

The Official Title

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

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide and accounts for about 13,000 deaths in the United States per year [1]. Liver transplantation offers selected patients with localized HCC a chance for cure. For those meeting the Milan criteria, defined as a single tumor 2–5 cm or three or fewer nodules, each 3 cm or less, and no gross vascular invasion, 5 year survival for transplanted patients is about 75% [2, 3]. Meeting these criteria provides additional priority for transplantation in the US. However, for those with HCC beyond the Milan criteria, whether determined pre-transplant or by pathologic evaluation of the explant, the risk of recurrence may be as high as 70% at 2 years after transplantation [4]. There are few studies evaluating adjuvant therapy after resection or 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.

1. Research Purpose

The aim of this study is to observe the efficacy and safety of lenvatinib in preventing high-risk recurrence of hepatocellular carcinoma patients after liver transplantation.

2. Research Protocol

The research is an open, randomized, single-center study. Patients with high-risk recurrence of hepatocellular carcinoma who underwent liver transplantation are included according to the criteria of admission. After operation, the regimen of calcineurin inhibitors, mycophenolate mofetil, sirolimus or everolimus with glucocorticoids removed at an early stage are used. Patients enrolled in the study were randomly allocated in the lenvatinib group (54 patients) and the control group (54 patients) after stable condition. Patients in the control group are given supportive treatment and regular follow-up. Patients in the lenvatinib group are given lenvatinib within 1-2 months after operation (dose: body weight < 60 kg: 8 mg/day, body weight \geq 60 kg 12 mg/day). The baseline data of patients are collected before allocation. Serum and imaging examination are checked regularly every month to monitor the

recurrence of hepatocellular carcinoma and the side effects of lenvatinib. The efficacy and safety of lenvatinib in patients of high-risk hepatocellular carcinoma are observed, and the clinicopathological factors affecting the efficacy of lenvatinib are analyzed.

When side effects of lenvatinib occur, the dosage can be reduced according to the patients' condition until discontinuation. When tumor recurrence occurs, a multidisciplinary team will draw up specific treatment plans according to the patients'

condition, including surgical resection, interventional therapy, radiofrequency therapy, radiotherapy and targeted therapy (Patients in the control group can add lenvatinib, and patients in the lenvatinib group can decide whether to continue using it according to the patients' condition).

3. Research population

3.1 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.

3.2 Inclusion criteria

- Patients at high risk of recurrence of hepatocellular carcinoma 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.
- Child-Pugh A grade of liver function.
- Targeted therapy is acceptable within 1-2 months after liver transplantation.
Immunosuppressive regimen consists of calcineurin inhibitor, mycophenolate mofetil and sirolimus.
- No history of surgical resection of liver tumors and targeted drug therapy before liver transplantation.
- Good liver, kidney and bone marrow function: serum albumin > 28g/L, total bilirubin \leq 3 mg/dL (51.3 μ mol/l), ALT and AST \leq 5 times the upper limit of

normal range; serum creatinine \leq 1.5 times the upper limit of normal range; hemoglobin > 90 g/L, neutrophil count (ANC) $> 1.5 \times 10^9$ /L, platelet count $> 60 \times 10^9$ /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.

3.3 Exclusion criteria

- Life expectancy is less than 3 months
- The recurrence and metastasis of hepatocellular carcinoma are highly suspected.
- Patients are with other malignant tumors simultaneously. λ 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.
- Other anti-angiogenesis therapies, surgery, TACE, local therapy and systemic

chemotherapy were given before the treatment after liver transplantation.

3.4 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

4. Research Progress

4.1 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.

4.2 Allocation

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

4.3 Research Protocol

- Control group: Immunosuppressive regimen consisting of calcineurin inhibitor, mycophenolate mofetil, sirolimus or ivermectin
- 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.

4.4 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 months.
- Multidisciplinary teams determine whether tumors recur 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.

5. Safety

Lenvatinib is a clinically approved drug. This study will be conducted in strict accordance with drug specifications and doses.

6. Data analysis and statistical methods

6.1 Sample size

Logrank test is used to analyze the survival rates. The median recurrence time after liver transplantation for HCC which extends the Milan criteria is 12 months according to the literature. The median recurrence time is expected to increase to 24 months after treatment with lenvatinib. The experimental group and the control group were enrolled in the group according to the ratio of 1:1. The recruiting time is expected to be 12 months and the study time is expected to be 36 months. At least 47 cases were calculated for each group. Since it is assumed that 10% of the samples may be lost due to the adjustment of the intentional treatment population, 53 cases will be needed for each group eventually.

6.2 Statistical Methods

The researcher is responsible for checking and preserving all the data, and handing over the data results to professional statisticians for analysis. Survival curves are estimated using the Kaplan – Meier method. For identification of independent prognostic factors, the Cox proportional hazard model was used in the univariate and multivariate analyses. All statistical analyses were performed using the SPSS (version 22.0). Statistical significance was defined as $p < 0.05$.

7. Emergency Event Management

7.1 Emergency contact

Doctor Sun Hanyong

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Tong University

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7.2 Emergency management

During this research period, Dr. Sun Hanyong has professional skills and is responsible for medical emergencies and related treatment. If you encounter large-scale or critical events, please report to the head of the department head and hospital timely.

8. Data security and monitoring plan

None.