The Official Title

A Randomized Controlled Study of Lenvatinib Following Liver Transplantation in Patients with High-Risk Hepatocellular Carcinoma

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Informed Consent Form

BACKGROUND

Liver transplantation (LT) is the most attractive therapy for Hepatocellular Carcinoma (HCC) because it removes detectable and undetectable tumor along with the underlying cirrhosis. Theoretically, LT not only removes the tumour, but also the diseased liver parenchyma in which the tumour developed; however, with the expansion of the criteria of LT, the likelihood of recurrence becomes common. There are few studies evaluating adjuvant therapy after transplantation for HCC, and there is no standard of care for the treatment of these patients. Finding an effective agent which decreases recurrence rates in high-risk patients would be a significant advance.

Lenvatinib is an oral multikinase inhibitor that has been approved to be a new treatment option for advanced hepatocellular carcinoma. To date there are no data on safety and effectiveness of lenvatinib in LT recipients at high risk of HCC recurrence. So, we conducted a prospective study describing the safety and outcome of lenvatinib in this particular setting.

AIM

The aim of this study is to investigate the efficacy and safety of lenvatinib preventing HCC recurrece in LT recipients at high risk of HCC.

Research population

This study is a single center clinical study. The cases are from patients with hepatocellular carcinoma who underwent liver transplantation in the liver surgery department of Shanghai Renji Hospital.

Inclusion criteria

- Patients at high risk of HCC recurrence after liver transplantation: extended Milan criteria, without vascular invasion (except for microvascular invasion suggested by pathology after operation)
- Male or female patients aged 18 to 75.
- ECOG physical condition was 0-2 points.
- Targeted therapy is acceptable within 1-2 months after liver transplantation.
- Child-Pugh A grade of liver function.
- Good liver, kidney and bone marrow function: serum albumin > 28g/L, total bilirubin ≤3 mg/dL (51.3 umol/l), ALT and AST ≤5 times the upper limit of normal range; serum creatinine ≤ 1.5 times the upper limit of normal range; hemoglobin > 90 g/L, neutrophil count (ANC) > 1.5 * 10 ^ 9/L, platelet count > 60 * 10 ^ 9/L; PT-INR < 2.3, or PT within 6 seconds over normal upper limit.
- For fertile female patients, the serum/urine pregnancy test should be negative within 7 days before treatment.

- All male and female participants must take reliable contraceptive measures during the trial and within four weeks after the end of the trial.
- The participants have the capability of oral medication.
- The participants must sign the consent form.

➢ Exclusion criteria

- Patients are with other malignant tumors simultaneously.
- Patients are anaphylaxis to the inactive ingredients of lenvatinib or drugs.
- Pregnant or lactating women (Female participants need pregnancy test within 7 days before treatment).
- Preoperative history of severe cardiovascular disease: congestive heart failure > NYHA grade 2; active coronary heart disease (myocardial infarction occurred within 6 months before entry into the study); severe arrhythmia requiring antiarrhythmic treatment (allowable use of beta-blockers or digoxin); uncontrolled hypertension.
- History of HIV infection.
- Severe clinical active infections (> NCI-CTCAE version 3.0).
- Epilepsy patients requires medication (e.g. steroids or antiepileptic drugs).
- Patients with kidney diseases requires renal dialysis.
- Drug abuse, medical symptoms, mental illness or social status that may interfere with participants'participation in research or evaluation of research results.
- Patients who could not swallow oral drugs, such as those with severe upper gastrointestinal obstruction and need gastric tube feeding.

➢ Exit research

Participants who have one of the following conditions must stop using drugs immediately and exit the study. At the same time, a comprehensive evaluation will be conducted within 1-2 weeks of the last medication (adverse events, recurrence of tumors, medication for treatment):

- Patients are with poor compliance.
- Prohibited drugs or other drugs that are likely to produce toxicity or result in deviation are used.
- Concurrent diseases or situations that may significantly affect the clinical status and the end point of the study have occurred.
- Clinical signs and laboratory examinations confirm the diagnosis of pregnancy.
- Another malignant tumor has developed.
- The participants are lost to follow-up.
- The participants died.
- Participants or their legal representatives demanded withdrawal from the study.

STUDY PROCEDURES

➢ Participants

- Participants must sign the consent form.
- Participants are confirmed in compliance with inclusion and exclusion criteria.

- Basic data including height, weight and blood pressure are collected.
- Clinical blood test including liver and kidney function, complete blood count, coagulation function, blood glucose and lipid index are collected.
- Serological and imaging examinations are collected before treatment.

➢ Allocation

- Participants are randomly allocated to lenvatinib group and control group through software.

➢ Research Protocol

- Control group: Immunosuppressive regimen consisting of calcineurin inhibitor, mycophenolate mofetil, sirolimus or ivermus
- Lenvatinib group: Participants are given the same anti-rejection therapy as the control group after liver transplantation. 1-2 months after liver transplantation, participants are given lenvatinib with an initial dose of 8 mg (body weight < 60 kg) or 12 mg orally once a day. The initial dose was 8 mg (body weight < 60 kg) or 12 mg orally once a day.
- Delayed administration or reduced dosage may be required if significant clinical toxicity associated with the treatment occurs. If there are some toxicity manifestations and different opinions on treatment, it is recommended to adjust the dose, which can be reduced to the lowest level. All dose adjustments will follow the established dose level.

➢ Follow up

- Once the treatment is initiated, patients will be regularly monitored for blood and imaging examination. Blood test includes alpha-fetoprotein, alpha-fetoprotein variants, abnormal prothrombin once a month. Imaging examination includes liver ultrasonography once a month, liver MR or CT scanning every 3 months, lung CT every 3 month.
- Multidisciplinary teams determine whether tumors recurrence based on imaging and serological examinations.
- The follow up duration time is 5 years.
- The primary endpoint is tumor recurrence which refers to the time from treatment to tumor recurrence. Overall survival refers to the time from treatment to death for any reason. The 1, 3, 5-year recurrence-free survival rate and the 1, 3, 5-year overall survival rate will be analyzed.
- The side effects during treatment were recorded. At the same time, patients' status will be scored according to ECOG PS score. Acute or subacute toxicity is classified as level of 0-4, 0 as non-response, 1 as mild, 2 as moderate, 3 as severe and 4 as life-threatening. The severity of adverse events was judged, reported and handled according to GCP requirements of clinical trials.

RISKS

Lenvatinib is a clinically approved drug. This study will be conducted in strict accordance with drug specifications and doses. Although, the data about the efficacy and safety of lenvatinib in preventing HCC recurrence after LT is still lacking. Theoretically, the LT recipients at high risk of HCC may benefit from the drug, and the side effects are controllable. The below table shows

the side effects, which will be closly monitored and promptly treated.

Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage reductions of LENVIMA for adverse reactions.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions

Adverse Reaction	Severity [a]	Dosage Modifications for LENVIMA
Hypertension *[see Warnings and Precautions (5.1)]*	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	• Permanently discontinue.
Cardiac Dysfunction *[see Warnings and Precautions (5.2)]*	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	• Permanently discontinue.
Arterial Thromboembolic Event *[see Warnings and Precautions (5.3)]*	Any Grade	• Permanently discontinue.
Hepatotoxicity *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment *[see Warnings and Precautions (5.5)]*	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria *[see Warnings and Precautions (5.6)]*	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation *[see Warnings and Precautions (5.8)]*	Any Grade	• Permanently discontinue.
Fistula Formation *[see Warnings and Precautions*	Grade 3 or 4	• Permanently discontinue.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions		
Adverse Reaction	**Severity [a]**	**Dosage Modifications for LENVIMA**
(5.8)]		
QT Prolongation *[see Warnings and Precautions (5.9)]*	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.11)]*	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions *[see Warnings and Precautions (5.7, 5.10, 5.12)]*	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
	Grade 4 adverse reaction	• Permanently discontinue.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Cite from lenvatinib instruction (Eisai Inc., Woodcliff Lake, NJ, USA)

BENEFITS

The disease-free survival and overall survival of LT recipients at high risk of HCC may be improved.

ALTERNATIVE PROCEDURES

You may choose not to participate in this study. If you do not want to take part in the study, there are other choices such as closely monitoring, other new drugs, chemotherapy, etc. You may discuss these options with your doctor.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study and you may have been injured from being in this study, you can contact Dr. Qiang Xia at +8615921197267.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The Renji hospital IRB may be reached by phone at (86)021-68383364 or by e-mail at rjllb3364@163.com

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at +8615021628183 or by email at hanyongsun@163.com

RESEARCH-RELATED INJURY

If you is injured from being in this study, medical care is available at the Renji hospital, as it is to all sick or injured people. The Renji hospital has not set aside any money to pay the costs for such care. The Renji hospital will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance). Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The Renji hopital is a public hospital. If you is injured in this study, and you want to sue the Renji hospital or the doctors, nurses, students, or other people who work for the hospital, special laws may apply. The Shanghai medical association is a law that controls when a person needs to bring a claim against the hospital. Please refer to the regulations on the “Revention and Management of Medical Disputes” of China.

VOLUNTARY PARTICIPATION

If you decide to take part in this study you are still free to withdraw at any time and without giving a reason. Refusal to participate or the decision to withdraw from this study will involve no penalty or loss of benefits to yours is otherwise entitled. If youdoesn’t take part, you can still receive all standard care that is available to you. This will not affect the relationship you has with your doctor or other staff, nor decrease the standard of care that you receives as a patient. If you decide to withdrawal from being in this study, please let the research doctor know. That way you can find out what should be done about your routine care outside of the study.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS

The investigator can withdraw you without your approval. Possible reasons for withdrawal include noncompliance with treatment, noncompliance with follow-up, etc.

COSTS AND COMPENSATION TO PARTICIPANTS

All costs associated with this study will be billed to you or your insurance company in the ordinary manner.

In case of injury related to this study, corresponding economic compensation will be given according to national laws and regulations.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about the lenvatinib that is being studied. If this happens, your child's research doctor will tell you about it and discuss with you whether you want your child to continue in the study.

NUMBER OF PARTICIPANTS

We expect to enroll 106 participants at the Renji hospital.

AUTHORIZATION FOR USE OF YOUR CHILD'S PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, address telephone number, and email address
- Related medical information about yours like family medical history, allergies, current and past medications or therapies, and information from physical examinations, such as blood pressure reading, heart rate, temperature, and lab results
- All tests and procedures that will be done in the study

How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify your child. At most, the website

will include a summary of the results. You can search this website at any time.

- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
  - Members of the research team;
  - The Renji Hospital Ethics Committee, which reviews research involving people to make sure the study protects your rights;
- If we share your information with groups outside of Renji hospital, we will not share your child's name or identifying information. We will label your child's information with a code number, so they will not know your child's identity.
- If you do not want us to use information about your health, you should not agree to allow your child to be part of this research. If you choose not to participate, you can still receive health care services at Renji hospital.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about yours, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

CONSENT:

I confirm that I have read this document and have had the opportunity to ask questions. I will be given a signed copy of the informed consent form to keep.

I agree to participate in this research study and authorize you to use and disclose health information about mine for this study, as you have explained in this document.

_____ _____

Participant's Signature Date

WITNESS STATEMENT:

The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is illiterate
☐ The participant is visually impaired
☐ The participant is physically unable to sign the consent form. Please describe:

_____

_____

☐ Other *(please specify)*:

_____

_____

I confirm that I was present as a witness for the consent process for this study. I confirm that the participant named above was read the information in the consent document and that the participant has agreed to take part in the research study.

_____
Name of Witness

_____ _____
Signature of Witness Date