Effect and mechanism of YH0618 granule on chemotherapy- induced hair loss in patients with breast cancer: study protocol for a randomized, double-blind, multi-center clinical trial

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Study protocol

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Abstract

Background: Hair loss is one of the most common side effects of chemotherapy, which can cause persistent negative emotions, further affecting therapeutic effects and reducing the quality of life. However, there is no clinically safe and effective methods to solve the problem at present. Our previous clinical and animal studies showed that a medicinal and edible decoction YH0618 could significantly promote hair growth in cancer patients after chemotherapy, without interfering with the anti-tumor effect of chemotherapy. Besides, the theory of Chinese Medicine believes “Essence of the kidney is reflected on the hair”. Therefore, this study will further explore the efficacy of YH0618 granule on chemotherapy-induced hair loss in patients with breast cancer by a randomized, double-blind, multi-center clinical trial and elucidate the potential mechanism from the aspect of kidney deficiency or renal dysfunction. Methods/Design: Eligible breast cancer patients who will start chemotherapy will be randomly divided into group A (YH0618 granule) and group B (placebo). The chemotherapeutic agents contains Taxanes or/and Anthracyclines, and chemotherapy regimen will last at least 6 cycles with every three weeks a cycle. Subjects assigned to group A will receive YH0618 granules two times a day (6 g each time), 6 days a week, mixing with 300 ml warm water from the first to the fourth chemotherapy cycle. Subjects in group B will receive the placebo granule in the same manner. The primary outcome is the time point of occurrence of hair loss reaching grade II assessed by WHO Toxicity Grading Scale, and objective indexes of hair quality and hair follicle recorded by a hair and scalp detector before the fifth chemotherapy. Secondary outcomes include changes of facial color and thumbnails color, grading of thumbnails ridging, assessment of quality life, fatigue, routine blood test, hepatic and renal function, and some medical indicators which can reflect kidney deficiency in Chinese Medicine. Discussion: This research is of great significance for the treatment of cancer and improving the quality of life of patients. The study may provide the most direct evidence for meeting clinical needs and lay a solid scientific foundation for later product development. Trial registration: The trial was registered on 14 December 2018 at Chinese Clinical Trial Registry: ChiCTR1800020107.

Background

Chemotherapy is a major type of cancer treatment using chemical medications to affect cancer cells growth, division and reproduction. Regardless of the route of administration, chemotherapy drugs are introduced into the blood stream, so that chemotherapy can cause various degree of damage to other normal organs and tissues while killing cancer cells, further causing a series of serious adverse effects /toxicity.

Hair loss is an obvious side effect of chemotherapy. The incidence of chemotherapy-induced hair loss is as high as 65% in patients receiving chemotherapy and some is even up to 80-100% in patients receiving specific agents, such as doxorubicin and docetaxel [1-3]. Although hair loss itself does not cause damage to the body and threaten life, it can induce persistent negative emotions such as anxiety, depression and negative evaluation of self-image, which in turn reduces the quality of life [4]. The hair loss caused by chemotherapy is usually reversible, however, in most cases, the color of the newborn hair is grayish or

different from the previous color, and the hair texture also show some changes, such as rougher, slower growth and more sparse [5, 6]. Besides, contemporary social media and excessive attention to appearance have put more pressure on patients, with 8% of patients saying they refuse chemotherapy because of fear of alopecia [7]. Even some female patients said that no hair is more difficult to survive than without breasts [8].

The mechanism of chemotherapy-induced hair loss is still unclear because of the difference in animal model and actual human body, and human scalp cannot be extracted for research. The current reported mechanisms of chemotherapy-induced hair loss mainly involve DNA damage, hair follicle cell cycle inhibition, hair follicle cell apoptosis, and reactive oxygen species and signal transduction, etc. Accordingly, animal model studies have found that vasoconstrictors, antioxidants, hair growth cycle regulators and parathyroid hormone can improve hair loss caused by chemotherapy [9]. In clinical practice, it has been reported that minoxidil, AS101 and vitamin D3 can treat chemotherapy-induced hair loss, but the effect is not significant [10]. Currently, scalp cooling is the only method approved by U.S. Food and Drug Administration (FDA) used for chemotherapy-induced hair loss, and the hypothesis about its mechanism is that low temperature-induced rapid contraction of blood vessels can reduce blood flow into hair follicles, and cause a general reduction in cutaneous cell metabolism, which makes the hair be less affected by chemotherapy [11]. Unfortunately, the success rate of scalp cooling is also only 50%, and patients with cold allergy, cold agglutination, and cold globulinemia are not suitable for this method [9]. Although some progress has been made in the mechanism research and management to alopecia, there is no very effective way in solving the hair loss caused by chemotherapy so far. Therefore, it is necessary for clinicians and researchers to pay more attention to chemotherapy-induced alopecia and a series of relevant psychological problems, further elucidate the mechanism of hair loss and develop safe and effective solutions.

YH0618, a medicinal and edible compound prescription, is developed based on the theory “homology of medicine and food”, ancient prescription, and a long clinical practice. Our previous animal studies have shown that YH0618 decoction did not interfere with the anti-tumor effect of chemotherapy drugs [12]. And a randomized clinical trial also showed that YH0618 significantly accelerated hair regrowth and reduced thumbnail pigmentation in cancer patients who have completed chemotherapy (data was not showed, but the protocol was published in [13]). Therefore, this study will further explore the efficacy of YH0618 granule on chemotherapy-induced hair loss in patients with breast cancer by a randomized, double-blind, multi-center clinical trial. YH0618 consists of five medicinal and edible food (black soybean and liquorice, etc.) which are recommended by clinicians for cancer patients and all components have a history of safe use in other foods. Besides, each of the components possesses a distinct pharmacological profile, including removing free radicals in the body, regulating immune system, preventing cancer, detoxifying and enhancing the taste [14-16]. Black soybean and liquorice, as the main essential ingredients, have been used for detoxification over the millennia in China. Based on the theory of “essence of the kidney being reflected on the hair” in traditional Chinese Medicine, the color, texture and growth of hair is believed to be closely related to the kidney. However, there are no in-depth research on the relationship between kidney and hair, and no research is combined with the comprehensive evaluation of

renal function from the aspects of both Chinese and Western medicine to explore the mechanism of chemotherapy-induced hair loss. Kidney is an important detoxification organ of the human body and help to filter out toxins in the blood and other wastes through urine. Chemotherapy drugs may not cause renal organic lesions, but they consume kidney essence and kidney qi, which breaks the balance of the body. Therefore, we believe that chemotherapy agents not only directly produce toxic effects on hair follicle cells, but also depletes qi, blood and body fluid, especially kidney essence and kidney qi, and breaks the balance of yin and yang of the human body, which leads to the obstruction of microcirculation and the decline of immune function, further resulting in nutritional disorders of hair follicles and hair loss. Thus, the study will also elucidate the mechanism of YH0618 granule on reducing hair loss from the aspect of kidney deficiency or renal dysfunction. The hypothesis of the study is that YH0618 granules could delay chemotherapy-induced hair loss by improving kidney deficiency and renal dysfunction.

Methods/ Design

Study design

This is a randomized, double-blind, multi-center controlled trial which aims at exploring the efficacy of YH0618 granule on chemotherapy-induced hair loss in patients with breast cancer and elucidating the potential mechanism from the aspect of kidney deficiency or renal dysfunction. To achieve this goal, a total of 214 breast cancer patients who will receive first chemotherapy will be recruited for the study. The patients will be randomly divided into group A (YH0618 granule) and group B (placebo) using a 1:1 allocation ratio, adhering to the “CONSORT statement” [17] and “SPIRIT statement” [18]. The primary outcome of this study is the time point of occurrence of hair loss reaching grade II assessed by WHO Toxicity Grading Scale, and objective indexes of hair quality and hair follicle recorded by a hair and scalp conditioners (CBS-603, CBS-Medical Skin Analysis, Taiwan). Secondary outcomes include changes of facial color and thumbnails color, grading of thumbnails ridging, assessment of quality life, fatigue, routine blood test, hepatic and renal function, and some medical indicators which can reflect kidney deficiency in Chinese Medicine. The flow chart of the study is shown in Figure 1 and Table 1. The recruitment, evaluation and data collection will be conducted at Galactophore Department of Guangdong Provincial Hospital of Chinese Medicine, Galactophore Department of The First Affiliated Hospital of Guangzhou University of Chinese Medicine, and Galactophore Department of The Third Hospital of Nanchang.

Ethics

Ethical approvals have been confirmed from the institutional review board at Guangdong Provincial Hospital of Chinese Medicine (BF2018-100-01), The First Affiliated Hospital of Guangzhou University of Chinese Medicine (ZYYECK□2019□006) and The Third Hospital of Nanchang (2018-011). The trial was registered in the Chinese Clinical Trials Registry: ChiCTR1800020107. Patients will receive a detailed information sheet and complete written consent forms.

The trial is managed by the School of Chinese Medicine, HKU and data will be supervised by Data and Safety Monitoring Board (DSMB), which is an independent group of experts that advises funding agency and study investigators. DSMB members includes three experts from different fields (Western medical sciences, Chinese medicine and statistics). The DSMB is for quality control of this research data and make sure the integrity of the study. The protocol compliance, safety, and on-schedule study progress are also monitored by the DSMB. Auditing trial will be conducted every 3 months and the process will be independent from investigators. Study documents (soft- and hard-copies) will be retained in a secure location for 5 years after trial completion.

Subjects

A total of 214 eligible patients will be recruited at different clinical centers. Inclusion criteria include: (1) females with stage I or II breast cancer aged between 18-75 years; (2) will receive first chemotherapy; (3) planning to receive chemotherapeutic agents containing taxanes or/and anthracyclines; (4) chemotherapy regimen will last at least 6 cycles with every three weeks a cycle; (5) adverse events assessed using WHO toxicity classification criteria< II grade; (6) a life expectancy is at least 6 months. Exclusion criteria are: (1) subjects with a medical history of hair transplantation; (2) suffer from psoriasis or severe scalp infection; (3) hair loss induced by alopecia areata, alopecia totalis or scalp injury, etc.; (4) pregnancy, lactation or potential pregnancy; (5) allergic to some specific food, like black soybean, etc.; (6) severe cardiac, hepatic, renal, pulmonary and hematic lesions or other diseases which will affect their survival; (7) who have any severe mental or behavioral disorders that cannot be fully informed; (8) be suspected or do have a history of alcohol and drug abuse; (9) cannot understand or fill in questionnaires because of cognitive disorders or low level of literacy; (10) a variety of factors affecting drug taking and absorption, such as inability to swallow, chronic diarrhea, intestinal obstruction, etc. Eligible patients will be invited to participate in this study after obtaining their written consent form. All participants will be closely monitored in the study.

Estimation of sample size

The primary outcome in this study is the time point of occurrence of chemotherapy-induced hair loss reaching grade II measured by WHO Toxicity Grading Scale for Determining the Severity of Adverse Events. Our previous results showed that YH0618 could cause the incidence of hair loss grade <II to reach 50% for patients who have completed chemotherapy, and the difference between the incidence of hair loss grade <II in YH0618 group and control group was 15%. Thus, the difference in proportion between the two groups will be measured by Z-test. To achieve a two-sided type I error alpha = 0.05 and power: (1-beta) = 80%, the minimal number of subject need in each group is 85. We estimated a 20% attrition rate at the end of follow-up; hence, a sample size of at least 107 in each group (214 in total) is planned for this study.

Randomization and blinding

Each subject will obtain an unique number after completing written consent. A computer blocked random number sequence with a block size of four will be generated centrally by a statistician not involving in this study. As YH0618 granule and placebo show the same appearance, a double-blind model will be adopted. Therefore, the randomization sequence and different groups will be kept hidden from subjects, practitioners, data collectors and statisticians.

Intervention and control condition

Prior to intervention, baseline data will be collected including demographics, medical characteristics, assessment of chemotherapy-induced hair loss, facial color, thumbnails color, grading of thumbnails ridging, quality of life, blood routine test, and hepatic and renal function. After that, subjects assigned to group A will receive YH0618 granules three times a day (6 g each time), 6 days a week, mixing with 300 ml warm water from the first to the fourth chemotherapy cycle. Subjects in group B will receive the placebo granule in the same manner. Then, all the subjects will be followed up until one month after chemotherapy. All specific methods, such as scalp cooling, used for reducing hair loss will be prohibited during the clinical trial. Both YH0618 granules and placebo are produced by Guangzhou Kanghe Pharmaceutical Co., Ltd., which meets national standards.

Outcome evaluation

Primary outcome

The primary outcome is the time point of occurrence of hair loss reaching grade II assessed by WHO Toxicity Grading Scale, and objective indexes of hair quality and hair follicle recorded by a hair and scalp detector (CBS-603, CBS, Taiwan) before the fifth chemotherapy.

Grading of chemotherapy-induced hair loss

WHO Toxicity Grading Scale is commonly used to monitor and rate severity of anticancer drugs-induced toxicity [19, 20]. The grading criteria for hair loss is shown in Table 2. Alopecia assessments will be conducted by a clinician blinded to treatment assignment, and by the participant.

Objective measurement of hair loss

In order to objectively evaluate the hair quality and hair follicle, a hair and scalp detector (CBS-603) will be used. The detector obtained patents in the United States, German, Japan, China, and China Taiwan, and many international authentication from Conformite Europeenne (CE), Federal Communications Commission (FCC), and Restriction of Hazardous Substances (RHoS). The detector is composed of 10X-200X Hair and Scalp Camera and software. The whole top of the head, a wide range of hair loss and the condition of hair follicles could be clearly filmed with 10X, 50X and 200X, respectively. The software has a function of testing through which hair test and analysis can be conducted. In this study, identification and classification of the level of hair loss, hair diameter and quality will be analyzed.

Secondary outcomes

Secondary outcomes include changes of facial color and thumbnails color, grading of thumbnails ridging, assessment of quality life, fatigue, routine blood test, hepatic and renal function, and some medical indicators which can reflect kidney deficiency in Chinese Medicine.

Facial color and thumbnails color

The assessment of facial and thumbnails color is used by L*a*b system, which is the same as the clinical trial we conducted before [13]. In the fixed surroundings, the skin color of the forehead, right and left cheeks, jaw, and the thumbnail color will be recorded by the hair and scalp detector with 50X.

Grading of thumbnails ridging

The grading of left and right thumbnail ridging will be measured by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). The definition of nail ridging is a disorder characterized by vertical or horizontal ridges on the nails. The grading criteria for nail ridging is shown in Table 3.

Quality of life measurement

Quality of life has been regarded as an important index to measure and monitorcancer patients' treatment outcomes [21]. Chinese version of the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) with good reliability and validity will be used to measure breast cancer-specific quality of life [22].The tool includes 37 items scored on a 5-point Likert scale, ranging from 0 to 4 with higher scores indicating better quality of life [23, 24]. The items are classified into five subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being and Functional Well-Being, which constitute the FACT-General, and the additional concerns for breast cancer, which is called the Breast Cancer Subscale. A total score is calculated by summing all subscale scores.

Fatigue measurement

Fatigue will be measured by the Chineseversion of FACIT-Fatigue version 4, a 13-item FACIT Fatigue Scale,which could be used for patients of any tumor type [25]. Each itemscored on a 5-point Likert self-report scale, ranging from 0 to 4. A totalscore is obtained by summing all item scores and a high scoreindicates less fatigue.

Clinical objective examination

Routine blood test, and assessment of liver and kidney function are the same as our previous trial [13]. Based on the evaluation standard of kidney deficiency in Chinese Medicine, kidney deficiency will be divided into deficiency of kidney qi, deficiency of kidney yang and deficiency of kidney yin. Modern studies also found that kidney deficiency syndrome has a modern pathophysiological basis, clinically manifested as changes in the relevant medical indicators such as the adrenal axis, thyroid axis, gonadal axis, renin-angiotensin, immune energy, liver and kidney function and hematopoietic function [26]. So in this study,

Immune indices including immunoglobulinM (IgM), alexin C3, Helper T cells CD4+, CD8+T cell and some metabolic index of microelement such as Mg, Cu, Zn, Fe.

All participants will be assessed within 3 days before every chemotherapy from the first to the fifth chemotherapy. Then, all the subjects will be followed up and the final assessment will be conducted at one month after the last chemotherapy. Professional research assistant will assign YH0618 granules or placebo, and notify the subjects of dosage and time. Quality and compliance to intervention will be achieved by checking attendance records and the diary of self-record kept by each participant.

Adverse events

Adverse events will be recorded through self-reports spontaneously by participants or asking the participants the open-ended question “How are you feeling?” via phone or face-to-face. Any questions concerning adverse events will be reported regardless of whether they were deemed to be related to the treatment be assessors and be sent to the Institutional Review Board of every clinical centers.

Statistical analysis

All analyses will be performed based on intention-to-treat principles, any missing data in the follow up visits will be imputed using multiple imputation. Descriptive analyses as means and standard deviations (SDs) will be used to describe the demographics and clinical characteristics of the participants. The primary efficacy analysis compared the hair loss grading between YH0618 granule and control before the fifth chemotherapy using Fisher exact test. The changes of hair diameter between the two groups after 4 cycles of chemotherapy will be compared by independent samples t-test. A multivariable logistic regression model will be used to explore the treatment effect. Potential confounding variables will be identified as those that differ among treatment groups at baseline and are significantly associated with outcomes. Changes from baseline to the final assessment in quality of life assessed by the FACT-B and objective indicators in blood will be compared using Wilcoxon rank sum tests. Unless otherwise specified, 2-sided statistical tests will be used and the significance level will be set at $p < 0.05$.

Discussion

Chemotherapy induced hair loss occurs usually due to the high mitotic rate of hair follicles instead of a non-androgenic mechanism, and can manifest as alopecia totalis, telogen effluvium, or less often alopecia areata [27]. Severe hair loss occurs most often with drugs such as doxorubicin, daunorubicin, docetaxel, paclitaxel, cyclophosphamide and etoposide, which are common chemotherapy agents used for breast cancer patients. Even some standard chemotherapy regimens can induce permanent thinning or hair loss. Although scalp cooling is a method approved by FDA used for preventing both permanent and temporary hair loss, concerns about this method have been raised [6, 28]. Therefore, this is the first strict randomized, double-blind, multi-center controlled trial to evaluate the effect of a medicinal and edible compound prescription on chemotherapy-hair loss. The proposed study may provide direct and convincing evidence to support YH0618 as an adjuvant treatment for reducing chemotherapy-induced toxicity, which could be

introduced into clinical settings. Our achievements will provide a safe and effective way for reducing chemotherapy-induced hair loss and improving their quality of life.

Trial status

The protocol version is NO.1. Recruitment will start in June, 2019 and the trial is expected to be completed in December 2020.

Abbreviations

WHO: World Health Organization; FDA: Food and Drug Administration; DSMB: Data and Safety Monitoring Board; CE: Conformite Europeenne; FCC: Federal Communications Commission; RHoS: Restriction of Hazardous Substances; FACT-B: the Functional Assessment of Cancer Therapy-Breast Cancer; WBC: white blood cells; HGB: hemoglobin (HGB); PLT: platelets; ALT: alanine aminotransferase; AST: aspartate transaminase; BUN: blood urea nitrogen; UA: uric acid; IgM: immunoglobulinM; GEE: Generalized Estimating Equation

Declarations

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Availability of data and material

Not applicable.

Authors' contributors

JPC was responsible for this trial and authored this manuscript. JPC and JSY jointly conceived the original idea and led on the trial design and protocol. JSY drafted the manuscript. HLL and QX led on the statistical design and randomization. LG, MH, XLS, MDL, ZG, YLC, YZS, MML and YL helped to apply for ethical approval and will contribute to the methods of patients recruitment and assessment. All authors read, commented on and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approvals have been confirmed from the institutional review board at Guangdong Provincial Hospital of Chinese Medicine (BF2018-100-01), The First Affiliated Hospital of Guangzhou University of

Chinese Medicine (ZYYECK□2019□006) and The Third Hospital of Nanchang (2018-011). The trial was registered in the Chinese Clinical Trials Registry: ChiCTR1800020107.The trial was registered in the Chinese Clinical Trials Registry (ChiCTR1800020107). Written inform consent will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Trial Process Chart

	Before baseline screening	Baseline	Visit 1 treatment phase	Visit 2 treatment phase	Visit 3 treatment phase	Visit 4 treatment phase	Visit 5 Follow-up phase
		(before chemo)	Before 2nd chemo	Before 3rd chemo	Before 4th chemo	Before 5th chemo	One month after chemo
Patients							
Inclusion and exclusion criteria	×						
Informed consent		×					
Demographics		×					
Medical characteristics	×	×	×	×	×	×	×
Randomization and allocation concealment		×					
Primary Outcomes							
Grading of hair loss		×	×	×	×	×	×
Objective indexes (hair quality and hair follicles)		×	×	×	×	×	×
Secondary Outcomes							
Facial color and thumbnails color		×	×	×	×	×	×
Grading of thumbnails ridging		×	×	×	×	×	×
Quality of life and fatigue		×	×	×	×	×	×
Routine blood test		×	×	×	×	×	×
Liver function		×	×	×	×	×	×

(ALT, AST, total protein, and Alba)						
Renal function (Cr, UA and BUN)	×	×	×	×	×	×
Kidney deficiency (IgM, C3□CD4 +, CD8 +Mg, Cu, Zn, Fe)	×		×		×	
Adverse events		×	×	×	×	×
Patients' diary records		Every day during the study				

Table 2 WHO Grading Criteria for Anti-drugs Induced Hair Loss

Grade 0	No hair loss
Grade I	Minor hair loss
Grade II	Moderate hair loss alopecia areata
Grade III	Complete hair loss with regrowing
Grade IV	Non-regrowing hair loss

Table 3 Criteria for assessing chemotherapy-induced nail ridging

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Distortion of nail shape; associated psychosocial impact

Definition of nail ridging: A disorder characterized by vertical or horizontal ridges on the nails.

Figures

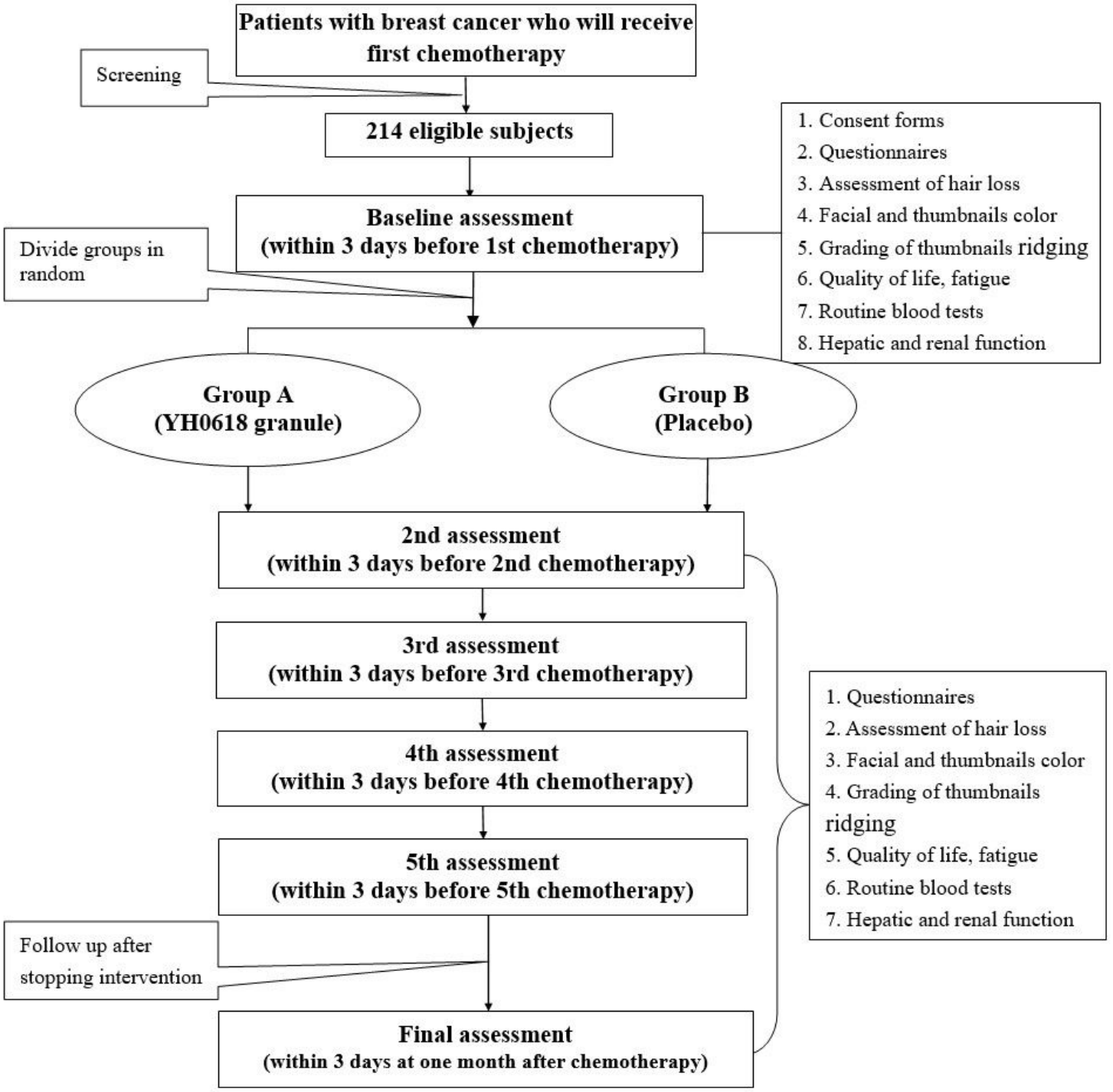

Figure 1

Flow chart of the clinical trial

Supplementary Files

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