

Safety and Short-term Efficacy of Licartin Combined with Conventional Transcatheter Hepatic Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma

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Yu *et al.*: Safety and Short-Term Efficacy of Licartin

To evaluate the safety and short-term efficacy of Licartin combined with conventional transcatheter hepatic arterial chemoembolization for patients with unresectable hepatocellular carcinoma, 13 patients with unresectable primary liver cancer treated with Licartin combined with conventional transcatheter arterial chemoembolization at the First Affiliated Hospital from January 2012 to December 2014, were

retrospectively analyzed. Licartin was infused via hepatic artery at a dose of 27.75 MBq/kg prior to conventional transcatheter arterial chemoembolization (pirarubicin 20 mg and iodized oil), supplemented with poly vinyl alcohol particles. Here, the iodized oil is used as an embolic agent and carrier of anticancer drugs. After entering into the small arteries and peritumoral sinusoid of hepatocellular carcinoma through a catheter, the iodized oil gets retained there to block the terminal blood flow. According to mRECIST evaluation criteria, the remission and control rates after 1, 3, 6, and 9 mo were 69.3 and 100; 69.3 and 84.6; 61.5 and 76.9 and 60 % and 80 %, respectively. The survival rate was 100 % after 6 mo. The 1 y and 2 y survival rates estimated with Life Tables were 68 and 45 %, respectively. Liver and kidney function showed no significant difference pre- and post-treatment. No serious infections, jaundice, gastrointestinal bleeding or bone marrow suppression occurred. Licartin combined with conventional transcatheter arterial chemoembolization showed short-term efficacy and minimal side-effects in patients afflicted with unresectable primary liver cancer. Long-term follow-up involving large cohorts is needed to determine the long-term efficacy of the intervention.

Key words: Licartin, transcatheter hepatic arterial chemoembolization, primary liver cancer, ¹³¹I-labeled metuximab

Hepatocellular carcinoma (HCC) is one of the most common primary lethal neoplasms worldwide^[1]. Despite significant improvement in clinical diagnosis and management of HCC in the last decades, this malignant disease is still associated with poor prognosis and high postoperative recurrence rate^[2,3]. Further, most HCC patients are contraindicated for radical treatment with surgical resection. Currently, transcatheter hepatic arterial chemoembolization (TACE) is the mainstay of treatment for patients with unresectable HCC. However, postoperative local recurrence and metastasis occur frequently, warranting the need for a long-term curative intervention. Combination of conventional TACE (cTACE) with radiotherapy has been shown to improve the therapeutic outcome. A lethal dose of conventional external irradiation is rarely administered to treat liver cancer due to limitations of cytotoxicity^[4]. Licartin or ¹³¹I-metuximab binds with HBsAg (CD147) antigens, which are distributed on the tumor cell surface, to enhance the lethal effect via release of radiation^[5]. However, its clinical efficacy and safety have yet to be established. The purpose of this study is to evaluate the safety and short-term efficacy of Licartin combined with conventional TACE for patients with unresectable HCC.

The medical records of 13 patients (13 males with a mean age of 59.77±14.58 in the age range of 31-79 y) with unresectable liver cancer treated with Licartin combined with cTACE from January 2012 to December 2014 at the First Affiliated Hospital, were retrospectively reviewed. Patients with liver

function graded Child-Pugh score A included 3 with hypertension, 10 with hepatitis B, 11 with multiple lesions and 2 with single lesion. Three patients had portal vein tumor thrombus (2 involving the left branch and 1 the right branch). Nine patients carried portal vein tumors with a maximum diameter less than 5 cm and 1 patient had tumor measuring greater than 10 cm in diameter. The details of 13 patients are presented in Table 1.

TABLE 1: BASELINE PATIENT DEMOGRAPHICS

Parameters	Quantitative value	Percent (%)
Gender		
Male	13	100
Female	0	0
Age	31-79	
Virus markers		
HBsAg positive	10	76.9
HBsAg negative	3	23.1
Child-Pugh grade A	13	100
Portal vein tumor thrombus		
Yes	3	23.1
No	10	76.9
Maximum diameter (cm)		
≤5	9	69.2
>5, ≤10	3	23.1
>10	1	7.7
AFP value (ng/ml)		
≤10	5	38.5
>10	8	61.5
Lesion number		
Single	2	15.4
Multiple	11	84.6

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Inclusion criteria were made after evaluating all cases based on the diagnostic criteria recommended by the Management of hepatocellular carcinoma^[6]. Patients were diagnosed with primary liver cancer by needle biopsy, enhanced CT, MRI, ultrasound, DSA and AFP. Patients with a life expectancy greater than 3 mo. All cases diagnosed with multiple lesions or unresectable single lesion. All cases with no other dysfunction and all cases undergoing TACE alone with less reliable results.

Exclusion criteria were, patients who received ablation, targeted drug or other therapies; patients switching to or combined with other therapies for tumor progression after multiple sessions of TACE; patients with extra hepatic metastasis; patients complicated with serious underlying diseases and patients allergic to Licartin or its components. Lugol's liquid was administered 3 d before treatment until day 7 after treatment (0.5 ml each time, 3 times daily). Skin test was carried out initially. Following confirmation of a negative response to subcutaneous injection of metuximab, an appropriate dose of ¹³¹I-metuximab was administered into the correct hepatic artery. Based on patients' weight, the amount of ¹³¹I target dose was calculated as 27.75 MBq/kg (0.75 mCi/kg).

After conventional preparation, bilateral inguinal disinfection and local anesthesia, radiography of the celiac trunk, common hepatic artery, superior mesenteric artery or inferior mesenteric artery was performed to determine the tumor location, size, number and blood supply in the right femoral artery using Seldinger's technique. A 2.7 F microcatheter was carefully advanced into the tumor feeding artery and Licartin was injected over a period of 5 to 10 min, followed by embolization with iodized oil (1-20 ml) suspended in pirarubicin (20 mg). Tumor size, blood flow, and degree of thickness dictated the speed of control injection. The iodized oil emulsion flow was monitored. The decision to stop injection was based on the sedimentary conditions of the iodized oil emulsion in the tumor area. The presence of small hepatic portal vein branches around the tumor was another factor. Polyvinyl alcohol particles were used in combination with iodized oil to occlude the feeding artery according to individual situation. Treatments protecting liver and stomach as well as antineoplastic interventions were routinely administered to patients. Antinausea, antipyretic and antiinfective treatments were used as needed.

Four weeks after treatment, CT or MRI, liver and

kidney function tests, α -fetoprotein (AFP) value, and routine blood evaluation were conducted to assess residual liver tumor and normal liver function. Local curative effect was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Disease remission rate was defined by CR combined with PR. Disease control rate was determined by the total remission rate and stable disease.

Ongoing follow-up was conducted in person at the outpatient clinic and inside the hospital, as well as remotely via telephone after the initial follow-up. The starting point of survival analysis was regarded as the day of initial treatment and the endpoint included death or until October 2015. All statistical analyses were conducted with SPSS version 13.0. Measurement data were analyzed by two related Wilcoxon test samples with $p < 0.05$. Survival analysis was estimated in the postoperative 1 y, and the 2 y survival rate using the life table method.

All patients were treated with Licartin combined with cTACE successfully after treatment with cTACE alone. Twelve patients were treated twice and the remaining patient underwent therapy once. The study involved 39 treatments, at an average of 3 times per patient. The average hospital time was 4.5 d. The preoperative and postoperative (1 mo later) tumor sizes were 4.95 ± 3.95 and 3.8 ± 3.23 cm, respectively, and the differences were statistically significant ($p < 0.05$). According to mRECIST evaluation criteria, the disease remission and control rates after 1, 3, 6, and 9 mo were 69.3 and 100 %; 69.3 and 84.6 %; 61.5 and 76.9 % and 60 and 80 %, respectively (Table 2).

All the 13 patients were followed up completely. The survival rate was 100 % after 6 mo. The 1- and 2 y survival rates estimated by Life Tables were 68 and 45 %, respectively. Six patients died by the end of follow-up and 7 patients were alive. The comparison of postoperative and preoperative AFP values showed no statistical significance ($p = 0.055$). Changes in liver and kidney function, blood parameters, except serum

TABLE 2: mRECIST CRITERIA FOLLOW-UP RESULTS

Follow-up time (month)	Number	Tumor status				(CR+PR %)	
		CR	PR	SD	PD	(CR+PR+SD%)	
1	13	3	6	4	0	69.3	100
3	13	4	5	2	2	69.3	84.6
6	13	4	4	2	3	61.5	76.9
9	10	4	2	2	2	60.0	80.0

creatinine, revealed no significant pre and postoperative (1 mo) differences (Table 3).

The clinical symptoms were carefully recorded after treatment (Table 4). Frequent adverse events included nausea, vomiting, abdominal pain, anorexia, and fever, which were improved after symptomatic treatment. No liver or kidney failure, severe infection, gastrointestinal bleeding or other serious complications was observed.

^{131}I , with a half-life of 8 d, emits γ and β rays. However, only β radiation is associated with therapeutic effect. The energy of β rays is 364 Kev and the radiation range is less than 1 mm, which is completely blocked by fat and muscle surrounding the liver. Therefore, ^{131}I therapy for liver cancer is highly efficient with low toxicity^[7]. However, delivery of ^{131}I and enrichment in the tumor microenvironment are always a challenge. Internal radiation therapy with ^{131}I -labeled lipiodol for HCC is effective^[8]. However, non-specific ^{131}I accumulation in the tumor is a limitation and lipiodol is easily excreted. Licartin is a new ^{131}I -labeled monoclonal antibody recommended for targeted radiation therapy of HCC. ^{131}I -metuximab has been shown to exhibit antitumor efficacy by delivering radioactive ^{131}I to the tumor location by specifically binding to HAb18G (CD147) antigen, which is expressed on the tumor cell surface, Antibody-dependent cellular cytotoxicity is another mechanism. ^{131}I -metuximab is effective against liver cancer since CD147 is expressed on HCC cells up to 70 to 80 %^[9]. Biodistribution studies showed that Licartin was absorbed by liver cancer tissue and the radioactivity increased constantly over time resulting in persistent high-dose radiation delivery to tumor,

TABLE 3: BLOOD PARAMETERS, LIVER AND KIDNEY FUNCTION BEFORE AND 1 MONTH AFTER TREATMENT

Test items	Preoperative	Postoperative	p value
AFP (ng/ml)	1125.52±2986.95	604.47±1572.76	0.055
TBIL (BIL57±1)	15.92±7.15	16.92±6.60	0.552
AST (U/l)	58.92±38.39	47.38±13.3	0.388
ALT (U/l)	60.69±60.97	34.15±10.62	0.382
ALB (g/l)	37.09±5.19	38.90±5.34	0.279
Cre ($\mu\text{mol/l}$)	67.62±13.21	62.38±13.41	0.041
WBC ($10^9/\text{l}$)	5.96±3.15	4.46±1.95	0.346
PLT ($10^9/\text{l}$)	111.77±45.52	123.00±60.00	0.552

TABLE 4: CLINICAL SYMPTOMS IMMEDIATELY AFTER TREATMENT

Adverse event	Abdominal pain	Fever	Nausea vomiting	Fatigue anorexia	Diarrhoea constipation
Number	12	6	8	10	3
%	92.3	46.2	61.5	76.9	23.1

without damaging the surrounding tissue^[5]. Licartin combined with conventional TACE may benefit patients with HCC by prolonging the concentration of ^{131}I in the HCC tissues. It acts synergistically to enhance the radio sensitivity of chemotherapeutic drugs.

Lu *et al.*^[10] reported that the objective response rates of the 2 treatments at 4 to 8 w after therapy were 69.1 and 62.8 %, respectively. The response rate tended to be significantly higher in the combination group than in the conventional therapy group. Another study reported similar results suggesting that the effective rates of the two groups after 1 mo of, treatment were 71.23 and 38.89 %. The present study also found that Licartin combined with cTACE for patients with unresectable HCC was effective in controlling the tumor locally^[11]. The disease remission and control rates after 1, 3, 6, and 9 mo were 69.3 and 100 %; 69.3 and 84.6 %; 61.5 and 76.9 %; and 60 and 80 %, respectively. The postoperative and preoperative AFP values showed no significant differences and relates to fewer number of cases.

In the current study of Licartin combined with cTACE for unresectable HCC and post-operative recurrence, the curative effect was local and resulted mostly in short-term survival. The results showed that combination therapy showed survival rates of 88.2 %, 79.1 % and 57.4 % at 6, 12, and 18 mo, respectively^[10]. The survival rates of HCC patients treated with cTACE alone were 81.6 %, 67.4 % and 38.6 %, respectively, and the difference was statistically significant. In another study the combination group at 6, 9 and 12 mo showed significant survival rates of 86.4, 74.1 and 60.5 % compared to 60.0, 45.2 and 34.4 % in the control group, respectively. In the present study, the postoperative survival rate was 100 % at 6 mo, 1 y and 2 y, and the survival rates estimated by Life Tables were 68 and 45 %, respectively^[11]. By the follow-up end point, a total of 6 patients died, and 7 patients survived. The above data showed that the combination treatment was superior to cTACE for unresectable HCC.

All patients complained of gastrointestinal symptoms after the treatment, including nausea, vomiting and stomach ache, low-level fever and diarrhoea were less frequent and managed with symptomatic treatment. No liver or kidney failure, severe infection, gastrointestinal bleeding or other serious complications were observed. Evaluation of liver and kidney function revealed no major changes in blood parameters, except for serum creatinine. The preoperative results showed no

significant differences compared with postoperative results at 1 mo. The probability of bone marrow suppression due to ^{131}I irradiation therapy was higher compared with TACE alone. However, the incidence of bone marrow suppression was not observed in this study. The risk associated with bone marrow suppression was reported by other studies^[10-12]. The incidence of bone marrow suppression was mainly level I or level II. Findings similar to this study were reported by other researchers^[13]. The discrepancy may be patient-specific or related to the drugs used. Current study demonstrated that Licartin was safe for patients with unresectable and recurrent HCC.

In conclusion, the findings of this study indicated that the combination of Licartin and cTACE is an effective treatment for patients diagnosed with unresectable HCC. The adverse side effects were minor. The efficacy was local and superior to the individual therapy. The principal limitation of this study relates to its small sample size as well as the overall survival rate is limited to 68 % and 45 % respectively in the first and second year. On the other hand the study depicts, that the treating surgical oncologists has tried vigorously to improve the survival rate. Therefore, long-term, prospective, controlled and randomized studies with large sample sizes are needed.

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Informed consent:

Informed consent was obtained from all individual participants included in the study.

Conflict of interest:

The all authors report no conflicts of interest in this work.

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