The Effect of Comprehensive Rehabilitation Program plus Chemotherapy on Quality of Life of Patients with Postoperative Non-Small Cell Lung Cancer: A study protocol of multi-center randomized clinical trial

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Method Article

Keywords: Chinese herbal Medicine; Liuzijue exercise; Rehabilitation; Non-small cell lung cancer; Quality of Life

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Abstract

Background: Comprehensive rehabilitation therapy based on Traditional Chinese Medicine (TCM) has been widely applied in various cancer treatments in China. Thus far, Chinese herbal medicine (CHM) has been shown to be effective in reducing the adverse effects of chemotherapy and improving the quality of life (QoL) during chemotherapy. In the present study, a more rational and effective therapeutic scheme is to be applied to assess the effects of comprehensive rehabilitation program based on CHM and Liuzijue (LZJ) exercise combined with adjuvant chemotherapy on patients with postoperative non-small cell lung cancer (NSCLC).

Methods: A multi-center, randomized clinical trial is to be performed 354 Ib-IIIa NSCLC patients in 5 centers in China. Patients satisfying the inclusion criteria are to be randomly divided into 3 group according to the ratio of 1:1:1, namely intervention group A (IGA), intervention group B (IGB) and controlled group (CG). Each group will receive adjuvant platinum-based doublet chemotherapy for 4 cycles. IGA participants receive chemotherapy combined with CHM and LZJ exercise, IGB participants receive chemotherapy combined with CHM and rehabilitation education, and CG participants receive chemotherapy combined with placebo and rehabilitation education. The primary outcome is QoL (The European Organization for Research and Treatment of Cancer: EORTC QLQ LC43), the secondary outcomes include: (1)2 years disease-free survival rate and disease-free survival (DFS); (2) TCM symptoms; (3) tumor markers; (4) safety and adverse events (NCI CTC version 4.0).

Discussion: Our previous study reported that TCM in combination with chemotherapy could lower the overall incidence of adverse events but increase the digestive and gastrointestinal (GI) side effects than chemotherapy alone in postoperative NSCLC. The study is to lay a basis for the effectiveness of chemotherapy with or without comprehensive rehabilitation program in QoL for patients with postoperative NSCLC.

Trial Registration: ClinicalTrials.gov, NCT03372694. Registered on 17 December 2018 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03372694.

Keywords: Chinese herbal Medicine; Liuzijue exercise; Rehabilitation; Non-small cell lung cancer; Quality of Life.

Background

Lung cancer is the leading cause of cancer death in China and worldwide[1, 2]. Non-small cell lung cancer (NSCLC) takes up nearly 92%, a significant increase over the past few years. Surgery is considered the best treatment for patients with early stage lung cancer, yet a high risk of recurrence or metastasis remain. The 5-year survival rate for stage IIIa is less than 40%[3]. Cisplatin-based chemotherapy could reduce the risk of death by 13% and increase the 5-year survival rate by 5% in patients with completely resected NSCLC[4]. Accordingly, platinum-based adjuvant chemotherapy has been recognized as the

standard treatment for patients with stage II-IIIa[5, 6], and several studies suggested that some IB patients with high-risk prognosis can consider chemotherapy[7].

However, the toxicity and side effects of chemotherapy can reduce the quality of life (QoL) of patients and even terminate chemotherapy. 14% and 10% of the completely resected patients underwent only one and 2 cycles of cisplatin-based chemotherapy, respectively. Refusal, toxicity, and early death or progression were the major causes of termination. 66% NSCLC patients would endure the grade 3 to 4 toxicity during the adjuvant chemotherapy[8]. In the meantime, though there was no difference in the QoL in lung cancer patients after lobectomy and sleeve resection, JBR.10 study suggested that adjuvant chemotherapy had a direct negative effect on many aspects of QoL. For instance, the main symptoms are fatigue, loss of appetite, nausea and vomiting. Due to the toxicity and side effects of platinum-based regimens, NSCLC patients after radical resections need a relatively slow recovery [9]. In the early post-surgery period (baseline to three months), more patients without chemotherapy improved QoL in global functioning[10]. However, receiving adjuvant chemotherapy can improve the long-term QoL of patients. The most vital goal for adjuvant chemotherapy is to extend the overall survival of early cancers. Clinical oncologists and patients are beginning to accept the risks of some side effects to achieve survival benefits, whereas only 48%-50% of patients could complete 4 cycles of chemotherapy[8]. Over 50% of NSCLCs are diagnosed in patients aged over 65 years. Compared with young patients, fewer elderly patients completed treatment and more refused treatment [11]. A considerable number of randomized controlled trials revealed that complementary therapy may solve numerous different problems in lung cancer patients (e.g. anxiety, pain, QoL and treatment-related side effects). An evidenced-based approach to modern cancer care should combine complementary therapies with standard cancer therapies (e.g. surgery, radiation, chemotherapy as well as the optimal supportive care measures)[12]. TCM, as one of the crucial components of complementary therapy for cancer, covers Chinese herbal medicine (CHM) and non-drug therapy (e.g. acupuncture, massage, function rehabilitation, etc.). Previous studies suggested that Oral CHM can improve tolerance to chemotherapy, alleviating symptoms and improving the QoL in lung cancer patients[13-17]. Liuzijue (LZJ) exercise, one of the TCM health exercise, has been widely accepted in lung cancer patients. It is employed to improve pulmonary function, regulate blood circulation and improve physical fitness by 6 different pronunciations emitted during exhalation. Several clinical trials verified that LZJ exercise is capable of significantly improving pulmonary function and QoL in patients carrying chronic obstructive pulmonary disease[18, 19]. It is expected that the combination of CHM and LZJ exercise will not only improve the postoperative motor function in lung cancer patients, but also reduce the toxicity resulting from postoperative adjuvant chemotherapy to successfully achieve 4 cycles of chemotherapy. Our previous study reported that the adverse events in CHM combined with chemotherapy had lower overall incidence than chemotherapy alone, especially in the improvement of symptoms (e.g. pain, diarrhea, hemoptysis, etc.). However, it was also observed that CHM would increase the incidence of nausea and vomiting in the combined chemotherapy [20].

Accordingly, it is recommended to suspend the CHM on the day of chemotherapy and to take regulating stomach prescription within one week after chemotherapy. Besides, TCM syndrome differentiation prescriptions are to be given in 2-3 weeks. This helps to improve the QoL and increase the passing rate of

chemotherapy. From the first month to the second year after surgery, the QoL of NSCLC patients decreased significantly. The influencing factors include age, female, the increase of symptoms before and after surgery, the extent of surgical resection as well as more postoperative complications[21-23]. Alleviating symptoms and improving the QoL are vital for the subsequent treatment of postoperative NSCLC patients.

Pulmonary rehabilitation is critical for the treatment of chronic lung diseases, which can improve exercise tolerance, relieve dyspnea, increase muscle strength and improve health-related quality of life[24-28]. However, bicycle cycling with the increase in load, a frequently used method of pulmonary rehabilitation, is unsuitable for NSCLC patients with adjuvant chemotherapy after surgery. For these patients, low-volume respiratory rehabilitation (e.g. respiratory function exercise) is more suitable. LZJ exercise refers to a traditional health and fitness practice focused on control of the breath. It is a type of respiratory function exercise widely serving as a traditional rehabilitation exercise in China. LZJ exercise can regulate and control the rise and fall of Qi (vital energy) inside the body and related inhalation and exhalation through different mouth forms-six in all-to breathe and pronounce the" XU, HE, HU, SI, CHUI, and XI" exercises. LZJ exercise contributes to balance the energy and the functions of the inner organs.

The present study aims to (1) verify the efficacy of CHM plus LZJ exercise on QoL in NSCLC patients receiving adjuvant chemotherapy after surgery compared with controls and (2) compare the disease-free survival time (DFS), 2-year disease-free survival rate, variations of TCM symptoms, tumor markers, toxicity, side effects and safety of the treatments.

Methods

Study design

This is a multi-center, randomized, three-arm, controlled trial. Subjects from 5 clinical research centers in China are to be recruited by the trial. Yueyang Hospital affiliated to Shanghai university of TCM, Shanghai Chest Hospital affiliated to Shanghai Jiao Tong University, Shanghai Pulmonary Hospital affiliated to Shanghai Tong Ji University, Shanghai Cancer Hospital affiliated to Shanghai FuDan University, Huadong hospital affiliated to Shanghai Fudan university. Eligible participants are to be randomized into 3 groups at a ratio of 1:1:1, namely intervention group A (IGA), intervention group B (IGB) and controlled group (CG). Each group received adjuvant platinum-based doublet chemotherapy for 4 cycles. IGA participants receive chemotherapy combined with CHM and LZJ exercise, IGB participants receive chemotherapy combined with CHM and rehabilitation education, and CG participants receive chemotherapy combined with placebo and rehabilitation education. This study protocol has been approved by the Regional Ethics Review Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine (No.2016-059), will follow the Declaration of Helsinki. The study design is based on SPIRIT 2013 statement[29]. Flow diagram of the study is given in Fig. 1 and the schedule of enrolment, intervention, and assessments is presented in Fig.2.

Study participants and recruitment

Participants of this study are NSCLC postoperative patients who will complete adjuvant chemotherapy after complete resection with confirmed pathological diagnosis of stage Ib-IIIa; TCM syndromes include Yin deficiency, Qi deficiency, Qi and Yin deficiency. Recruitment is mainly through doctors' referrals and recruitment posters and brochures.

Diagnostic criteria

In accordance with "Standards for the diagnosis and treatment of primary lung cancer (2015 version) in China" (National Health and Family Planning Commission of the People's Republic of China, 2015), meet the diagnostic criteria of primary bronchial lung cancer, and pathologically or cytologically confirmed of NSCLC patients, which include squamous carcinoma, adenocarcinoma, adenosquamous carcinoma and large cell carcinoma. TNM staging of primary bronchogenic carcinoma: following the 2009 International Anti-Cancer Alliance (UICC) staging system, version 7.

Syndrome differentiation criteria

Syndrome differentiation criteria follow "Clinical Practice Guidelines of Chinese Medicine in Oncology " (published by People's Medical Publishing House, National Health and Family Planning Commission of the People's Republic of China, 2014), lung cancer symptoms are stratified into 3 basic TCM syndromes and are judged by 2 senior physician/deputy chief physicians before treatment.

1. Qi deficiency syndrome

Major symptoms: cough, lots of sputum, loss of appetite, fatigue and weakness, pale and bulgy tongue. Secondary symptoms: spontaneous perspiration, loose stool, thin superficial as well as smooth pulse.

2. Yin deficiency syndrome

Major symptoms: cough, less sputum, dry mouth, red tongue. Secondary symptoms: night sweat, insomnia, low fever, thready pulse as well as rapid pulse.

3. Qi and Yin deficiency syndrome

Major symptoms: cough, less sputum, fatigue and weakness, as well as dry mouth without polydipsia. Secondary symptoms: spontaneous perspiration, night sweat, reddish tongue or tongue with teeth imprints, thready and weak pulse.

Patients with at least 2 main symptoms and 1 secondary symptom can be diagnosed.

Inclusion criteria

Inclusion criteria are as follows: Patients with completely resected stage Ib-IIIa NSCLC who will receive adjuvant chemotherapy for the first time in 6 weeks after surgery; aged between 18 and 74 years; an Eastern Cooperative Oncology Group performance status (ECOG PS) scale of 0-2; without major organ

dysfunction: hemoglobin ≥10 g/dL, absolute neutrophil count (ANC) ≥1.5*10^9/L, platelets ≥100 *10^9/L; with normal hepatic and renal functions, voluntary participation in clinical study and sign informed consent.

Exclusion criteria

Exclusion criteria are as follows: Indefinite pathological diagnosis; expected survival time□6 months; with heart, liver, kidney and hematopoietic system and other serious diseases; treated with antibiotics or infected one week before the test; Pregnant or child breast feeding women; Mental or cognitive disorders.

Sample size calculation

The primary outcome of the study will be the change of the QoL score assessed by QLQ-C30 scale. According to the results of JRB.10 study, 27% lung cancer patients at stage Ib to IIIa after 3-month adjuvant chemotherapy had lower QoL scores than baseline[9]. Based on the validity assumptions and clinical experience of the past, it is estimated that 15% of patients had no deterioration in QoL combined with comprehensive rehabilitation program compared with treatment without comprehensive rehabilitation program for patients receiving 3-month postoperative adjuvant chemotherapy. Inspection level α= 0.05, 1-β= 0.90, the QoL score after 3 months in the intervention group decreased by 10% while by 27% in the control group compared with the baseline, 98 cases of sample size were obtained in each group and 20% off rate is considered, 354 cases (n=118) will be observed in 3 years. It is suggested that comprehensive rehabilitation combined with chemotherapy can improve the QoL of NSCLC postoperative patients compared with chemotherapy alone.

Randomization

The stratified and randomized methods are to be employed to randomize the patients enrolled here. Stratified Block randomization is designed and implemented by Shanghai Clinical Research Center, Shanghai, China) via the internet. A block size of 6 and patients are stratified in line with clinic stages and the center.

Intervention

Researchers will conduct a one-day training course for this trial, covering the study of the protocol, the recording methods for clinical record forms (CRF), basic information about clinical research, researcher responsibility as well as research monitoring. All eligible participants are to be randomly divided into 3 groups at 1:1:1 ratio (IGA, IGB and CG). Each group will be assessed at baseline and before each cycles of chemotherapy. The treatment lasted for 3 months.

Chemotherapy

Platinum-doublet chemotherapy regimen will be recommended for patients at stage Ib to IIIa in 6 weeks after surgery, and one of the following five regimens is available:

- Cisplatin 75-80mg/m^2 day 1 or carboplatin AUC 5 day 1; Vinorelbine 25-30mg/m2 days 1, 8, per 21 days for 4 cycles
- Cisplatin 75-80mg/m^2 day 1 or carboplatin AUC 5 day 1; Gemcitabine 1250mg/m^2 days 1, 8, per 21 days for 4 cycles
- Cisplatin 75-80mg/m^2 day 1 or carboplatin AUC 5 day 1; Docetaxel 75mg/m^2 day 1 per 21 days for 4 cycles
- Cisplatin 75-80mg/m^2 day 1 or carboplatin AUC 5 day 1; Pemetrexed 500mg/m^2 day 1 for non-squamous per 21 days for 4 cycles
- Cisplatin 75-80mg/m^2 day 1 or carboplatin AUC 5 day 1; Paclitaxel 135-175mg/m^2 day 1 per 21 days for 4 cycles

For patients having received fewer than the intended number of cycles of chemotherapy, the study duration is to be calculated by the basis of the projected interval.

Chinese herbal medicine and placebo

1.Chinese herbal medicine (CHM)

Prescriptions are formulated into granules provided by Professor Ling Xu. Package of granules is to be made into 5 types with functions (e.g. regulating stomach granules, Qi granules, nourishing Yin granules, supplementing Qi and nourishing Yin granules, regulating stomach granules, and detoxifying and resolving masses granules). Each package contained water-soluble herbal granules manufactured at a Good Manufacture Practice (GMP) standard facility (Tian Jiang Ltd, Jiangyin, China). Each package is labeled by a serial number. The prescription form comprised the stock list with both the name and serial number. Participant will take regulating stomach granules in the first week after chemotherapy and started to take TCM syndrome differentiation prescriptions in the second week after chemotherapy (Fig.3).

The TCM syndrome differentiation prescriptions are employed based on the following regimens (Table1):

2.Placebo

The raw materials for the placebo including edible pigment and artificial flavors without CHM are compromised. Placebo and therapeutic packages are stored in different cabinets, and only the dispensing technician knew the contents of the packages.

Liuzijue exercise and rehabilitation education

1.Liuzijue (LZJ)exercise

Participant in IGA will learn LZJ exercise within 1 month after surgery under the leadership of a specialist at the Yue-Yang Integrative Medicine Hospital of the Shanghai University of Traditional Chinese Medicine

and receive LZJ exercise 4 times a week at home during adjuvant chemotherapy.

The program of LZJ exercise include: 1) Warm-up: patients perform 5 min joint activities; 2) LZJ exercise: patients exhale through 6 different mouth forms to breathe and pronounce the "XU, HE, HU, SI, CHUI, and XI" exercises in turn with corresponding actions for about 30mins at all; 3) relaxation: patients adjust the breathing and relax the muscles for 5 minutes.

2.Rehabilitation education

Participant in IGB and CG are to be instructed to do 30 min exercises 4 times a week, which could satisfy their physical strength (e.g. deep breathing training, slow walking and jogging) during the chemotherapy.

Outcome measure

Patient characteristics

Information (e.g. sex, age, pathological type and stage) will be extracted from baseline questionnaires.

Primary outcome

Quality of life

Quality of Life Scale: QLQ-LC30 and QLQ-LC13 scales produced by EORTC is used to assess the QoL of patients. The scoring method is used to determine the results based on the score changes. Before and after the intervention, the international quality scoring system is used to calculate the scores of general QoL and various fields. The physical condition of the patient is to be assessed following the ECOG PS standard before and after treatment.

Secondary

2-year disease-free survival rate

It refers to the percentage of patients without recurrence and metastasis within 2 years after surgery.

Disease-free survival (DFS)

It refers to the interval time either from date of randomization to the date of first documented progression or date of death from any cause, whichever comes first. Response evaluation criteria in solid tumors (RECIST version 1.1) is to be applied for the assessment of tumor response.

TCM symptoms changes

The TCM symptoms scores are to be recorded and calculated based on grading scale of lung cancer symptoms required in "The Guiding Principles of Clinical Research of New Chinese Medicine treating

Primary Bronchial Lung Cancer" (2002) issued by the State Drug Administration. The changes before and after each treatment are to be applied for the assessment of efficacy.

Tumor markers

Tumor markers would be measured before and after treatment which include CEA, CA-125 and CYFRA21-1.

Safety and adverse events

According to Common Terminology Criteria for Adverse Events V4.0 (CTCAE) issued by National Cancer Institute (NCI)(https://ctep.cancer.gov), all the patients will be assessed before and after treatment. The evaluation includes hematological and non-hematological adverse events. Complete blood count, hepatic and renal function, urine and stool routine tests and electrocardiogram will be measured to assess hematological toxicity. Other adverse events including toxicity and side effects of each group will also be recorded and reported during treatment.

If there is a serious adverse event (SAE), the treatment will be stopped immediately, and appropriate treatment will be provided. The types and frequencies of adverse events in each group will be reported.

Statistical analysis

The data will be accessed and saved into the project database of Shanghai Clinical Research Center. SAS software is to be applied for statistical analysis after the access. The methods of statistical analysis are as follows:

A paired t-test is to be performed to compare the average score before and after treatment in each group, and an independent-sample t-test is to be performed to compare the scores between the two groups. According to the homogeneity of variance test, a rank sum test between two groups is performed for those whose P value is not consistent with normal distribution. A chi-square test is used for variable data (baseline, medicine for adjuvant chemotherapy). A rank sum test is performed to analyze Ordered hierarchical data (NCI-CTC graded adverse events). The Kaplan-Meier method is employed to analyze the median survival time of the 2 groups. The Log-Rank is used to test the median survival time. There exists a statistical significance, when P□0.05 occur with two-sided test.

Quality control

Researchers must be trained in Good Clinical Practice for those who have the expertise, qualifications and competence to participate in clinical trials. All medical staff will be uniformly trained before the start of the project, so that they have a full understanding of the clinical trial. Each researcher is required to have an "Investigator's Brochure" for easy access. All data quality control should be carried out every three months, and the problems of supervision and inspection should be corrected within 48 hours after the end of quality control.

Confidentiality

Only researchers involved in clinical trials may be exposed to and confidential to the subject's personal medical records. The personal information of the identifiable subject will be omitted anonymously during data processing.

Discussion

Postoperative adjuvant therapy has been a useful attempt in recent years, several studies revealed that EGFR-TKI targeted therapy can effectively extend the recurrence and metastasis time of patients with sensitive mutations after surgery[30]. However, adjuvant chemotherapy remains the preferred treatment for postoperative NSCLC patients since the follow-up strategy for drug-resistance to targeted therapy has not yet been clear. Toxicity and side effects of chemotherapy not only affect the QoL of patients, but also decrease the completion rate of treatment. As a part of integrated medicine, TCM has been vital for improving efficacy and reducing toxicity of chemotherapy. In previous studies, it has been preliminarily verified that adjuvant chemotherapy (NP/NC) combined with CHM in NSCLC patients after resection improves the QoL compared with chemotherapy alone. It also enables patients to complete adjuvant chemotherapy more safely and effectively. In this study, the selection of chemotherapy regimens is enriched, all the adjuvant chemotherapy regimens commonly used in postoperative patients with NSCLC are basically included, and the treatment of CHM interventions are adjusted. To improve the patients' digestive tract reaction within 1 week after chemotherapy and avoid the nausea and vomiting caused by taking CHM, TCM granules are to be suspended during chemotherapy, and participants in intervention group will take regulating stomach granules in the first week after chemotherapy. Patients will begin to take TCM syndrome differentiation prescriptions from the recovery period of chemotherapy to recover their physical strength and prepare for the next cycle of chemotherapy.

The aim of this study is to further prove whether chemotherapy combined with comprehensive rehabilitation program based on CHM and LZJ exercise can improve the QoL and prolong the survival of patients. A placebo-controlled double-blind RCT design and protocol are proposed, which provides evidence for the QoL in patients with NSCLC after chemotherapy combined with or without comprehensive rehabilitation program. The results will support comprehensive treatment of patients with NSCLC.

Abbreviations

ANC: absolute neutrophil count

CHM: Chinese herbal medicine; CG: Controlled Group; CRF: clinical record forms; CTCAE: Common Terminology Criteria for Adverse Events

DFS: disease free survival

ECOG PS: Eastern Cooperative Oncology Group performance status

GI: gastrointestinal; GMP: Good Manufacture Practice

IGA: Intervention Group A; IGB: Intervention Group B

LZJ: Liuzijue

NSCLC: Non-Small Cell Lung Cancer; NCI: National Cancer Institute

QoL: Quality of Life

SAE: serious adverse event

TCM: Traditional Chinese Medicine

Declarations

Trial status

The protocol version 2.0 was finished on September 13, 2016. Participant recruitment started in October 2016 and is expected to end in December 2019.

Ethics approval and consent to participate

Ethics approval for this study protocol has been obtained from the Ethics Committee of Yueyang Integrated Traditional Chinese and Western Medicine Hospital, Shanghai University of Traditional Chinese Medicine (No.2016-059). Each of the local ethics Committees will comply with central ethical approval confirmed from the Ethics Committee of Yueyang Integrated Traditional Chinese and Western Medicine Hospital. Recruitment of other centers must be approved by the central ethics review before proceeding. Informed consent will be obtained from all study participants before the clinical trial communicators begin to collect any data. All patients will provide their consent in writing before participating in the study. In addition to the investigators, no one can access to the final data.

Consent for publication

All authors gave their consent for publication.

Availability of data and material

As the research has not yet been completed, the datasets generated and analyzed during the current study are not publicly, but are available from the corresponding author on reasonable request.

Competing interests

All the authors have no conflicts of interest

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Authors' contribution

JLY planned the study protocol and drafted the manuscript, LJJ planned the study protocol and revised the manuscript. YBG and LX participated in the conception and design of the trial and managed the study. LX was responsible for obtaining ethics approval and the acquisition of funding. JLY, LJJ, YQY, YL, JS, and JQL recruited and screened eligible patients. PQC were responsible for the data record. All authors have read and approved the final manuscript.

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Tables

Table 1 - Regimens of Chinese herbal medicine based on different syndromes

Syndrome Differentiation	Chinese Medicine (unit: package)			
	Supplementing Qi Granules	Nourishing Yin Granules	Supplementing Qi and Nourishing Yin Granules	Detoxifying and Resolving Masses Granules
Qi deficiency	+	-	-	+
Yin deficiency	-	+	-	+
Qi and Yin deficiency	-	-	+	+

Figures

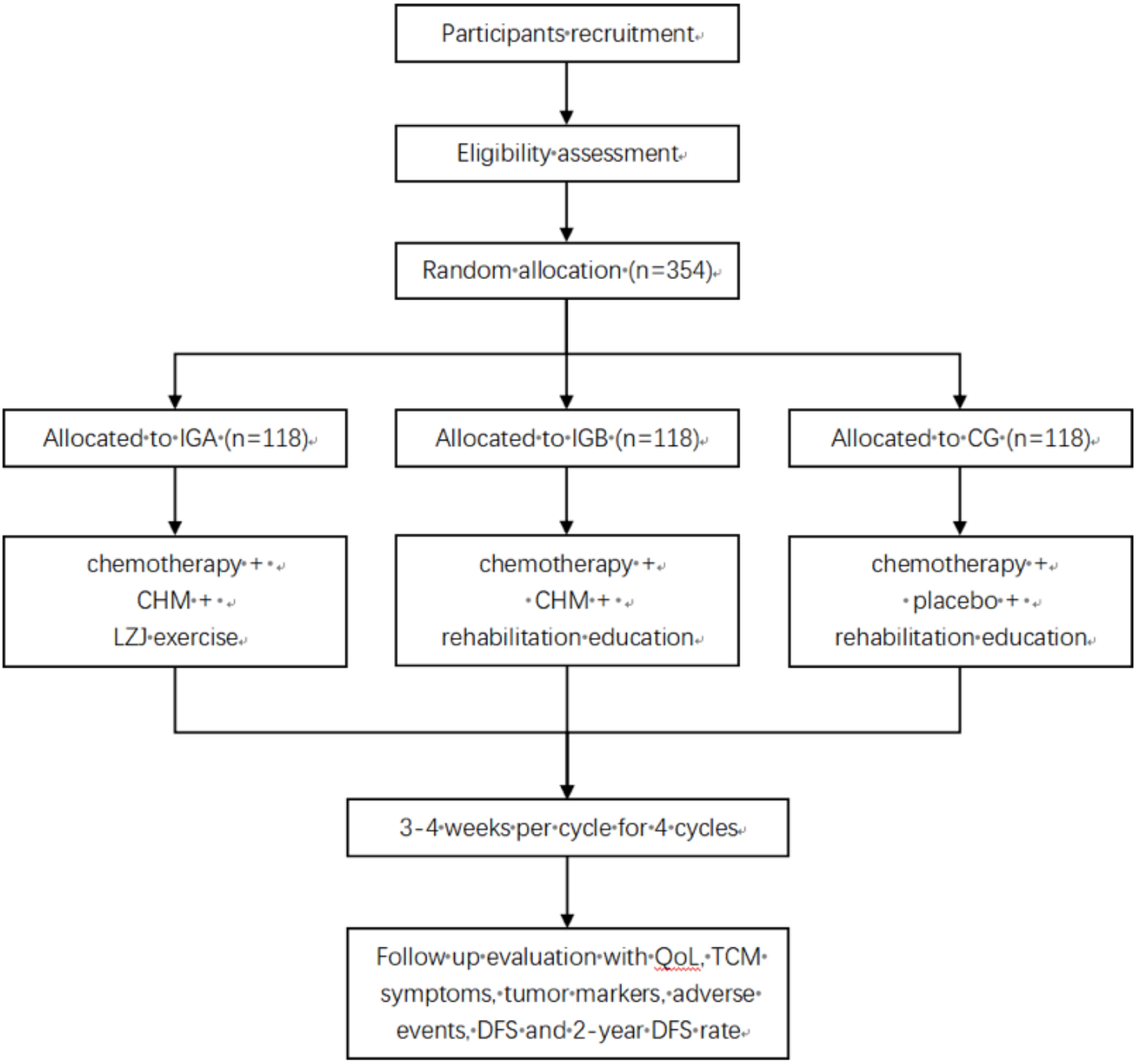


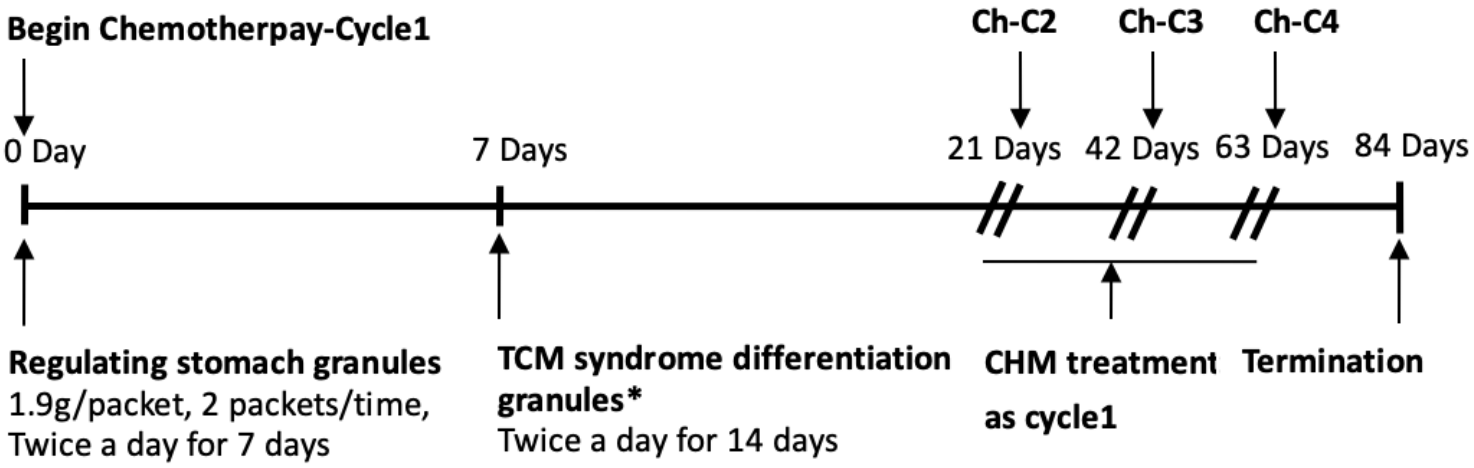
Figure 1

Flow diagram of the study.

	STUDY PERIOD							
	Enrollment	Allocation	Treatment period				Post treatment	
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	2nd year	3rd year
ENROLLMENT:								
Eligibility screen	×							
Informed consent	×							
Randomization		×						
INTERVENTIONS:								
Intervention A			×	×	×	×		
Intervention B			×	×	×	×		
control			×	×	×	×		
ASSESSMENTS:								
Demographics	×							
Medical history	×							
QoL (QLQ-LC30 and QLQ-LC13)		×	×	×	×	×		
TCM symptoms		×	×	×	×	×		
Blood count	×		×	×	×	×		
Hepatic function	×		×	×	×	×		
Renal function	×		×	×	×	×		
Tumor markers	×		×			×		
Adverse events			×	×	×	×		
Chest CT (6 months interval after surgery)	×					◄	———	►
Telephone interview (3 months interval)						◄	———	►
Secondary outcome							×	×

Figure 2

Schedule of treatment and assessment.



* Supplementing Qi Granules:9g/packet, 2 packets/time
Nourishing Yin Granules:11g/packet, 2 packets/time
Supplementing Qi and Nourishing Yin Granules:10.2g/packet, 2packets/time
Detoxifying and Resolving Masses Granules:3.3g, 2packets/time

Figure 3

Chinese herbal medicine taking process.

Supplementary Files

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

- supplement1.doc