set is used to analyze the main outcome for evaluating efficacy and to examine the consistency of the results from the mITT. The mITT population considered as full analysis set (FAS). The per-protocol set (PPS) is defined as follows: (1) full compliance with inclusion and exclusion criteria; (2) the compliance of medication consumption is over 80%; (3) completion of the clinical trial without major protocol violation. The safety analysis set (SAS) is defined as patients who received any amount of study treatment and at least one time safety evaluation. The SAS will be used for the analysis of all safety indicators.  

**Composition of the coordinating center and trial steering committee \textsuperscript{[5d]}**

The study is led by Shanghai Municipal Hospital of Traditional Chinese Medicine. The trial steering committee consists of the following members: Jia-hui Lu, Jun Shi, Chun-kang Chang, Xiao-yang Li and Wen-wei Zhu.  

**Monitoring**

**Description of the data monitoring committee \textsuperscript{[21a]}**

The independent Data Monitoring Committee (DMC) is responsible for reviewing the reports regarding protocol adherence and making recommendations to continue or terminate the study. The DMC members are all independent of the sponsor/funders and have no financial or other conflicts of interest.
**Safety assessment**

Physical examination, symptom diary, laboratory tests, urine/stool routine and adverse events will be conducted for safety assessment. Doctors mainly focus on blood routine test, liver and kidney function, electrolyte test, bleeding and coagulation function, and myocardial enzyme. *Realgar* in SHP is highly toxic and may cause gastrointestinal symptoms, skin damage, myocardial damage, liver and kidney function damage, etc. This trial will be performed in accordance with the established safety standards\(^{[19]}\) of realgar in treating MDS in China. The study monitored the safe dose range of realgar by monitoring the blood concentration of arsenic in regular follow-up to minimize realgar-related adverse events. If arsenic poisoning occurs, emergency detoxification can be carried out according to Chinese safety regulations, such as the use of sodium dimercaptopropanesulfonate and other drugs\(^{[19]}\). After a full multidisciplinary assessment of the patient's condition, the doctor will determine whether to adjust the dose of the drug or stop taking it.

**Assessment of adverse events**

Any adverse event will be recorded in the CRF regardless of relationship to the intervention. All serious adverse events will be reported within 24 h to the Principal Investigator, Steering Committee, Institute review board (IRB), the sponsor, and CFDA. Adverse reaction grading standards refer to Common Terminology Criteria for Adverse Events (CTCAE)\(^{[20]}\). How to judge the correlation between adverse events and trial drugs will refer to WHO-UMC assessment method\(^{[21]}\). Participants may experience exacerbations due to natural disease progression, poor drug efficacy, or other reasons. If the participant is judged to be critically ill, the doctor should report to the sponsor and the ethics committee within 24 h and stop the intervention. The investigator should immediately initiate a treatment regimen on severe clinical situation. When necessary, the sponsoring unit and the project funding department will organize multidisciplinary consultations, propose a comprehensive clinical treatment plan and be jointly responsible for the treatment, follow-up monitoring, and follow-up of critically ill participants.

**Frequency and plans for auditing trial conduct**\(^{[23]}\)

The supervision team directly led by principal investigator (PI) will be responsible for monitoring the trial. On-site monitoring and remote monitoring visits will be conducted in accordance with the study monitoring plan to ensure the completeness and accuracy of research data. Audits may be conducted at any time during or after the study.

**Ethics and dissemination**

*Research ethics approval, Consent and protocol amendments* \(^{[24, 25, 26a]}\)

The IRB of Shanghai Municipal Hospital of Traditional Chinese Medicine of has approved the protocol (IRB approval No.2022SHL-KY-09). The investigators must issue informed consent to participants or
authorized surrogates and fully inform the benefits, risks and precautions of participating in this trial. The informed consent will be obtained from participants. Protocol amendments will be submitted to the IRB and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the IRB and regulatory authorities before implementation of any changes.

Confidentiality (27)

The PI maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location. Medical information of patients is confidential and may be disclosed only as permitted by separate authorization for use and disclosure of personal health information signed by participants or authorized surrogates, unless permitted or required by law.

Access to data (29) and Dissemination plans (31a, 31b, 31c)

After the trial is completed, we will publish the results to the public in academic journals or public platforms. There are currently no plans to share data unless requested by the competent authorities or for other public benefit purposes.

Trial registration (2a, 2b)

We registered our protocol (ChiCTR2200064230) on the Chinese Clinical Trial Registry (ChiCTR) on September 30, 2022, which is one of the primary registries of the World Health Organization International Clinical Trials Registry Platform. All items from the World Health Organization Trial Registration Data Set requirements are met with the trial's registration in the ChiCTR.

Discussion

Despite the current progress in drug development for MDS, how to improve the quality of life and prognostic outcomes of LR-MDS remains a challenging task\[7\]. In China, arsenic-containing TCM preparations have been widely used in MDS populations for decades. Based on the preliminary clinical evidence accumulated in long-term practice, China has formed guidelines for the treatment of MDS with arsenic-containing traditional Chinese medicines\[19\]. However, there is no adequate evidence based on high-quality randomized controlled trial to clarify the efficacy and differences of arsenic-containing TCM in different MDS populations. The quality of many prior studies on TCM was assessed to be generally low due to methodological limitations such as inadequate randomization, lack of double blinding and non-placebo control, incomplete outcome data\[22\]. Therefore, we hope to carry out this RCT to clarify the impact of SHP on disease progression and survival prognosis of LR-MDS and its potential effect mechanism, and to provide exploratory data for follow-up studies.

Why did we not design a placebo as a control in this trial? Because SHP contains arsenic, it is necessary to regularly measure the blood drug concentration and adjust the drug dose, and adverse drug reactions
are relatively common, so the blinding of researchers and subjects cannot be achieved during the implementation of the study. During the implementation of clinical research, the blinding method of traditional RCT is often impossible to achieve due to the ethics of protection of special populations or the limitation of special intervention methods such as surgery. PROBE study (Prospective Randomized Open, Blinded End-point) was first proposed in 1992 to answer this question, in which end-points are evaluated by a blinded end-point committee\textsuperscript{[23]}. Therefore, we chose to blind the outcome evaluator to minimize measurement bias. It is undeniable that this trial is insufficient in controlling information bias due to subjective factors of the investigator and the subjects.

Although both National Comprehensive Cancer Network (NCCN) guidelines and Chinese guidelines recommend lenalidomide for the treatment of MDS\textsuperscript{[8, 9]}, thalidomide is included in the basic treatment regimen after considering the feasibility of implementation, availability of drug resources, and economic cost. Subgroup analysis based on actual use of thalidomide or lenalidomide was required after the study was completed. Previous studies have suggested that arsenic may play a role in MDS by regulating apoptosis, cell proliferation, DNA methylation and angiogenesis\textsuperscript{[24, 25]}. Therefore, ORR is selected as the primary endpoint that is a complexed outcome index including survival, bone marrow, hematology, and cytogenetics, which is pragmatic, informative and objective to evaluate the overall effect of SHP on LR-MDS.

**Abbreviations**

AML: acute myeloid leukemia; ChiCTR: the Chinese clinical trial registry; CMH: Cochran-Mantel-Haenszel; CR: complete remission; CTCAE: common terminology criteria for adverse events; CRF: clinical report form; DMC: Data Monitoring Committee; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FAS: full analysis set; GCP: Good Clinical Practice; GLM: generalized linear model; G-CSF: granulocyte colony stimulating factor; HI: hematologic improvement; HIF1A: hypoxia inducible factor 1 subunit alpha; IPSS: the International Prognostic Scoring System; IST: immunosuppressant; IWG: the International Working Group; IRB: institute review board; KPS: Karnofsky performance status; LR-MDS: lower-risk myelodysplastic syndrome; MDS: myelodysplastic syndrome; mCR: cytogenetic complete remission; mITT: modified intent to- treat; NCCN: National Comprehensive Cancer Network; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; PD: disease progression; PPS: per-protocol set; PI: principal investigator; PROBE study: prospective randomized open blinded end-point study; RBC: red blood cell; RCTs: randomized controlled trials; Recommendations for Interventional Trials; sEPO: serum erythropoietin; SHP: Sanzi-huangshi pill; SPIRIT: Standard Protocol Items: TCM: Traditional Chinese medicine; TPO: Thrombopoietin.

**Declarations**

**Ethics approval and consent to participate**
The IRB of Shanghai Municipal Hospital of Traditional Chinese Medicine has approved the protocol (IRB approval No.2022SHL-KY-09). Informed consent to participate will be obtained from patients for this study. The use of human tissue samples and human data in the trial were performed in accordance with the Declaration of Helsinki.

**Protocol version**

The protocol version is number 1.0, dated November 15, 2021.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets generated during and/or analyzed during the current study will be made available. The datasets will be available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Hao Xu, Qi Hu, Jizhang Bao and Jiahui Lu conceived and designed the study and are responsible for the coordination of the study. Hao Xu, Qi Hu, Yuchen Tao, Shuyang Cai, Yanlu Wang, Kexin Hu and Tingting Xue participated in the work of enrolling the patients and collecting the data. Jizhang Bao and Jiahui Lu sought funding and ethical approval. All authors contributed to the writing of the manuscript and read and approved the final manuscript. All authors are from Shanghai Municipal Hospital of Traditional Chinese Medicine, No. 274 Zhijiang Middle Road, Jingan District, Shanghai, People's Republic of China.

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**References**


**Figures**
Study flowchart. Eligible participants with LR-MDS will be recruited and assigned randomly into two groups who will receive 6 months of intervention and 18 months of observation.
This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial1SPIRIT2013Checklistforprotocol.docx
- Supplementarymaterial2Informationoftrialdrug.docx
- Supplementarymaterial3EvaluationScaleTool.docx