PATIENT INFORMATION SHEET AND CONSENT FORM

Ethiodized oil-based Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: A Randomized Controlled Trial of Aqueous Cisplatin Emulsion versus Cisplatin Particle Suspension

NCT03268499

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A signed copy of this form must be provided to the patient prior to study entry.

Patient name:_____ ID no.:_____

Trial No.:_____

This is a clinical trial (a type of research) that has been approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. This trial will be conducted in accordance to the Declaration of Helsinki and International Conference on Harmonisation-Good Clinical Practice (ICH-GCP). Seventy-seven patients known to have hepatocellular carcinoma (HCC) will be recruited. Clinical trials include only patients who choose to participate. Please take your time to make your decision. Discuss it with your friends and family.

Background of the study

Transcatheter arterial chemoembolization (TACE) has been playing an important role in the treatment algorithm for patients with multifocal or large intrahepatic lesions not eligible for surgical resection, transplantation, or local ablative therapy. In Hong Kong, the TACE regimen currently being utilized in the great majority of hospitals is based on an aqueous form of cisplatin (1mg per mL) mixed in a one-to-one ratio by volume with Lipiodol to form a relatively large volume of 40mL emulsion at 20mg cisplatin as the maximum dose. Although TACE with this regimen has been shown to be effective in prolonging overall survival, there is probably room for further improvement because the objective tumor response rate is limited to 39%. One of the approaches to improve the treatment effectiveness of TACE could be to increase the dose of chemotherapeutic agent. In the United States, the most common regimen of chemotherapeutic agent in TACE is the mixture of cisplatin 100mg, doxorubicin 50mg, and mitomycin C 10mg, dissolved in 10ml of water-soluble contrast medium, then emulsified in an equivalent volume of lipiodol to form a 20mL emulsion (4). We introduce a relatively new regimen in which a relatively high dose of cisplatin up to 100mg in particle form is given as a suspension in 20mL of Lipiodol, this regimen has been used and found to achieve an improved objective tumor response rate of 51%.

Purpose of the study

This randomized phase II study is aimed to evaluate the safety and efficacy of using the new formulation (Lipiodol-cisplatin suspension) for TACE in the treatment of HCC as compared to the conventional formulation (Lipiodol-cisplatin emulsion)**.**

About the treatment

The procedure of TACE is the same irrespective of which formulation is used. Hospitalization is required. Prophylactic antibiotic may be given intravenously. TACE is performed under local anesthesia with right femoral puncture. The feeding lobar hepatic artery is selectively catheterized for drug delivery. In the new formulation, a maximum of 100mg cisplatin particle in 20mL Lipiodol suspension will be given. In the conventional formulation, a maximum of 20mg of aqueous cisplatin in 40mL Lipiodol emulsion will be given.

What are the risks

The risk of adverse effects and complications of the study treatment is expected to be not different from that of conventional TACE.

Potential adverse effects of conventional TACE include:

1. Post-embolization syndrome (80-90%). It consists of fever, nausea, vomiting, right upper abdominal pain, sluggish bowel motion, and deranged liver function. This syndrome is self-limiting, usually lasts for a few days.
2. Transient liver function derangement is common. Risk of reversible liver failure is 20% per session. Risk of irreversible liver failure is 3% per session.
3. Puncture site bleeding or hematoma (1.6-7%).
4. Septicemia (1.5%).
5. Renal function impairment (1-2.5%).
6. Tumour rupture leading to intraperitoneal bleeding (1.2-1.5%).
7. Liver abscess (0.2%).
8. Gastric or duodenal ulceration (1-3%).
9. Pulmonary oil embolism (1%). The condition is due to intratumoral arteriovenous shunt. The patient presents with shortness of breath or respiratory distress. This may occur 2-10 days after TACE, may lead to respiratory failure.
10. The overall adverse reactions related to iodine-base non-ionic contrast medium is below 0.7%. The mortality due to reaction to non-ionic contrast medium is below 1 in 250000.

Potential adverse effects of intravenous cisplatin infusion include the following, but these are less likely to occur in intraarterial administration of the drug in the dose and formulation described above:

1. Renal function impairment - the second treatment of TACE will be withheld until renal function return to normal.
2. Ototoxicity - manifested by unilateral or bilateral and/or hearing loss.
3. Myelosuppression - manifested by leucopenia, thrombocytopenia, or anemia. Fever and infections may occur in patients with neutropenia. A Coombs' positive hemolytic anemia may occur.
4. Gastrointestinal effects - marked nausea and vomiting occur in almost all patients, usually begin within 1 to 4 hours after treatment and last up to 24 hours. Diarrhea may occur.
5. Electrolyte disturbance - hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, hypophosphatemia, or hyperuricemia may occur.
6. Nervous system side effects - the most common form of nerve damage from cisplatin is a sensory polyneuropathy. Other forms of nerve damage from cisplatin include autonomic neuropathies, seizures, encephalopathy, myasthenic syndrome, and cortical blindness.
7. Hypersensitivity - anaphylactic-like reactions consisting of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be treated with intravenous epinephrine, corticosteroids and/or antihistamines.
8. Ocular side effects - including optic neuritis, papilledema, cortical blindness, focal deficits, and cerebral blindness have been infrequently reported.
9. Hepatotoxicity - transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported. However, the incidence and clinical importance is relatively low.
10. Cardiovascular side effects - chronic lipid and blood pressure abnormalities have been reported. Possible cardiotoxicity (ST-T wave abnormalities and bundle branch block) have rarely been reported. Atrial fibrillation, supraventricular tachycardia, and a case of bradycardia have also been reported.
11. Dermatologic side effects - rash and alopecia have been reported. A case of digital necrosis has also been reported.

What special investigations are needed?

Apart from the routine blood test, CT scan and clinical follow up, which will be required whether you are eligible to participate in the study or not, the study does not involve additional investigations.

What are the benefits?

There is a potential chance for your disease to be better controlled by the study treatment resulting in greater objective tumor response, higher chance for the tumor to be down staged to become surgically resectable, prolongation of time to disease progression, and longer overall survival. The study treatment will continue to be available to you without additional charge if it is proven to be beneficial to you.

Confidentiality

Only authorized people will be allowed to see your medical records. Any study related information, in which you may be identified, will remain confidential and will not be made publicly available. All data collected from the center will be made anonymous.

Voluntary Participation

Taking part in this study is voluntary without any loss of any legal or ethical rights. If you decide not to take part in the study or to withdraw from the study, this decision will not affect the subsequent care and treatment you may receive in any way. The standard care, which is the conventional TACE, may be offered to you. You may withdraw from the study at anytime without giving a reason. If you withdraw because of a side effect, you are asked to tell your doctor about this. If it is at your best interests, your doctor may withdraw you from the study at any time without your consent. You will not be charged or paid for this study.

Compensation and rights

In the event of occurrence of trial-related injury, you will be given appropriate medical treatment free of charge, your right in claiming compensation will be reserved.

Further information

You or your legally acceptable representative will be informed in a timely manner if information relevant to your willingness to continue participation in the trial becomes available. If you have any questions about this study, or experience any symptoms that you are concerned about, or you require further information regarding your rights in this trial, please contact one of the following study personnel through the hospital operator or direct lines.

XXXXXXXXX	(Department of Imaging and Interventional Radiology)
(Principal investigator)	Telephone no. XXXXXXXX
XXXXXXXXX	(Department of Imaging and Interventional Radiology)
(Research nurse)	Telephone no. XXXXXXXX
XXXXXXXXX	(Department of Imaging and Interventional Radiology)
(Research nurse)	Telephone no. XXXXXXXX

If you have any question about your own right concerning your participation in this study, please contact The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee at telephone no. XXXXXXXX

If you require emergency medical treatment, you are strongly advised to go to the nearest Accident and Emergency Department and not to rely on phone contact.

Patient Consent Form

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I have read the Patient Information Sheet. The requirements of this study have been explained to me.

I have had an opportunity to ask questions and all of my questions have been answered at this moment.

I have been given sufficient time to consider my participation and I have freely chosen to participate.

I understand that I can withdraw my consent at any time without affecting my future treatment.

I understand that I shall not be paid for my participation in this study.

I have been given a copy of the Consent Form and the Patient Information Sheet.

I _____ (Print Name) consent to participate in this study.

Patient's signature _____ Date: _____

Investigator's signature _____ Date: _____

Investigator's name_____

Witness' signature _____ Date: _____
(where appropriate)

Witness' name_____
(where appropriate)