A single-center, open-label, exploratory trial of autologous immunotherapy for Hepatocellular carcinoma (HCC) with microvascular invasion (MVI) after radical resection

Sponsor: Cancer Institute and Hospital, Chinese Academy of Medical Sciences

Collaborators: Newish Technology (Beijing)Co.,Ltd.

Investigator Name: Hong Zhao

ClinicalTrials.gov ID: NCT03575806

Document date: 31 October 2019

Background

Hepatocellular carcinoma (HCC) is one of the common cancer worldwide, which is the third cause of cancer related deaths. Radical hepatic resection remains the main treatment for hepatocellular carcinoma, the 5-year survival rate of HCC after surgery was 60-70%. In east Asian countries, the mortality rate for HCC is estimated at 360,000 pre year. Unfortunately, HCC is prone to postoperative recurrence that more than 50% of patients relapse within 2 years, which has become the key to restrict the therapeutic effect of HCC.

Multi-factor analysis showed that vascular invasion, tumor number and size, preoperative AST increase, tumor resection margin and liver capsule invasion were the main factors influencing prognosis, among which vascular invasion was the most closely related variable to postoperative recurrence of HCC.

Autologous cell immunotherapy is to collect patient's own immune cells and then given back to the patient after amplified in vitro that can improve the anti-tumor immune response and is effective treatment of the cancer. Tcm (central memory T cells) are effective anti-tumor immune cells that exhibit the long-term survival and self-renewal capacity in vivo. Autologous Tcm immunotherapy combining chemotherapy, surgery or radiotherapy would effectively prolong survival period, prevent tumor recurrence and metastasis, then improve quality of life in patients.

Methods/design

Study setting

This trial is conducted at Cancer Institute and Hospital, Chinese Academy of Medical Sciences.

Objective

To investigate the clinical efficacy and safety of Tcm immunotherapy in hepatocellular carcinoma with microvascular invasion after radical resection.

Trail design

Single-center, open-label, exploratory trial.

Eligibility

Inclusion criteria

1. Be willing and able to provide written informed consent for the study.

2. Subject has accepted radical hepatic resection, and preoperative imaging is no vascular invasion.

3. Postoperative pathology confirmed Hepatocellular carcinoma with negative margin and microvascular invasion (MVI).

4. Age between 18-75 years old.

5. Radiology confirmed complete response (CR) after radical surgery.

6. Child-Pugh A.

7. Eastern Cooperative Oncology Group(ECOG) body condition score 0.

8. Adequate hepatic and renal function:

Hemoglobin ≥ 9.0g/dl

Absolute neutrophil count (ANC) > 1,500/mm3

platelets ≥ 50,000/ul

Total bilirubin (TBIL) ≤ 2mg/dl

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 5 the upper limit of normal (ULN) for the institution

Alkaline phosphatase (ALP) ≤ 4 the upper limit of ULN

Prothrombin time (PT) > 50% or prothrombin time-international normalized ratio (PT-INR) < 2.3

Serum creatinine (CREA) ≤ 1.5 the upper limit of ULN.

9. Female subjects have had a negative blood pregnancy test within 2 week,

10. Subjects be willing to use appropriate contraception during the trial and 2 weeks after the last administration of immunotherapy.

11. Radiology such as CT and MRI were performed in 4 weeks before the study.

Exclusion Criteria:

1. Recurrent HCC.

2. Portal vein embolus

3. Cardiovascular disease:

(1) Evidence of NYHA functional class III or IV heart disease.

(2) Unstable coronary artery disease (CAD) is not allowed, while Myocardial Infarction (MI) 6 months of starting study is allowed.

(3) Cardiac arrhythmias requiring antiarrhythmic drugs except β-blockers or digoxin are not allowed.

(4) Uncontrolled hypertension.

4. History of Human Immunodeficiency Virus (HIV) or syphilis infection.

5. Severe inflammation, NCI CTCAE Version 3.0 grade > 2.

6. Epilepsy requiring steroid or antiepileptic drugs.

7. History of allotransplantation.

8. History or any evidence of hemorrhage.

9. patients undergoing renal dialysis.

10. Pregnancy or breast-feeding.

11. Prior or undergoing cancers that primary sites are different from the carcinoma of this study. Exceptions to this are:

Cervical carcinoma in situ (CIS)

Cured basal cell carcinoma

Superficial bladder tumor

Cured cancers over 3 years before the study

12. Uncontrolled Ascites by diuretic treatment.

13. History of encephalopathy.

14. Gastrointestinal hemorrhage in 30 days before the study.

15. History of esophageal variceal hemorrhage and it is no effective treatment to prevent the recurrence of hemorrhage.

16. Major surgery except radical hepatic resection was performed in 4 weeks before the study.

17. Autologous bone marrow transplantation (ABMT) in 4 weeks before the study.

18. Concurrent treatment on another clinical trial or treatment on another clinical trial in 4 weeks before the study.

19. Drug abuse, medical treatment, mental illness or social disorders that would interfere with subjects' participation, or confound the results of the trial.

20. Any condition that would interfere with or endanger the safety and compliance of subjects.

Arms and interventions

Experimental arm (Tcm + TACE group)

After radical resection, subjects will receive TACE in a month instead of chemotherapy or targeted drugs. Peripheral Blood Mononuclear Cell (PBMC) obtained from peripheral blood that is extracted within 2 to 4 days before TACE will be cultured in vitro for 14 days, and then subjects will be treated with auto-immune cell transfusion. This is done for two cycles at a one-month interval.

Active comparator (TACE group)

After radical resection, subjects will receive TACE in a month instead of chemotherapy or targeted drugs.

Outcomes

we will evaluate the clinical efficacy and safety of autologous Tcm immunotherapy for HCC with MVI after radical resection according to Recurrence-Free Survival (RFS)as the

primary outcome measure.

The data showed that the median RFS time was 9.5 months in control group, and did not reach the cut-off date in Tcm group for that both 12-month RFS rate and 24-month RFS rate were still greater than 50%. Gehan-Breslow-Wilcoxon test showed the time of RFS in Tcm group were significantly better than the control group when follow-up duration was 12 months (P=0.049; HR=0.40; 95%Cl: 0.16-0.99), but the difference of the time of RFS between two groups did not have statistical significance when follow-up duration was 24 months (P=0.06; HR=0.49; 95%Cl: 0.21-1.12). Above all, Tcm combined with TACE can obviously extended the time of RFS in early period after hepatectomy, and this protective efficacy might last for 12 months.

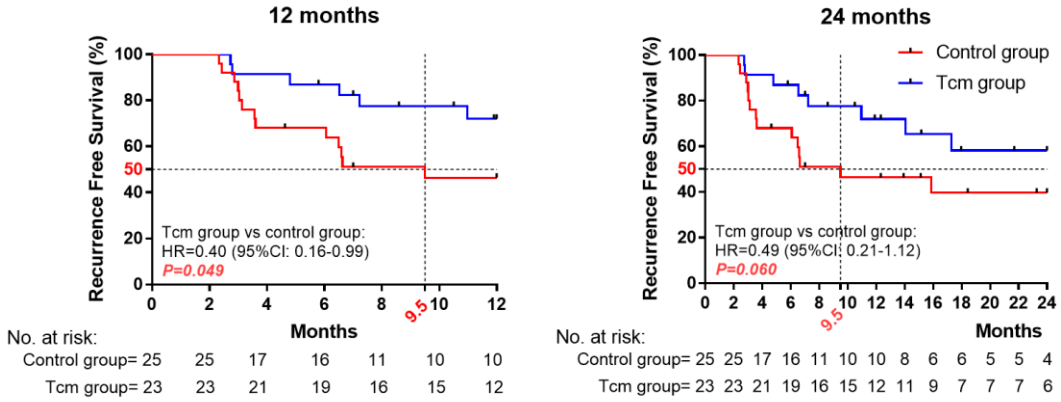

Figure 1: Comparison of RFS between Tcm group and control group at 12 months (P=0.049) and 24 months (P=0.060). P value were calculated by Gehan-Breslow-Wilcoxon test.

Sample size

Overall number of participants：48 Subjects (23 in Tcm + TACE group and 25 in TACE group)

Statistical analysis

Kaplan-Meier curves and Gehan-Breslow-Wilcoxon test are used to analyze the RFS in the two group.

Trial status

Study period: 1 November 2016 to 31 October 2019

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences (Approval Number: 16-134/1213).

The physician in charge will provide a detailed oral explanation supported by a written document to the patient or their legal representative and will then ascertain the patient's understanding of the study. When the patient or their legal representative consents to participate in the study, the physician providing the explanation will enter the date and their name and that of the patient (or their legal representative) and the physician will sign the form. The physician will hand a copy of the signed consent form to the patient or their representative and store a copy (in electronic image format) in the electronic health record. The principal investigator will keep the original signed document. Withdrawal of consent will not disadvantage the patient or affect patient care.

Participation in this study is voluntary, and participants can withdraw from the study at any time during the study as they wish. Non-participation will not cause any disadvantage to patients. The patient (or their legal representative) will confirm intent to withdraw by signing a withdrawal form. The physician in charge will countersign the withdrawal form.

Informed Consent Form

Research number: CH-IT-001

Research institute: Cancer Institute and Hospital, Chinese Academy of Medical Sciences

The physician in charge of the study: Hong Zhao

Dear patient:

you are welcome to volunteer for the clinical trial of autologous immunotherapy for Hepatocellular carcinoma (HCC) with microvascular invasion (MVI) after radical resection. Before deciding whether be willing to participate in, you need to understand this study about the purpose and treatment, advantages and disadvantages, and expect you to do things in the process of research as well as the rights of you as a volunteer. Please read it carefully. If you have any questions, please ask the researcher responsible for the study.

Background

Hepatocellular carcinoma (HCC) is one of the common cancer worldwide, which is the third cause of cancer related deaths. More than 75% of the cases occurred in the Asia-Pacific region, which is largely related to the hepatitis β virus infection. The mortality rate for HCC is estimated at 360,000 pre year in the east Asian countries. Radical resection is still the major treatment for HCC, radical hepatic resection remains the main treatment for hepatocellular carcinoma, the 5-year survival rate of HCC after surgery was 60-70%. Unfortunately, HCC is prone to postoperative recurrence that more than 50% of patients relapse within 2 years, which has become the key to restrict the therapeutic effect of HCC. Multi-factor analysis showed that vascular invasion, tumor number and size, preoperative AST increase, tumor resection margin and liver capsule invasion were the main factors influencing prognosis, among which vascular invasion was the most closely related variable to postoperative recurrence of HCC.

It is concluded that there is no proven beneficial adjuvant therapy for HCC according to the analysis about published open-label trails of the adjunctive therapy of HCC. Therefore, it has become a priority in the treatment of HCC that conduct clinical trials to evaluate the

efficacy of adjuvant therapy after radical treatment.

Memory T cells which are divided into Tem (effector memory T cells) and Tcm (central memory T cells) according to the function. Tcm are specific and durable anti-tumor immune cells according the result of study that the long-term observation of 19 fibroblastoma patients after receiving autologous cell immunotherapy. The autologous cell immunotherapy in this clinical trail is provided by Newish Technology (Beijing)Co.,Ltd..

The informed consent form has been approved by ethics committee.

Research purpose

The purpose of this study is to assess the efficacy and safety of autologous immunotherapy in HCC patients after radical resection, and provide the basis for further study.

Eligibility

Inclusion criteria

1. Be willing and able to provide written informed consent for the study.

2. Subject has accepted radical hepatic resection, and preoperative imaging is no vascular invasion.

3. Postoperative pathology confirmed Hepatocellular carcinoma with negative margin and microvascular invasion (MVI).

4. Age between 18-75 years old.

5. Radiology confirmed complete response (CR) after radical surgery.

6. Child-Pugh A.

7. Eastern Cooperative Oncology Group(ECOG) body condition score 0.

8. Adequate hepatic and renal function:

Hemoglobin ≥ 9.0g/dl

Absolute neutrophil count (ANC) > 1,500/mm3

platelets ≥ 50,000/ul

Total bilirubin (TBIL) ≤ 2mg/dl

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 5 the upper limit of normal (ULN) for the institution

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Exclusion Criteria:

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(4) Uncontrolled hypertension.

4. History of Human Immunodeficiency Virus (HIV) or syphilis infection.

5. Severe inflammation, NCI CTCAE Version 3.0 grade > 2.

6. Epilepsy requiring steroid or antiepileptic drugs.

7. History of allotransplantation.

8. History or any evidence of hemorrhage.

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12. Uncontrolled Ascites by diuretic treatment.

13. History of encephalopathy.

14. Gastrointestinal hemorrhage in 30 days before the study.

15. History of esophageal variceal hemorrhage and it is no effective treatment to prevent the recurrence of hemorrhage.

16. Major surgery except radical hepatic resection was performed in 4 weeks before the study.

17. Autologous bone marrow transplantation (ABMT) in 4 weeks before the study.

18. Concurrent treatment on another clinical trial or treatment on another clinical trial in 4 weeks before the study.

19. Drug abuse, medical treatment, mental illness or social disorders that would interfere with subjects' participation, or confound the results of the trial.

20. Any condition that would interfere with or endanger the safety and compliance of subjects.

Study methods

Experimental arm (Tcm + TACE group): After radical resection, subjects will receive TACE in a month instead of chemotherapy or targeted drugs. Peripheral Blood Mononuclear Cell (PBMC) obtained from peripheral blood that is extracted within 2 to 4 days before TACE will be cultured in vitro for 14 days, and then subjects will be treated with auto-immune cell transfusion. This is done for two cycles at a one-month interval.

Active comparator (TACE group): After radical resection, subjects will receive TACE in a month instead of chemotherapy or targeted drugs.

Withdrawal from the study

In the following cases, the researcher could suspend the test without your consent:

1. When researcher decides that continue test is not good for you.

2. When you happened severe adverse events in the process of trial.

3. When you fail to take the medicine according to the doctor's instructions.

Research process

The subjects had to sign a consent form before participating in this trial, you will participate in this trail into the treatment group or control group as you meet the criteria. According to the principle of random grouping and into experimental arm (Tcm + TACE group) or active comparator (TACE group). Requirements as follows:

experimental arm (Tcm + TACE group): After radical resection, you must be in accordance with the requirements of the trail and the researcher during the trail. You are informed to sign the informed consent after meeting criteria by the researcher screening your conditions. twenty days later you would return to research institute and 80-100 ml blood is extracted that will be sent to the laboratory for amplification of 14 days. It will be two days in advance to inform you that you are returning to research institute and will be treated with auto-immune cell transfusion intravenously. you would be treated with TACE one month later. This is done for two cycles at a one-month interval. During this trail, comprehensive interrogation, physical examinations, laboratory examinations and imaging examinations are required before the first auto-immune cell transfusion and every three months postoperatively, the observation time is 24 months.

active comparator (TACE group): you would be treated with TACE one month after radical resection, this would be done for two cycles at a one-month interval. During this trail, comprehensive interrogation, physical examinations, laboratory examinations and imaging examinations are required before the first auto-immune cell transfusion and every three months postoperatively, the observation time is 24 months.

Benefits

By studying your case, it will provide the necessary advice for your treatment, or provide useful information for the study of the disease.

Rights and interests of subjects

1. You have the right to know the study about the purpose, methods, advantages and disadvantages, rights and interests by consulting the researcher.

2. You may choose not to participate in this study, or at any time inform the researcher to request withdrawal from the study. Your data will not be included in the study results, and any medical treatment and benefits will not be affected.

3. You have the right to privacy: see the confidentiality section of this text.

Adverse reactions and safety measures

Any research will have risk, discomfort and inconvenience. In preclinical trials, It is found no severe side effects about cells immunotherapy, but any kind of treatment may cause some adverse reactions. Due to individual difference, possible adverse reactions are infection, fever, etc., or any unanticipated adverse reactions that could be very serious even life threatening. If adverse reactions occur, the doctor will take timely corresponding treatment methods. During the treatment, the doctor will monitor you for possible adverse reactions strictly and may terminate your continued participation in the study if necessary.

Subject responsibilities

As a study subject, you have the following responsibilities: If you are willing to participate in the clinical trial, you should sign the informed consent after carefully reading the informed consent. keep appointments and see doctors regularly; provide true information about your medical history and current physical condition; Inform the study physician of any discomfort during the study period; Tell your research doctor if you have been involved in other studies recently or are currently involved in other studies.

Costs

The study will no additional cost, cell immunotherapy are provided free of charge for you by Newish Technology (Beijing)Co.,Ltd., other fees shall be borne by you.

Compensation

If you have severe adverse events which caused by cell immunotherapy such as death, life-threatening and severe dysfunction confirmed by the study doctor in the study, please contact your study doctor, he/she will provide you with diagnosis and treatment timely, at the same time, you will get the appropriate economic compensation provided by Newish Technology (Beijing)Co..Ltd..

Confidentiality

if you decide to participate in this study, your personal data in and during the study are confidential. Your tissue specimen will be identified by a study number rather than your name. Information that identifies you will not be disclosed to anyone other than members of the research group unless your permission is obtained. All research members and research bidders are required to keep your identity confidential. Your file will be kept in a locked filing cabinet for researchers only. To ensure that the study is conducted in accordance with the regulations, if necessary, members of the government management department or the ethics review committee may refer to your personal data in the research unit as required. When the results of this study are published, no information about you will be disclosed.

Informed consent signature

If you understand the content of this study and agree to participate in it, please sign the informed form. Each copy should be retained by the investigator and the subject or the client in duplicate.

Declaration of consent:

1. I confirm that I have read and understood the informed consent of this study, the possible problems in the process of study and solution have been explained to me, and I have the chance to make their own questions.

2 I have been clear that participating in the study belongs to the voluntary, I can choose not to participate in this study and my rights and interests will not be affected.

3. I agree to participate in this study after much consideration.

Subject's name: _____ Date:_____

(note: if the subject is unable to sign the informed consent, please ask statutory agent to sign it.)

statutory agent's name: _____ Relationship with the subject:_____

Date:_____

(note: if both the subject and statutory agent are unable to sign the informed consent, please ask independent witness to sign it.)

Independent witness's name: _____

Date:_____

The following completed by the doctor who performs the process of informed consent:

The researcher stated: I confirm that I have explained and discussed the purpose, requirement and potential risk of this study. Subjects volunteered for this study. I ensure that a signed informed consent is given to the subject or client for retention.

Researcher's name:_____ Date:_____