Study Protocol

Ethiodized oil-based chemoembolization for hepatocellular carcinoma: Randomized controlled trial of aqueous cisplatin emulsion versus anhydrous cisplatin suspension

Date: 16 July 2016

Introduction

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 (1). In Hong Kong, the TACE regimen currently being utilized in the great majority of hospitals is based on an aqueous form of cisplatin (Platinol, Bristol-Myers Squibb Company, Princeton, New Jersey, 1mg per mL) mixed in a one-to-one ratio by volume with ethiodized oil (Lipiodol Ultra Fluid, Guerbet, France) to form a relatively large volume of 40mL emulsion at 20mg cisplatin as the maximum dose (2). 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% (3). 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 formulation 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 ethiodized oil to form a 20mL emulsion (4). We introduce a modified formulation in which a relatively high dose of cisplatin up to 100mg in anhydrous particle form (Chemoparticle cisplatin powder, Four Seasons International Limited, Hong Kong) is given as a suspension in 20mL of Ethiodized oil, this regimen has been used and found to achieve an improved objective tumor response rate of 51% (5). Pure cisplatin powder has been used in the formulation of cisplatin-Lipiodol suspension for TACE in several phase I and phase II studies (6-9). Pharmacokinetics study showed the formulation of cisplatin-Lipiodol suspension can

effectively retain cisplatin within HCC with a delayed release of the drug to systemic circulation (7). It is hypothesized that treatment of HCC with ethiodized oil-based TACE using a formulation of anhydrous cisplatin suspension can lead to significant improvement in treatment outcome and comparable safety as compared to that using a formulation of aqueous cisplatin emulsion with. This study is aimed to compare the efficacy and safety of using the novel formulation versus the conventional formulation in TACE for treating patients with HCC.

Materials and methods

Study design

This is a prospective, multi-center, parallel-group, open-label, phase III randomized control trial that is conducted in accordance to the Declaration of Helsinki and international standards of Good Clinical Practice, approved by the institution's Ethics Committee, and registered in Clinicaltrial.gov. (NCT03268499). This is an investigator-initiated study without direct industry sponsorship. Eligible patients are randomized into either a treatment arm in the Suspension Group or a control arm in the Emulsion Group with a 1:1 ratio. Eligibility to the study is assessed according to newly acquired clinical and imaging data within 30 days.

Eligibility criteria

Assessment of eligibility is based on clinical, laboratory, and imaging data that are obtained within 30 days prior to randomization:

Inclusion criteria

1. Written informed consent

2. Age above 18 years

3. Hepatocellular carcinoma (HCC) unsuitable for resection or ablation

4. Child-Pugh A cirrhosis

5. Eastern Cooperative Oncology Group performance score 0 or 1

6. Barcelona Clinic Liver Cancer staging system below or equal to stage B

7. No previous treatment for HCC except for liver resection

8. HCC diagnosed by typical enhancement patterns on cross sectional imaging or histology.

9. No extra-hepatic involvement on non-enhanced CT thorax and triphasic contrast enhanced CT abdomen.

10. No invasion of portal vein or hepatic vein

11. Massive expansive tumor morphology with measurable lesion on CT (characterized by well-defined spherical or globular configuration, with or without tumor capsule or satellite lesions)

12. Total tumor mass < 50% liver volume

13. Size of any individual tumor ≤ 10cm in largest dimension

14. Serum creatinine < 130 umol/L or Creatinine clearance > 55 ml/min.

<u>Exclusion criteria</u>

1. Known active malignancy within the last 3 years

2. History of acute tumor rupture presenting with hemo-peritoneum

3. Biliary obstruction not amenable to percutaneous or endoscopic drainage

4. History of hepatic encephalopathy

5. Intractable ascites not controllable by medical therapy

6. History of variceal bleeding within last 3 months

7. Infiltrative tumor morphology (characterized by ill- defined tumor margin and amorphous configuration) or diffuse tumor morphology (characterized by large number of small nodules)

8. Un-correctable Arterio-portal venous shunt affecting >1 hepatic segment on CT

9. Arterial-hepatic venous shunt with hepatic vein opacified in arterial phase on CT

Randomization

Stratified randomization with permuted block method and 1:1 ratio is performed centrally by an independent statistician. Stratification factors include the diameter of largest tumor (≤5cm or > 5cm) and total number of tumors (≤3 or > 3). Random permuted block method with block size of 4 to 6 is used according to a computer-generated allocation sequence. The patients, doctors and other caretakers are unblinded to group allocation while data collectors and analysts who assess the study outcome and radiologists who assessed tumor response are blinded to group allocation.

Sample size

Based on the results of a preliminary study involving 13 subjects (Suspension Group) and 14 subjects (Emulsion Group), complete tumor response rates on 6-months CT scan were 84.6% (11/13) and 28.5% (4/14) respectively. Assuming the anticipated incidences to be 70% and 35% respectively, two-sided alpha level 0.05 and power 85%, it is estimated that 70 subjects (35 subjects in each group) are required for the study. Assuming a 10% drop out rate from final analysis, the final sample size is set at 80.

Study endpoints

The primary endpoints:

The primary efficacy endpoint is complete tumor response rate after the first 3 treatments as evaluated by triphasic contrast enhanced CT at 6 months according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST)(10) criteria as well as DSA findings during the second and third treatment. Complete tumor response is defined as the absence of enhancing tumor on CT and/ or absence of residual tumor on selective DSA of the feeding arteries to the tumors and absence of enhancing tumor on the subsequent CT. The primary safety endpoint is severe adverse events occurring within 30 days of all treatment procedure, measured by the number of subjects involved, defined as any undesirable symptom, sign or medical condition which was fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, or was medically significant, might jeopardize the patient and might require medical or surgical intervention.

Secondary endpoints:

1. Complete tumor response after the first treatment;

2. Objective tumor response, defined as complete response or partial response at 6 months, according to mRECIST criteria;

3. Intralesional tumor progression, defined as tumor recurrence at the site of treated tumor after initial complete tumor response, or any degree of enlargement of treated tumor after initial partial response;

4. Extralesional tumor progression, defined as occurrence of new tumor at a new site of the liver;

5. Extrahepatic tumor progression, defined as occurrence of venous invasion by tumor or extrahepatic tumor metastasis;

6. Time to progression (TTP), defined as the interval between the randomization date and the date of specific type of tumor progression;

7. Progression free survival, defined as the interval between the randomization date and the date of any kind of tumor progression or death from any cause;

8. Overall survival (OS), defined as the interval between the randomization date and the date of death from any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive;

9. Adverse events occurring within 30 days after the first treatment, measured by number of subjects involved.

Treatment schedule

Treatment is given within 4 weeks after randomization. Up to three treatments at 2 months apart (baseline, 2 months, 4 months) are given. After 2 treatments have been given, the decision whether to give a third treatment or not is based on CT assessment at 3 months. The third treatment is omitted when there is no evidence of any residual tumor on the 3-months CT. A third treatment is given when there is residual tumor but without evidence of continuous tumor growth unresponsive to treatment, vascular

invasion or extrahepatic metastasis. For patients with large tumors or bi-lobar tumors in which the tumor vasculature could not be completely filled with ethiodized oil emulsion or suspension in one treatment session, an additional treatment is performed within 4 weeks, provided the patients' condition does not fall outside the eligibility criteria, the two sessions are considered as part of one treatment.

Beyond 6 months, when there is CT evidence of residual tumors or occurrence of new intrahepatic tumors, TACE of the same formulation is given, otherwise no other treatment is given. Further treatment is withheld when there is CT evidence of continuous tumor growth unresponsive to treatment, extrahepatic tumor progression, or patients' condition falling outside the eligibility criteria. Under such circumstances, systemic therapy is considered.

Treatment procedure

Prophylactic antibiotics is not mandatory but could be given according to the standard practice of individual centers. Patients are fasted for 4 hours before TACE. Intravenous hydration is started at the onset of fasting. The maximum drug dose to be delivered in one treatment session is 40mL of emulsion (20mg cisplatin) or 20mL of suspension (100mg cisplatin) for the Emulsion Group or Suspension Group respectively.

<u>Guidelines on preparation of cisplatin formulations</u>

1.Ethiodized oil-aqueous cisplatin emulsion:

The formulation consists of 10mg aqueous cisplatin (10mL) mixed with 10mL ethiodized oil to form an emulsion (0.5mg cisplatin/mL emulsion)(Platinol, Bristol-

Myers Squibb Company, Princeton, New Jersey)(Reference 11). The formulation is prepared with aseptic technique within a negative pressure isolator by a pharmacist or a radiology nurse in the pharmacy or the radiology department. Cisplatin for injection (Platinol, Bristol-Myers Squibb Company, Princeton, New Jersey) 10mg in 10mL is used to mix with 10mL of ethiodized oil (Lipiodol Ultra Fluid, Guerbet, France) using the pumping method through a two-way connector between two 20mL syringes, with aqueous cisplatin pumped into the ethiodized oil first, using 40 times forward and backward pumping, to create aqueous droplets encapsulation by ethiodized oil in the emulsion.

2. Ethiodized oil-anhydrous cisplatin suspension:

The formulation being introduced consists of a suspension of 100mg pure anhydrous cisplatin in 20mL ethiodized oil (5mg cisplatin /mL suspension)(Chemoparticle cisplatin powder, Four Seasons International Limited, Hong Kong). The formulation is prepared with aseptic technique by a pharmacist in the pharmacy or a radiology nurse in the radiology department. The use of negative pressure isolator is not mandatory because the cisplatin is in solid form and drug evaporation is not a concern. Anhydrous cisplatin powder is supplied in 20mg bottles (Chemoparticle cisplatin powder, Four Seasons International Limited, Hong Kong). Four mL of ethiodized oil is introduced slowly into the cisplatin containing bottle to capture the 20mg cisplatin powder. Cisplatin powder is washed from the bottle wall into the suspension with gentle shaking of ethiodized oil against the bottle wall in all directions. The suspension is homogenized with the use of an ultrasonic vibrator for 1 minute, or by shaking the bottle in a circular motion of about 5cm in diameter on a horizontal plane, with the bottle bottom down, for about 100 times. When the

suspension is homogenized, it is aspirated into a syringe. If the suspension is not prepared immediately before delivery into the patient, sedimentation of cisplatin powder would invariably occur, the suspension is then homogenized again with a pumping method through a two-way connector between two syringes.

Patient preparation and TACE procedure specific to Suspension Group

Within 60 minutes before TACE, antiemetic regimen is started as per standard clinical practice for highly emetogenic systemic chemotherapy, choices include 5-HT3 antagonist (Zofran or Kytril), dexamethasone, NK1 receptor antagonist (SFI), or metoclopramide (Maxolon). After TACE, intravenous mannitol 40gm is given over 30 minutes, and intravenous normal saline 1000mL (with addition of 20 mmol KCL, 0.5gm Magnesium Sulfate, and 2.5ml 10% Ca Gluconate) is given over 12 hours. During transarterial delivery of the formulation, attention is paid to hold the syringe in a tip-down and vertical position to facilitate complete emptying of cisplatin powder together with ethiodized oil as the powder invariably falls gradually towards the tip of the syringe with time due to gravity.

TACE procedure and procedure endpoint applicable to both groups

Arterial catheterization to segmental, subsegmental, or sub-subsegmental level is achieved depending on the tumor size, to gain arterial access as close to the tumors as possible. The formulation is delivered under fluoroscopic control until the vasculature of all tumors is entirely filled, or until the maximum dose is reached. Inadvertent drug delivery to non-hepatic organs through non-hepatic arteries originating from hepatic arteries is avoided by controlling the rate of delivery or selective coil embolization.

The completeness of filling of tumor vasculature is assessed with flat panel CT or multi-planar CT. Attention is paid to identify non-hepatic arterial supply to tumors to ensure complete treatment of all tumor components. Embolization is performed using 1mm-sized gelatin-sponge pellets following the delivery of cisplatin, with an aim to achieve flow reduction but not complete stasis.

Patient assessment

Pre-treatment evaluation

1. Complete history and physical examination
2. Non-enhanced CT thorax and triphasic abdominal CT scan
3. Complete blood picture (CBP) and differential counts
4. Liver and renal function tests (L/RFT)
5. Serum AFP
6. Clotting profile PT, APTT, INR
7. HBsAg status
8. Anti-HCV

Peri-procedure evaluation

1. Clinical observation during hospitalization
2. Blood test for CBP, L/RFT, INR at day 1 and day 2 of treatment procedure

Radiological assessment

Non-enhanced CT thorax and triphasic contrast enhanced CT of abdomen are performed at 3 months intervals from date of first treatment until untreatable progression, symptomatic progression, or death.

Clinical visits

Patients are followed up at day 14, 30 days after each treatment. After the first 30 days, follow up are subsequently scheduled at 1 to 3 months intervals.

Clinical observation and physical examination are carried out in each visit (including ECOG performance status)

Blood tests on day 7 and in each visit include CBP, L/RFT, INR. Serum AFP is also checked after day 30.

(+/- 3 days applies to clinical visit and blood taking on day 7 and beyond)

Laboratory findings were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Outcome assessment

Tumor response

Triphasic contrast enhanced CT of abdomen is performed at 3 months intervals after the first treatment until untreatable progression, symptomatic progression, or death. Tumor response at 3 month and 6 month is classified into complete response (CR), partial response (PR), or stable disease (SD), according to Modified Response Evaluation Criteria in Solid Tumors (mRECIST)(10). Progresive disease is subdivided into intralesional progression, extralesional progression, and extrahepatic progression. Intralesional tumor progression is defined as tumor recurrence at the site of treated tumor after initial complete tumor response, or any degree of enlargement of treated tumor after initial partial response. Extralesional tumor progression is

defined as occurrence of new tumor at a new site of the liver. Extrahepatic tumor progression is defined as occurrence of venous invasion by tumor or extrahepatic tumor metastasis.

Disease progression is adjudicated in retrospect at the time it is first detected. CT images are reviewed centrally for response classification by a team of independent radiologists. Discrepancy in classification among radiologists is resolved by consensus.

Clinical outcome

Patients are observed as in-patient for 3 to 5 days after TACE and followed clinically at day 14, 30 days after each treatment. After the first 30 days, clinics are scheduled at 1 to 3-months intervals. Adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. Serious adverse events are reported to the institution's Clinical Research Ethics Committee within 24 hours of learning of its occurrence.

Adverse events

Information about all adverse events, whether volunteered by the patient, discovered by the investigators, or detected through physical examination, laboratory tests or by other means, will be collected and recorded on the Adverse Event Case Report Form (CRF) in every visit and followed as appropriate. An adverse event is defined as any undesirable symptom, sign or medical condition occurring after starting the trial even if the event is not considered to be related to the study medication or placebo.

Serious adverse events

To ensure patient safety, every serious adverse event will be reported to the CREC within 24 hours of learning of its occurrence. A serious adverse event is an undesirable symptom, sign or medical condition which:

1. is fatal or life-threatening,
2. requires or prolongs hospitalization,
3. results in persistent or significant disability/incapacity, or
4. is medically significant, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
5.

Statistical analysis

Efficacy analyses are performed on the per-protocol population according to the treatment finally received with adherence to the protocol. Post-randomization exclusion is limited only to those who withdrew themselves from the study or who have not completed the required treatments. For continuous variables, median with inter-quarter range (IQR) are provided and compared using U test between the groups. For dichotomic variables, comparison between groups is performed using Chi-square test or Fisher's exact test. The time-to-event data in months are estimated with the method of Kaplan-Meier analysis for TTP, PFS and OS, and presented with median and 95% confidence interval (CI). If the median is not reached, 3-year and 5-year rate are given. Survival outcomes between the groups are compared using log-rank test, hazard ratio (HR) and corresponding 95% confidence interval (CI) are computed using cox regression model. SPSS software is used for analysis. Statistical significance is $p< 0.05$.

Reference

1. El-Serag HB. Current concepts hepatocellular carcinoma. N Engl J Med 2011;365: 1118-27.

2. Ngan H, Lai CL, Fan ST, Lai EC, Yuen WK, Tso WK. Treatment of inoperable hepatocellular carcinoma by transcatheter arterial chemoembolization using an emulsion of cisplatin in iodized oil and gelfoam. Clin Radiol 1993;47:315-320.

3. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of Transarterial Lipiodol Chemoembolization for unresectable HCC. Hepatology 2002;35:1164-71.

4. Liapi E, Geschwind JFH. Transcatheter Arterial Chemoembolization for Liver Cancer: Is It Time to Distinguish Conventional from Drug-Eluting Chemoembolization? Cardiovasc Intervent Radiol 2011 Feb;34(1):37-49.

5. Kasai K, Ushio A, Sawara K, Miyamoto Y, Kasai Y, Oikawa K, et a. Transcatheter arterial chemoembolization with a fine-powder formulation of cisplatin for hepatocellular carcinoma. World Journal of Gastroenterology 2010;16(27):3437-3444.

6. Yamamoto K, Shimizu T, Narabayashi I. Intraarterial infusion chemotherapy with lipiodol-CDDP suspension for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2000; 23:26-39.

7. Moriguchi M, Takayama T, Nakamura M, Aramaki O, Higaki T, Nakayama H, et al. Phase I/II study of a fine-powder formulation of cisplatin for transcatheter arterial chemoembolization in hepatocellular carcinoma. Hepatol Res 2010; 40:369-375.

8. Kawaoka T, Aikata H, Takaki S, Katamura Y, Hiramatsu A, Waki K, et al. Transarterial infusion chemotherapy using cisplatin-lipiodol suspension with or without embolization for unresectable heptocellular carcinoma. Cardiovasc Intervent Radiol 2009; 32:687-694.

9. Kasai K, Ushio A, Sawara K, Miyamoto Y, Kasai Y, Oikawa K, et al.Transcatheter arterial chemoembolization with a fine-powder formulation of cisplatin for hepatocellular carcinoma. World J Gastroenterol 2010; 16:3437-3444.
10. Lencioni R, Llovet JM: Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Seminars in liver disease 30: 52-60, 2010