Protection of Cardiovascular Function with Crocin in BrEast Cancer patients undergoing Radiotherapy and Chemotherapy （ProtECtion Study）

Informed Consent

Dear patient:

We will invite you to participate in a clinical research. The research protocol has been reviewed by the ethics committee and the clinical research has been approved.

Please read the following as carefully as possible before you decide whether to participate in this research. It can help you understand the research and why it is being done, the procedure and duration of the research, and the possible benefits, risks and discomforts that may come with taking part in the research. If you want, you can also discuss it with your relatives, friends, or ask your doctor to explain and help you make a decision.

In recent years, with the continuous development of medical technology, the diagnosis and treatment of malignant tumor patients has made great progress, and the long-term survival rate has improved significantly. The 5-year survival rate of malignant tumor in China has increased from 30.9% 10 years ago to the current 40.5%. The 5-year survival rate of cancer patients has gradually increased, from 75.9% to 83.2%, and even 91.8% in some areas. However, while great progress has been made in anti-tumor therapy, cardiovascular disease related to tumor therapy largely restricts the long-term survival of patients. Cardiovascular events caused by tumor therapy have become the second leading cause of death in cancer patients. The mortality rate of myocarditis caused by immunotherapy represented by PD-1 can reach 46%. Traditional chemotherapeutic drugs, newly emerging biological agents, and cardiothoracic radiotherapy can all act on the

cardiovascular system, causing structural and functional damage to the corresponding organs. Screening and early diagnosis of malignant tumor patients with high cardiovascular risk factors, and then early intervention, in order to maximize the protection of patients' cardiac function, its important position in the secondary prevention of cardiovascular disease in cancer patients is no doubt. Echocardiography is the clinically preferred non-invasive monitoring modality, but traditional ultrasound is limited in the early detection of cardiac injury associated with tumor therapy. In recent years, the new ultrasound technology represented by speckle tracking imaging has shown the advantages of early diagnosis of cardiac dysfunction.

Prevention of cardiovascular events has become one of the bottlenecks in improving the prognosis of cancer patients. Crocus, also known as saffron, is the dry stigma of the perennial Iridaceae plant, saffron, and is a valuable Chinese medicinal material. Crocin is a water-soluble carotene compound of saffron. It is a series of ester glycosides composed of saffron acid and different sugars. It is one of the main active components of saffron. It has various effects such as anti-oxidative stress, anti-platelet aggregation, anti-thrombosis, and anti-myocardial ischemia.

A number of studies at home and abroad suggest that crocin may help prevent or improve myocardial injury induced by radiotherapy and chemotherapy in cancer patients and protect cardiovascular function. The main component of saffron total glucoside tablets is crocin, which has been approved to be used in patients with chest pain and heart pain (coronary heart disease, angina pectoris) and blood stasis syndrome. At present, the protective effect of crocin on cardiovascular mainly focuses on basic research and small-sample clinical research, and serological indicators are the main observation indicators.

This research is a randomized, double-blind, parallel-controlled, single-center clinical study. Based on the previous study, echocardiography was used to follow-up to observe the effect of crocin on cardiac function in patients with breast cancer undergoing radiotherapy and chemotherapy. The implementation of this study will help to further reveal the preventive and protective effects of crocin on the damage of cardiac function caused by radiotherapy and chemotherapy, and provide a new basis for the protection of cardiac function related to tumor therapy. We look forward to your joining.

Who is suitable for participating in the research

A total of 120 breast cancer patients undergoing chemotherapy in our hospital were included in this study.

All participants must meet the following criteria:

(i) Age 25-80 years old, female;

(ii) Patients diagnosed with breast cancer by histopathology;

(iii) Patients who plan to receive adjuvant radiotherapy, chemotherapy or combined adjuvant trastuzumab or pertuzumab targeted therapy;

(iv) Patients who was to complete at least 6 cycles of treatment after enrollment;

Who should not participate in the research:

(i) Pregnant or breastfeeding women;

(ii) Patients with poor echocardiographic image quality;

(iii) Persistent atrial fibrillation and severe arrhythmia affect the collection and analysis of ultrasound data;

(iv) Patients who are participating in other clinical studies.

What will I need to do if I participate in the study?

Before you are enrolled in the study, your doctor will ask and record your medical history, and perform a physical examination and blood chemistry tests. If you are an eligible enrollee, you may voluntarily participate in the study by signing an informed consent form. If you do not want to participate in the study, we will treat you according to your wishes.

If you volunteer to participate in the study, the following steps will be followed:

After you signed the informed consent, you will be divided into the crocin group or the placebo group according to a random, double-blind, placebo-controlled method. Your initials, gender, age, and other general information will be recorded by the oncologist and coded into follow-up observational follow-up studies. Dosage of crocin group or placebo: 3 times a day, 4

tablets each time. The follow-up period was 6 months. Crocin group: take crocus total glucosides tablets for 8 days during each radiotherapy and chemotherapy (started on the 1st day before radiotherapy/chemotherapy), 4 tablets/time, 3 times a day; Placebo group: take placebo during radiotherapy and chemotherapy for 8 days, start to take 1 day before radiotherapy/chemotherapy, 4 tablets/time, 3 times a day.

You will be followed up every 3 months for 6 months after you are enrolled in the study. The follow-up time is determined according to the clinical situation. We will ask you whether you have chest tightness, chest pain, palpitation and other special symptoms, conduct routine physical examinations, and record clinical events;

In order to monitor the safety of medication, we will collect blood and urine samples at each follow-up after you are enrolled in this study, and measure blood and urine routines, liver and kidney function, and blood sugar indicators; ask and record the medical history. Adverse reactions and severity. Carry out appropriate laboratory tests when necessary;

In order to observe the end points and evaluate the efficacy, we will perform echocardiography, electrocardiogram, dynamic electrocardiogram, serum troponin, NT-ProBNP and other tests, calculate the relevant ultrasound indicators and electrocardiogram indicators, and compare the differences between the groups. If there is any abnormality during the follow-up period, the medication and follow-up methods can be adjusted according to the doctor's order. The inspection and treatment expenses needed during the normal treatment period are paid by yourselves.

After all patients were enrolled and followed up for 6 months, the study was terminated and unblinded, and the follow-up continued to 1 year, and transthoracic echocardiography was performed.

Other things that require your cooperation

You must come to the hospital at the follow-up time agreed between your doctor and you. Your follow-up is very important, because your doctor will determine whether the treatment you are receiving is really working and whether there are any adverse effects, and guide you in time. You must take the medicine as directed by your doctor.

Possible adverse reactions, risks, discomfort and inconvenience of participating in the research

Gastrointestinal discomfort may occasionally occur when taking saffron total glucoside tablets, and the symptoms may disappear after stopping the drug.

If you experience any discomfort during the study, or new changes in your condition, or any unforeseen circumstances, whether or not related to the study, you should promptly notify your doctor, who will make a judgment and give appropriate medical treatment . During the study, you need to visit the hospital on time for follow-up and do some examinations, which take up some of your time and may also cause trouble or inconvenience to you.

Explanation of the cost of participating in the trial

During your participation in this trial, you do not need to pay for the examinations such as electrocardiogram, dynamic electrocardiogram, echocardiography, etc. in the 3rd month and 6th month after enrollment. Crocin tablets and placebo were provided by Reyoung Pharmaceutical Co., Ltd. free of charge.

Is personal information confidential?

Your medical records (research medical records/CFRs, laboratory tests, etc.) will be kept intact at the hospital where you were treated. The doctor will record the test results on your medical record. Investigators, ethics committees and drug regulatory authorities will be allowed to access your medical records. Any public reporting of the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law.

How to get more information?

You can ask any question about this study at any time and get it answered accordingly. Your doctor will keep you informed if there is any important new information during the study that may affect your willingness to continue participating in the study.

You can voluntarily choose to participate in the research and withdraw from the research midway

Participation in research is entirely up to you. You may refuse to participate in this study, or withdraw from this study at any time during the study, without affecting your relationship with your doctor or loss of your medical or other benefits. Your continued participation in this study may be discontinued by the doctor or investigator at any time during the course of the study in your best interest.

If you withdraw from the study for any reason, you may be asked about your use of the investigational drug. You may also be asked to have laboratory tests and a physical exam if your doctor deems it necessary.

What should I do now?

It is up to you (and your family) to decide whether to take part in this study. Please ask your doctor as many questions as possible before making your decision to participate in the study.

Thank you for reading the above material. If you decide to take part in this study, please tell your doctor and he/she will arrange everything for you about the study. Please keep this information.

Informed consent form. Consent signature page

Clinical research project name: Protection of Cardiovascular Function with Crocin in BrEast Cancer patients undergoing Radiotherapy and Chemotherapy

（ProtECtion Study）

Subject undertaking unit: QILU HOSPITAL OF SHANDONG UNIVERSITY

Statement of Consent

I have read the above description of this study and have had the opportunity to discuss and ask questions about the study with my doctor. All the questions I raised got a satisfactory reply.

I am aware of the possible risks and benefits of participating in this study. I understand that participation in the study is voluntary, I confirm that I have had sufficient time to consider this, and understand that:

- I can always ask my doctor for more information.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also know that if I drop out of the study in the middle of the study, especially due to drug reasons, if I tell the doctor about the changes in my condition and complete the corresponding physical examination and physical and chemical examination, it will be very beneficial to the whole study.

If I need to take any other medication due to the change in my condition, I will seek the doctor's advice beforehand, or tell the doctor truthfully afterwards.

I consent to the review of my research data by the Ethics Committee of the Drug Administration or the sponsor's representative.

I will get a signed and dated copy of the informed consent form.

In the end, I decided to agree to participate in this study and pledged to do my best to follow my doctor's orders.

Patient signature_____ Date：_____, _____

Contact Number：_____

I confirm that the details of this trial, including its rights and possible benefits and risks, have been explained to the patient and given a copy of the signed informed consent.

Doctor's signature：_____ Date：_____, _____

Doctor's work phone：_____