Informed consent form of the subject

Project Title: Clinical study of ultra-transplantation for the treatment of thalassemia major

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Dear Patients,

We invite you to participate in the clinical study approved by the First People's Hospital of Yunnan Province for the treatment of thalassemia major. It is expected that 3-5 subjects will volunteer to participate. This study has been reviewed and approved by the Ethics Committee of the First People's Hospital of Yunnan Province.

This notice will provide you with some information to help you decide whether to participate in this clinical study, whether you participate in this study is completely voluntary, and your decision will not affect your normal diagnosis and treatment rights and treatment in our hospital, please rest assured! If you choose to participate in this study, our research team will do our best to ensure your safety and interests during the research process!

Please read this notice carefully and ask the researcher responsible for explaining the informed consent form to the researcher if you have any questions.

1. Background

Thalassemia (thalassemia, referred to as thalassemia), the third most common among all birth defects, is a major public health problem worldwide. Common treatments for thalassemia patients include blood transfusions and hematopoietic stem cell transplantation. Hematopoietic stem cell transplantation (HSCT) is the only clear means to cure thalassemia, and the development of gene therapy clinical research and basic research has led to a success rate of about 70%. Both HSCT and gene therapy require radiotherapy, chemotherapy and immunosuppression. Complications of HSCT include multi-organ dysfunction caused by conditioning drugs, poor stem cell implantation, acute and chronic GVHD, some special complications (capillary leak syndrome (CLS), hepatic sinusoidal occlusion syndrome (SOS), interstitial pneumonia, thrombotic microangiopathy (TMA), post-transplant lymphoproliferative disorder (PTLD), hemorrhagic cystitis, central nervous system complications, etc.). It seriously affects the prognosis and quality of life of patients, and causes varying degrees of damage to

children's reproductive development. The screening of HSCT donors is also an urgent problem to be solved. The success rate and long-term survival rate of HSCT were significantly lower than those of patients aged < 7 years old, and most of the patients aged > 19 years lost the opportunity for HSCT. The economic and social development of our province has been in a backward state for a long time, and there are many patients with severe thalassemia who are not eligible for transplantation due to the non-standard treatment of thalassemia and the lack of unrelated HLA donors. Therefore, finding a safer, more effective and low-cost treatment strategy for such patients with severe thalassemia who are not eligible for transplantation is a key problem in the prevention and treatment of thalassemia in our province and even in the whole country and the world.

As we all know, Professor XX's team pioneered non-myeloablative transplantation (NST) in Asia and China in the late 90s of the last century and led the Chinese non-myeloablative transplant collaborative group. Micrografting is simple, effective, and very safe, with almost no GVHD; Microtransplantation has been widely supported and replicated at home and abroad. On this basis, after more than ten years of research and discussion, Professor Ai's team has innovatively proposed and carried out new theories and models of hypertransplantation. Hypertransplantation does not require any pretreatment of the recipient, nor does it use any cytotoxic drugs, chemoradiotherapy, immunosuppressants, etc., and finally forms a completely stable donor implantation (FDC) through the immune response of the donor and recipient. The good results of hypertransplantation in animal experiments with thalassemia is a major breakthrough in the treatment of thalassemia transplantation, and it also lays a very good foundation for our upcoming clinical research on thalassemia hypertransplantation.

The center is the earliest unit in our province to carry out HSCT treatment of hematological diseases, and the technical level of HSCT is in the leading position in the province, and it has a solid clinical application conditions and foundation. We are willing to accept and adopt the new concept and treatment of hypertransplantation in Professor Ai Huisheng's team, and carry out clinical research on the treatment of thalassemia major under the guidance and help of Professor Ai, verify its "safety and efficacy", cure patients and promote the continuous development of science, and create a safe and effective new treatment model for the treatment of thalassemia major without pretreatment, reproductive damage, and post-transplant complications.

2. Purpose of the Study

It is planned to recruit 3-5 patients with thalassemia major without HSCT indication and unable to undergo thalassemia gene therapy from December 01, 2023 to June 2024, and use the super transplantation treatment plan of Professor Ai's team to observe the

cell reinfusion reaction, hematopoietic remodeling, hemoglobin level and blood transfusion, thalassemia clonal clearance, immune reconstitution, endocrine function recovery, gastrointestinal function recovery, infection and other complication rates. To verify the safety and efficacy of super transplantation in the treatment of thalassemia major.

3. Test subjects

Confirmed diagnosis of thalassemia major, regardless of α and β type; Age between 7-12 years old, male or female; Body weight< 40kg; Patients with or without HLA-matched or haphaidentical donors, but unconditionally transplanted or refused to undergo blood stem cell transplantation; Patients who are unconditional or refuse to undergo thalassemia gene therapy; If there is a HLA fully compatible or incompatible donor, the physical examination meets the donor's conditions; Patients and their families agree to receive ultra-transplantation and sign written informed consent prior to transplantation trial.

Fourth, the research process

This study is a prospective, single-center, single-arm clinical study, and it is planned to include 3-5 patients with thalassemia major who have no HSCT indication and cannot receive thalassemia gene therapy. The diagnosis of thalassemia major was determined by the thalassemia genotype and the clinical manifestations of the patients, and the patients who met the inclusion criteria were screened and enrolled and received super transplantation therapy. Hypertransplantation is an innovative treatment plan of Professor Ai Huisheng's team, which uses hematopoietic stem cell transplantation from healthy donors with the same haplotype as the patient, and observes the patient's cell reinfusion response, hematopoietic reconstitution, hemoglobin level and blood transfusion, thalassemia clonal clearance, immune reconstitution, endocrine function recovery, gastrointestinal function recovery, as well as the incidence of graft-versus-host disease, infection and other complications after transplantation. This study is insured for the enrolled patients, and the adverse reactions directly related to the transfusion of cell preparations, such as hemolysis, embolism, allergies, etc., can be compensated by the insurance company, with a maximum of 200,000 yuan.

The duration of follow-up was 24 months. Follow-up visits include:

1) Blood routine: free transplantation 0d-1m at least 3 times a week; 1m-3m at least 1 time per week; 3m-6m at least 1 time per month; ⩾6m at least once every 2 months. If the condition changes, the number of tests can be increased as appropriate.

2) DNA mosaicism rate of peripheral blood/bone marrow donors: +4, +7, +14, +30d, +90

for free monitoring; 1 time per month for 1 year after transplantation; Within 3 years after transplantation. 1 time from March to June.

3) Thalassemia gene: free monitoring 1 time before transplantation, 1 time per month within 1 year after transplantation.

4) Liver and kidney function and serum ferritin: transplant 0d-1m at least once a week; 1m-3m at least 2 times a month; 3m-6m at least 1 time per month; ⩾6m at least once every 2 months. If the condition changes, the number of tests can be increased as appropriate.

5) Cardiac color ultrasound: 1 time before transplantation, 1 time every 3 months within 1 year after transplantation.

6) Heart and liver MRI iron test: once before transplantation, once every 6 months within 1 year after transplantation.

7) Lymphocyte subsets: free monitoring 1 time before transplantation, 1 time per month within 1 year after transplantation.

8) Cytokines: 1 time before transplantation and 1 time per month within 1 year after transplantation.

9) Thyroid function, ACTH and gonadal function: once before transplantation, once every 6 months within 1 year after transplantation.

10) Other projects that need to be studied: free monitoring of TCR and child growth indicators for 1 year

5. Alternative treatments

If you do not participate in this study, there will be no impact on your usual treatment. Regular blood transfusions and iron removal therapy may be continued.

6. Possible risks and discomforts:

During the treatment, there is a risk of adverse reactions such as donor implantation failure, cytokine release syndrome, graft-versus-host disease, drug side effects, infection, etc., which are associated with transplant therapy and cannot be completely avoided.

7. Expected benefits

Thalassemia major has a chance of cure, but patients may not improve if implantation fails.

8. Treatment Process:

One week before transplantation, the center evaluated the patients, and those who met the inclusion criteria were screened and enrolled. The study doctor will inform the benefits and risks of participating in this study in detail, and sign the informed consent form with full understanding of this study.

1. G-CSF mobilization and donor collection (free): the same as the conventional peripheral blood mononuclear cell (PBMC) protocol.

2. Transplantation plan and treatment:

1) Pretreatment: In principle, there is none.

2) GVHD prophylaxis: 1/2 dose of conventional transplant GVHD prophylaxis.

3) Donor cell infusion.

4) Prevention and treatment of complications: fungal, pulmonary prevention programs and antiviral treatment.

3. Follow-up period: All subjects started on the first day after transplantation and were followed up to 24 months after transplantation. The patient's cell reinfusion reaction, hematopoietic reconstitution (free of charge for DNA chimerism monitoring), hemoglobin level and blood transfusion, thalassemia clonal clearance (free monitoring), immune reconstitution (free monitoring), recovery of endocrine function, recovery of gastrointestinal function, incidence of infection and other complications were recorded.

9. Fees:

1) Free testing items: 12 times of lymphocyte subset detection, 13 times of thalassemia gene detection, 12 times of donor DNA mosaicism rate monitoring, and at least 12 times of cellular immunity detection.

2) The cost of donor stem cell collection and mobilization is about 15,000 yuan, which is provided by the researcher.

3) Patients shall be responsible for the cost of diagnosis and treatment other than those provided free of charge above.

10. Compensation and Indemnification

For the subjects participating in this study, your research doctor will pay close attention to the changes in your condition, minimize or control any risks and inconveniences from the study, once the confirmed research-related injury occurs, please contact your research doctor in time, you will receive timely and appropriate treatment, adverse reactions directly related to the infusion of cell preparations, such as hemolysis,

embolism, allergies, etc., the treatment drugs can be paid by the insurance company, up to 200,000 yuan, if the insurance is not enough to fully compensate, the research party will compensate.

11. Precautions before, during and after the study

1. Lifestyle requirements

Patients should be on a hyperbaric sterile diet from the beginning of the super graft process, and dietary hygiene should be observed. Different stages of the period have different dietary requirements, and subjects and their families should follow the arrangements of medical staff.

2. Requirements for follow-up:

The duration of follow-up was 24 months. 1m-3m at least 1 time per week; 3m-6m at least 1 time per month; ⩾6m at least once every 2 months. If the condition changes, the number of tests can be increased as appropriate.

3. Relevant provisions on concomitant medications, permitted drugs, cautionary drugs, prohibited drugs and concomitant treatment

3.1 Concomitant medications: allowed drug treatment and concomitant treatment:

(1) Please consult the research doctor, and other therapeutic drugs and treatments that do not affect the effectiveness and safety evaluation of the research subjects are allowed.

(2) Any concomitant medication and concomitant therapy need to be approved by the investigator.

12. Confidentiality

In all the documents submitted by the investigator, the identity of the subject is indicated by the clinical identification code, and the patient's name, ID number, hospitalization number and other private information do not appear. The investigator strictly keeps the record of the subject's detailed information and does not submit it to the sponsor or other representatives.

The specimen information involved in the study is tested in our hospital, and no third-party testing or storage is involved. After the end of the study, the laboratory examination results of the specimens were kept in the clinical records of the research center. The data were collected based on follow-up and laboratory results, which may be used in other relevant studies after the end of the study.

13. Voluntariness

You can choose not to participate in the study, or withdraw from the study without discrimination or retaliation after notifying the investigator at any stage of the trial, and any of your medical treatment and rights will not be affected as a result. The investigator may terminate your continued participation in this study if you require additional diagnosis/treatment, or if you are not complying with the study plan, or if there is any other reasonable reason.

14. Contact Information

When there are questions about trial information, research progress and subject rights, as well as any discomfort and damage related to the trial, or complaints to researchers during the research process, you can contact the Medical Ethics Committee of the First People's Hospital of Yunnan Province at 0871-63648772.

Subject signature page

Subject Consent Statement:

☐ I have read the above introduction to this study, and the study doctor has explained the study content to me in detail, and I have no further doubts about the study before signing the informed consent form. On this basis, I voluntarily participated in the clinical study presented here, and my decision was based on a full understanding of the possible risks and benefits of participating in this study. In addition, the investigator did not use deception, inducement, coercion, etc., to force me to agree to participate in the study, and I knew that I could withdraw from the study unconditionally at any stage.

☐ the subject is incapacitated or has limited capacity, this informed consent shall be signed by his guardian or legal representative.

Signature of Subject: Signature of Legal Representative :

Date: Date:

Subject's contact information: Contact information of legal representative:

Guardian's Signature: Fairness Witness Signature:

Date: Date:

Guardian Contact Information: Fair Witness Contact Information:

Investigator's Statement:

I confirm that the details of this study have been explained to the patient, in particular the possible risks and benefits of participating in this study.

Investigator's Signature:

Date:

Investigator Contact:

Note: This page is the subject's signature page, the research doctor will explain the research content and related information to the subject in detail, and the informed consent will be signed by the subject/guardian/legal representative and the research doctor who explains to him. If the subject has any doubts about the content of the study, the investigator should immediately explain it in detail to the subject in person.