Efficacy and safety of recombinant human adenovirus type 5 injection combined with TACE-based comprehensive therapy in patients with primary hepatocellular carcinoma with portal vein tumor thrombus in stage IIIa

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One、Research purpose and main research content

Purpose of the study:

To evaluate and compare the efficacy and safety of recombinant human adenovirus type 5 injection combined with TACE-based comprehensive therapy in patients with primary hepatocellular carcinoma with portal vein tumor thrombus in stage IIIa.

The main research contents:

This study is the first to compare the efficacy and safety of recombinant human adenovirus type 5 injection via hepatic artery infusion combined with TACE-based combination therapy for the treatment of patients with primary hepatocellular carcinoma with portal vein carcinoma thrombosis in stage IIIa, providing a safe and reliable treatment for the clinical management of this group of patients, as well as a reference and basis for the treatment of other tumors with this new treatment modality.

Two、Research background and basis (research status at home and abroad, development trend, necessity, novelty, innovation, research significance)

According to statistics, hepatocellular carcinoma (hereafter referred to as hepatocellular carcinoma) accounts for 80% of primary liver cancer worldwide, has a heavy disease burden, and is the leading cause of cancer-related deaths in many parts of the world. Hepatocellular carcinoma is insidious in origin and develops rapidly, and most patients have local progression or distant metastasis by the time they are diagnosed, especially the formation of portal vein thrombosis. The incidence of hepatocellular carcinoma with portal vein thrombosis is high and the disease progresses rapidly, and the available treatments are limited and ineffective.

It has been found that through palliative treatments such as transarterial chemoembolization (TACE) and neoadjuvant three-dimensional conformal radiotherapy, some patients can experience regression or even disappearance of portal vein cancer thrombus, tumor volume reduction, and disappearance of satellite foci, thus reducing the stage of the lesion, increasing the surgical resection rate, and prolonging patient survival. TACE is the treatment of choice for unresectable or intermediate to advanced hepatocellular carcinoma, which is widely used in clinical practice with positive effects, but the tumor is prone to recurrence and metastasis after TACE. Therefore, in most cases, TACE is combined with other therapies to treat hepatocellular carcinoma.

Recombinant human adenovirus type 5 injection (H101) is a structural modification of wild-type human type 5 adenovirus, with the deletion of E1B 55KD fragment and E3 partial fragment, based on the characteristic that P53 pathway disorder is common to tumors. The deletion of E3 fragment enhanced the TNF-induced tumor lysis effect, enhanced the immune system's recognition and killing of the virus and infected tumor cells, induced immune infiltration, and activated specific anti-tumor immunity, so that the recombinant human adenovirus type 5 could play the role of precise tumor lysis and systemic immunity.

This study is the first to compare the efficacy and safety of recombinant human

adenovirus type 5 injection via hepatic artery infusion combined with TACE-based combination therapy for the treatment of patients with stage IIIa primary hepatocellular carcinoma with portal vein carcinoma thrombosis, providing a safe and reliable treatment method for the clinical treatment of this group of patients, and also providing a reference and basis for the treatment of other tumors with this new treatment model.

Three、Research methods and technical routes

Research methods:

1. Experimental Design

This is a prospective, single-arm study to evaluate the efficacy and safety of recombinant human adenovirus type 5 injection combined with TACE-based combination therapy in patients with primary hepatocellular carcinoma with portal vein carcinoma thrombosis in stage IIIa. Subjects will be screened and evaluated at the study center, and after determining that they meet the inclusion criteria, enrolled patients will be treated with recombinant human adenovirus type 5 injection via hepatic artery infusion combined with TACE regimen. The study is divided into screening period, baseline period, treatment period, and follow-up period. Follow-up after the end of treatment will be every 3 months until death or the end of this study.

2. Method of administration

1） Recombinant human adenovirus type 5 injection: Recombinant human adenovirus type 5 injection is administered intratumorally 48-72h prior to TACE treatment.Before administration, the recombinant human adenovirus type 5 injection was diluted to 30% of the total tumor volume with normal saline. H101 dose:

① The sum of the maximum diameters of the lesions was ≤10cm, and the total dose was 1.0×10^{12}vp (2 injections);

② The sum of the maximum diameters of the lesions was ＞10cm, and the total dose was 1.5×10^{12}vp (3 injections);

2）TACE：According to Seldinger technique percutaneous femoral artery puncture, arteriogram to determine the tumor location, number, size, distribution range and blood supply, microcatheter selectively inserted into the tumor blood supply artery, then slowly injected iodinated oil + chemical drugs fully mixed with emulsion. The specific chemotherapeutic drugs were: oxaliplatin 85mg/m2, calcium folinic acid 400mg/m2, 5-fluorouracil 1200mg/m2, and then super liquid iodinated oil embolization was given according to the intraoperative imaging tumor blood supply.

Recombinant human adenovirus type 5 was administered in combination with TACE in cycles of every 3 weeks for a total of 2-4 cycles. If patients experience serious adverse reactions during this period they need to discontinue the drug.

Technical route：

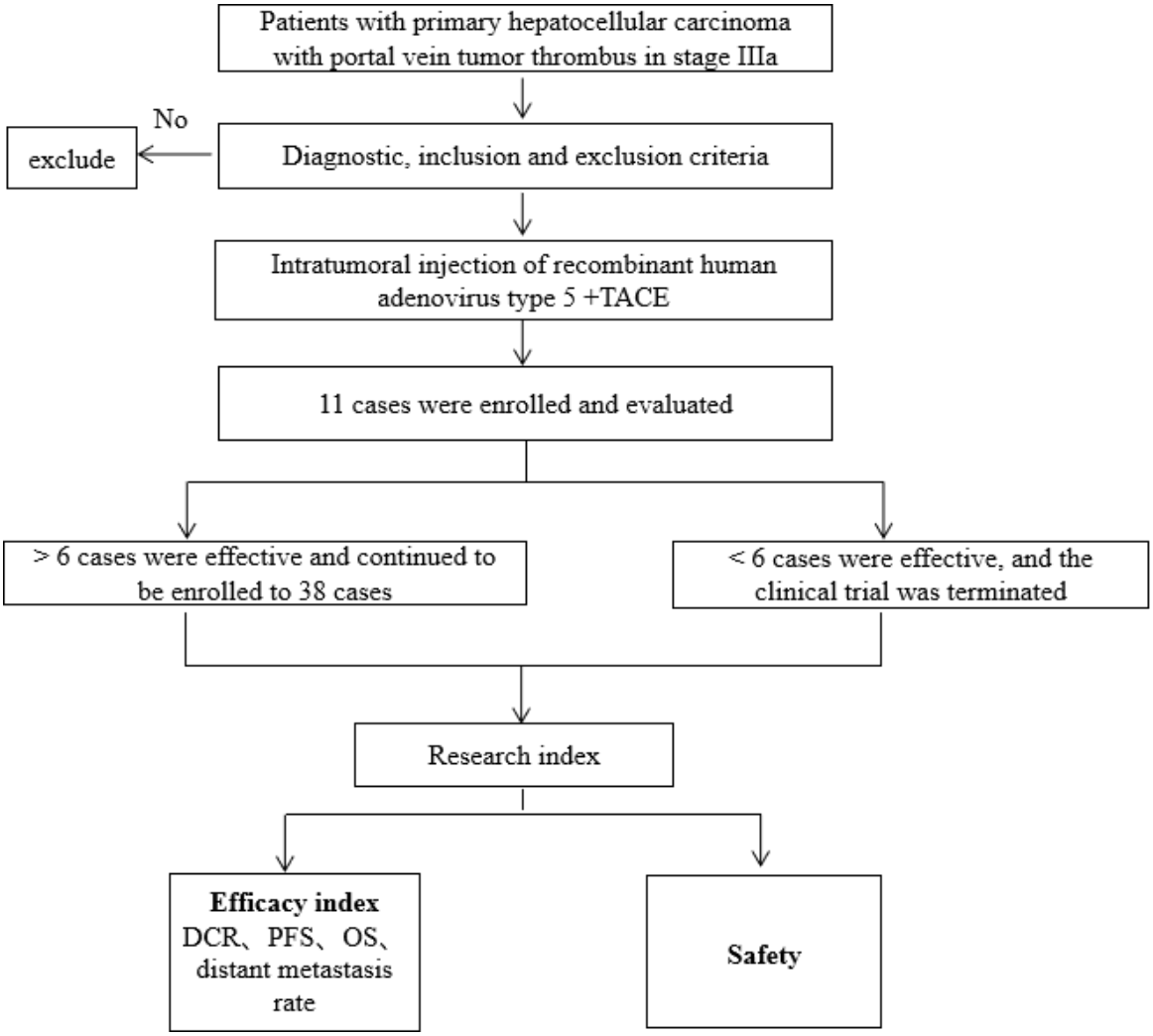

图 1 技术路线图

The admittance criteria of the research object

1. Inclusion Criteria:

The following criteria must all be met to be included:

1) Age ≥ 18 years and ≤ 75 years, regardless of gender;
2) Patients with stage IIIa primary liver cancer diagnosed by histology or imaging;
3) ECOG physical status score of 0-1;

4) Expected survival time ⩾ 3 months;

5) Received no liver protective and supportive treatment within two weeks before enrollment, and met the following conditions:

- White blood cell count ⩾3.0×10^9/L, neutrophil absolute value ⩾3.0×10^9/L, platelet count ⩾50×10^9/L, hemoglobin > 100g/L;
- INR≤1.5 and APTT≤1.5 upper limit of normal or partial prothrombin time (PTT) ≤1.5 upper limit of normal;
- Total bilirubin (TBIL) ≤2.5 times the upper limit of normal value; ALT and AST≤5 times the upper limit of normal value; Serum creatinine ≤1.5 times the upper limit of normal value;
- Creatinine clearance ≥50ml/min.

6) Voluntary participation in this study and signing of the informed consent form;

7) Female patients of childbearing age or male patients whose sexual partners are women of childbearing age are required to use effective contraception throughout the treatment period and for 6 months after the last dose.

2. Exclusion Criteria:

Any of the following circumstances shall be excluded and shall not be selected:

1）Pregnant or lactating women, men or women who do not wish to use effective contraception;

2) Patients who have received previous treatment with lysoviruses (e.g., T-VEC), interventional therapy, or TACE;

3) Those who are being treated with antiviral drugs;

4) having received any other experimental drug, antimicrobial drug, or participated in another interventional clinical trial within 4 weeks prior to enrollment

5) Those with a known allergy to the study drug or its active ingredient, or a history of allergy to similar biological agents

6) Evidence of Child-Pugh C hepatic function or hepatocellular dysregulation, including those with refractory ascites, ruptured esophageal or gastric variceal bleeding, and hepatic encephalopathy

7) presence of a history of immunodeficiency or autoimmune disease or long-term systemic steroid therapy or any form of immunosuppressive therapy within 7 days prior to enrollment

8) With any unstable systemic disease, including but not limited to: severe infection, hypertensive patients, uncontrolled diabetes mellitus, unstable angina pectoris, cerebrovascular accident or transient cerebral ischemia, abnormal mental status or active cerebral hemorrhage, myocardial infarction, congestive heart failure, severe arrhythmias requiring drug therapy, renal or metabolic disease, severe hepatic dysfunction (including severe jaundice, hepatic encephalopathy, refractory ascites or hepatorenal syndrome), multiple organ failure with renal dysfunction;

9) Previous or concurrent other malignancies;

10) Combined medical contraindications that preclude any contrast-enhanced imaging (CT or MRI);

11) Other conditions that, in the judgment of the investigator, make the patient unsuitable for participation in this study.

Four、Expected goals, prospects for application of results, social benefits

The project is expected to achieve the following results:

1) Treatment of patients with stage IIIa primary hepatocellular carcinoma with portal vein carcinoma thrombosis using recombinant human adenovirus type 5 injection combined with TACE-based combination therapy to improve the objective remission rate and provide clinical benefit to patients;

2) The use of recombinant human adenovirus type 5 injection combined with TACE-based combination therapy for the treatment of patients with stage IIIa primary hepatocellular carcinoma with portal vein carcinoma thrombosis reduces the incidence of adverse effects and results in better clinical safety for patients;

3) This study is expected to provide a new approach to the clinical treatment of hepatocellular carcinoma and provide a reference and basis for the treatment of other tumors.