Protocol title:
Evaluation the potential of colchicine for the palliative management of hepatocellular carcinoma patients with distant metastasis or large vessel invasion

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Ⅰ.Protocol title: Evaluation the potential of colchicine for the palliative management of hepatocellular carcinoma patients with distant metastasis or large vessel invasion

Ⅱ.Objectives: This trial is to evaluate the potential of colchicine for the palliative management of hepatocellular carcinoma patients with distant metastasis or large vessel invasion using the Department of Health R.O.C. approved doses and methods of administration.

Ⅲ.Test drug

1. **Name: colchicine**
2. **Dosage form: tablet**
3. **Dose(s): 0.5 mg/tablet**
4. **Dosing schedule: 2 tablets (1 mg) three times per day (after breakfast, lunch and dinner); continue 4 days and stop for 3 days (1 cycle); repeat this cycle until patients quit this trial**
5. **Mechanism of action: anti-mitosis**
6. **Pharmacological category: anti-inflammation and anti-cancer**

Ⅳ.Study design

1. **□ Control: □ placebo**
   □ active
   ■ others: The control group will be originated from review of hepatocellular carcinoma patients (2014/1/1 till the end of this trial) treated by sorafenib for more than 2 months by members of this research team with the same condition as this trial selected participants.
   □ Uncontrolled
2. **Blinding: ■ open-label □ single blind □ double blind □ others**
3. **Randomized: □ yes ■ no**
4. **□ Parallel □ cross-over □ others**
5. **Duration of study: from 2013-6-1 to 2019-5-31, total 72 months**
   Duration of Enrollment : from 2013-6-1 to 2018-5-31,total 60 months
   Duration of treatment: from 2013-6-1 to 2019-5-31, total 72 months
   Duration of follow-up: from 2013-6-1 to 2019-5-31, total 72 months

□ **Multi-national** ■ **multi-center(Taiwan)(Kaohsiung Medical University Hospital, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Municipal Ta-Tung Hospital)**

□ **single center(Taiwan)**

6. **Number of subjects: at least 60 participants**
7. **Is there any of the followings included DSMB, Data Safety Monitoring Board:**

□ **yes** ■ **no (only has DSMP)**

Ⅴ.Assessment criteria

1. **Efficacy:**

Primary objective: comparison the 1 year survival between the treated group and the control group

Primary end point: survival of participant

2. **Safety:**

Secondary objective: the safety of hepatocellular carcinoma patients treated by colchicine

Secondary end point: the side effects of colchicine

Ⅵ. Selection criteria

1. **Main inclusion criteria:**

(a). Patient has at least one of the following criteria: (1) positive for hepatocellular carcinoma evidenced by cytology or pathology, (2) serum alpha-fetoprotein level ≥ 400 ng/mL and has evidence of hepatocellular carcinoma provided by contrast-enhanced computed tomography or magnetic resonance imaging.

(b). Contrast-enhanced computed tomography or magnetic resonance imaging has evidence of distant metastasis or large vessel invasion caused by hepatocellular carcinoma.

(c). Patient has Child A hepatic reserved function

2. **Main exclusion criteria:**

(a). There are life-threatening hemorrhage including gastrointestinal hemorrhage and hemorrhage from other vital organs such as lungs or brain.

(b). There are life-threatening bacterial, fungal or viral infection (not included hepatitis B and C virus).

(c). Patient has serum creatinine level > 1.5 mg/dL.

(d). Patient must receive long-term medication of statin or fibrates drugs and these medications can not be changed.

(e). Patient has white blood cell count < 1500/μL, platelet count < 30000/μL or hemoglobin < 9.0 gm/dL after medication.

(f). Pregnant woman or plan to be a pregnant woman

(g). allergy to colchicine or has history of severe side effects caused by colchicine

(h). Patient has received systemic chemotherapy within 2 months before enrollment or plans to receive systemic chemotherapy in the future.

(i). Patient is under or plans to receive Nexavar or other clinical trial testing drug.

(j). Patient has severe malfunction of vital organs and can not participate in this study justified by the doctor in this research team.

(k). Patient is under or plans to receive Chinese traditional medicine or herb drugs.

Ⅶ.Study procedures(summary)

1. **Written informed consent must be obtained before any study specific procedures are undertaken.**

2.The process of the experiment

<u>Start to receive colchicine:</u>

Participant will start to receive colchicine according to our dosing schedule described above during the admission period.

<u>Adjustment the dosage of colchicine during study:</u>

1. The colchicine dosage will be changed when the hepatic reserved function of the participant changes from Child A to B according to the following rules.

(a) 2 tablets after breakfast, 1 tablet after lunch and 2 tablets after dinner; continue 4 days and stop for 3 days (1 cycle); repeat this cycle until patients quit this trial

(b) If the hepatic reserved function of the participant returns to Child A, The dosage for Child A will be restored.

(c) If the hepatic reserved function of the participant changes to Child C, colchicine will be stopped and participant receives regular follow-up only.

2. If participant suffers from severe diarrhea, colchicine will be temporarily stopped. When the symptom of diarrhea subsides, colchicine will be given again according to the following rules.

(a) For participant receives〔2 tablets after breakfast, 2 tablet after lunch and 2 tablets after dinner〕, the dosage of colchicine will be changes to〔2 tablets after breakfast, 1 tablet after lunch and 2 tablets after dinner〕.
If diarrhea attacks again, the dosage of colchicine will be changes to〔2 tablets after breakfast and 2 tablets after dinner〕.
If diarrhea attacks again, the dosage of colchicine will be changes to〔2 tablets after breakfast, 1 tablet after dinner〕.
If diarrhea also attacks again, colchicine will be stopped and participant receives regular follow-up only.
(b) For participant receives〔2 tablets after breakfast, 1 tablet after lunch and 2 tablets after dinner〕, the dosage of colchicine will be changes to〔2 tablets after breakfast and 2 tablets after dinner〕.
If diarrhea attacks again, the dosage of colchicine will be changes to〔2 tablets after breakfast, 1 tablet after dinner〕.
If diarrhea also attacks again, colchicine will be stopped and participant receives regular follow-up only.
3. If the participant has one of the following conditions, colchicine will be temporarily stopped. When the condition of the participant improves, colchicine will be given again after the judgment from the doctor of the research team. For participants unable to receive colchicine again, they will receive regular follow-up only.
(a) There are life-threatening hemorrhage including gastrointestinal hemorrhage and hemorrhage from other vital organs such as lungs or brain.
(b). There are life-threatening bacterial, fungal or viral infection (not included hepatitis B and C virus).
(c). Patient has serum creatinine level > 1.5 mg/dL.
(d). Patient has white blood cell count < 1500/μL, platelet count < 30000/μL or hemoglobin < 9.0 gm/dL after medication.
(e) The research team decides that the participant is not suitable to continue the study caused by abnormality of any vital organ or severe side effects caused by the study.
4. Colchicine will be temporarily stopped one day before transcatheter arterial chemoembolization until participant has body temperature < 38 ℃, same hepatic reserved function as before, and serum creatinine level < 1.5 mg/d after embolization.

<u>Follow-up procedures and items for the participants to co-operate:</u>

All participants will be followed according to the guide line of the National Health Council and the clinical practice in the treatment of hepatocellular carcinoma. Contrasted-enhanced computed tomography or magnetic resonance imaging will be performed within every 3 to 4 months. Serum alpha-fetoprotein will be determined at least one session within every 2 to 3 months in patients with elevated serum alpha-fetoprotein levels. The hepatic and renal function will be determined at least one session every month. The participants are asked to visit our outpatient clinic at least one session every month.

For participants admitted in Kaohsiung Medical University Hospital and the conditions of the participants permit, we will perform the examination for the determination of plasma colchicine concentrations. Blood sampling (7 mL each session) will be performed in the first cycle of colchicine administration: (a) before colchicine administration, (b) at the 4th day before breakfast, (c) at the 4th day before lunch, and (d) at the 4th day before dinner. If participant suffers from severe diarrhea during the first cycle of colchicine administration, the timing for blood sampling in (b) to (c) will be delayed until participant can tolerate stable colchicine dose.

<u>The conditions for the participant to withdraw or terminate this trial:</u>

1. Participant suffers from systemic itching, nausea, vomiting, abdominal pain, fever, or skin rash after colchicine administration.

2. Participant is unable to tolerate 1.5 mg total daily dose of colchicine for at least 4 cycles.

Ⅷ. Concomitant treatment:

1. Permitted: local irradiation therapy and transcatheter arterial chemoembolization

2. Prohibited: systemic chemotherapy, Nexavar, other clinical trial testing drugs, Chinese traditional medicine, herb drugs

Ⅸ.Statistical analysis

All participants belong to AJCC TNM Staging IIIB or IVB. For one-year survival analysis, we will enroll at least 30 participants in each of these two TNM stages to compare with the control groups. The safety analysis will be performed by collection of all the severe adverse events (SAE) and adverse event (AE) and described by descriptional analysis.