

Prospective Study

Chemoembolization alone vs combined chemoembolization and hepatic arterial infusion chemotherapy in inoperable hepatocellular carcinoma patients

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Abstract

AIM: To compare the efficacy and safety of chemoembolization alone or chemoembolization combined with hepatic arterial infusion chemotherapy (HAIC), including oxaliplatin (OXA), 5-fluorouracil (5-FU) and folinic acid (CF), in inoperable hepatocellular carcinoma (HCC) without distant metastasis.

METHODS: Eighty-four inoperable HCC patients were enrolled. Thirty-nine patients underwent chemoembolization alone, and the other 45 patients underwent chemoembolization + HAIC (OXA/5-FU/CF) treatment non-randomly. The progression free survival (PFS), objective response rate (ORR), disease control rate (DCR) and adverse reactions were compared between the two groups.

RESULTS: A significant difference in the ORR was observed between the chemoembolization alone and chemoembolization + HAIC groups. There was no statistically significant difference in DCR between the two groups. The median PFS (mPFS) showed a significant difference between the two groups. For patients with BCLC stage A/B disease, with or without vessel invasion, the chemoembolization + HAIC group showed better mPFS when compared to chemoembolization alone, but no significant difference was found in patients with BCLC stage C disease. The parameter of pain (grade III-IV) in the chemoembolization + HAIC group was increased statistically.

CONCLUSION: Chemoembolization combined with HAIC with OXA/5-FU/CF may be safe and more effective than chemoembolization alone for inoperable HCC patients without distant metastasis.

Key words: Chemoembolization; Hepatic arterial infusion chemotherapy; Oxaliplatin; Hepatocellular carcinoma

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Core tip: Eighty-four inoperable hepatocellular carcinoma (HCC) patients were enrolled, 39 patients underwent chemoembolization alone, and the other 45 patients underwent chemoembolization + hepatic arterial infusion chemotherapy (HAIC) [oxaliplatin (OXA)/5-fluorouracil (5-FU)/folinic acid (CF)] treatment non-randomly. The progression free survival (PFS), objective response rate (ORR), disease control rate (DCR) and adverse reactions were compared between the two groups. A significant difference in the ORR was observed between the two groups. There was no statistically significant difference in DCR between the two groups. The median PFS (mPFS) showed a significant difference between the two groups. For patients with BCLC stage A/B disease, with or without vessel invasion, the chemoembolization + HAIC group showed better mPFS when compared to chemoembolization alone, but no significant difference was found in patients with BCLC stage C disease. The parameter of pain (grade III-IV) in the chemoembolization + HAIC group was increased statistically. Chemoembolization combined with HAIC with OXA/5-FU/CF may be safe and more effective than chemoembolization alone for inoperable HCC patients without distant metastases.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide^[1]. Chemoembolization is an effective treatment that has been widely used to treat unresectable HCC^[2,3]. Combined with chemoembolization, treatments such as radiofrequency ablation (RFA), microwave ablation, absolute alcohol injection, sorafenib and hepatic artery infusion chemotherapy (HAIC) have been the recent focus of HCC interventional clinical studies^[4].

Because of the multidrug resistance mechanisms of HCC, traditional systemic chemotherapeutic drugs are generally not helpful in eliminating HCC cells. Recently, some new anti-tumor drugs and formulations, such as oxaliplatin (OXA), capecitabine and gemcitabine, have been investigated in HCC chemotherapy clinical studies. In addition, the treatment containing OXA demonstrated better safety and efficacy^[5,6]. Chemotherapy for unresectable cases of middle- and late-stage HCC again garnered attention. In 2010, an open, randomized, controlled, multicenter phase III clinical study (EACH test) of the use of FOLFOX4 venous chemotherapy to treat inoperable HCC showed that the FOLFOX 4 protocol had significant advantages in terms of overall survival (OS) and tumor progression (TTP); in terms of toxicities and side effects, this regimen was well tolerated^[7].

Compared to systemic chemotherapy, chemotherapeutic drugs are directly infused into the blood supply through the hepatic artery to directly expose HCC cells to high-concentration drugs, which may reduce the systemic side effects caused by excessively high concentrations of drugs in the peripheral blood during systemic chemotherapy^[8]. A number of clinical studies of HAIC with OXA used to treat hepatic metastasis for colon or rectal cancer have illustrated its good curative effect and safety^[9-11]. Rathore *et al.*^[12] reported a phase I study in which the single drug OXA was perfused in a dose-escalation test through the hepatic artery to treat HCC and a curative effect was observed; the administration of OXA (150 mg/m²) during HAIC treatment for middle- and late-stage HCC was safe and effective. However, few high-level evidence-based clinical studies of HAIC with OXA for the treatment of HCC have been reported^[13].

In our study, based on our previous results^[14,15], we aimed to conduct a phase II, prospective, non-randomized clinical study in inoperable HCC patients without extra-hepatic metastasis. The curative effect and safety of the combination of chemoembolization and HAIC with OXA/5-fluorouracil (5-FU)/folinic acid (CF) were investigated.

MATERIALS AND METHODS

Patient enrollment

From December 2010 to August 2011, patients who had been diagnosed with HCC based on clinical

and pathologic manifestations [using the American Association for the Study of Liver Diseases (AASLD) criteria] at the Department of Interventional Treatment in our hospital were enrolled^[16]. A total of 84 HCC patients were enrolled, including 39 patients who were treated with chemoembolization alone and 45 patients who were treated with chemoembolization combined with HAIC containing OXA/5-FU/CF. Our study was approved by the local ethics committee and conducted according to the standards of the Declaration of Helsinki, and informed written consent was obtained from all patients. The patients treated with chemoembolization were defined as the control group (group A). Patients who were treated with the combination of chemoembolization and OXA/5-FU/CF-containing HAIC were defined as group B. The curative effect (modified RECIST)^[17], progression free survival (PFS) rate and safety were compared between the two groups. Two groups of patients were enrolled on a non-randomized basis; approximately 40 patients were enrolled in each group.

The following inclusion criteria were applied: (1) male or female patients 18-80 years of age; (2) inoperable HCC patients (*i.e.*, the surgical department eliminated a surgical option) without extrahepatic metastasis, including patients who had undergone surgery but suffered recurrence; (3) Child-Pugh grade A or B for liver function; (4) Barcelona staging (BCLC staging) of hepatic lymph node metastasis (N1) and distant metastasis (M1), except for patients in stage A, B or C; (5) an Eastern Cooperative Oncology Group (ECOG) patient state (PS) grade of 0 or 1; (6) patients who had enough reserve functions in the liver, kidney and medulla ossium; and (7) an estimated survival time \geq 12 wk.

The following exclusion criteria were applied: (1) the development or simultaneous development of other histological tumors; (2) patients who had undergone liver transplant surgery or received any other prior anti-tumor treatments, including interferon (IFN- α), systemic chemotherapy, and sorafenib; (3) patients who had developed severe coronary heart disease, severe arrhythmia requiring treatment with medicines other than a β receptor blocking agent or digoxin, severe active infection (> grade 2, NCI - CTCAE v3.0 criteria), combined HIV infection, renal insufficiency [creatinine (Cr) level > 2 mg/dL], unconsciousness (including patients with a history of epilepsy), severe allergic constitution, or allergy to contrast media; (4) women who were pregnant or lactating at the time of enrollment; (5) ECOG grading, PS > 2; (6) Child-Pugh grade C for liver function; (7) BCLC staging, stage 0 or D; (8) the tumor volume accounted for > 70% of the liver volume; and (9) portal vein thrombosis with no obvious collateral circulation established.

Treatment regimen

As shown in Figure 1, the chemoembolization treatment for all enrolled patients was performed with a digital

subtraction angiography (DSA) machine (Innova 4100 IQ, GE Corporation, United States) in our hospital. Group A received the chemoembolization treatment alone using the right femoral approach; DSA of the celiac, superior mesenteric and splenic arteries was performed to evaluate the hepatic arterial anatomy and tumor blood supply. The portal venous system was evaluated in the portal venous phases of the superior mesenteric or splenic angiograms. A 2.7 F microcatheter (Progreat, Terumo, Japan) was advanced coaxially through the outer catheter for selective catheterization of the arteries supplying the tumor. A total of 40 mg of emulsified epirubicin (EPI) and lipiodol (total volume < 20 mL) was administered for embolization. For some large tumors, polyvinyl alcohol particles (PVA) embolization was performed. If there was extrahepatic parasitic blood supply to the tumor (*e.g.*, from the right phrenic artery, left gastric artery, or right inferior adrenal artery), chemoembolization was recommended and performed after selective catheterization through the parasitic artery.

For patients in group B, the chemoembolization treatment was performed as described above. If the microcatheter head was near the gastroduodenal artery or the right gastric artery, microcoil embolization was performed; to protect the normal gastrointestinal tract, the microcatheter was reserved at the proper hepatic artery or at the left or right hepatic artery. After the patient returned to the ward, the microcatheter was externally connected to the artery infusion pump (Model LP 2000-P2) to administer the following HAIC treatment: OXA [60-75 mg/m² (Child-Pugh A, 75 mg/m² and Child-Pugh B, 60 mg/m²)] intra-arterially administered for 0-4 h; CF (200 mg/m²) intravenously administered for 2-4 h; and 5-FU [1-1.5 g/m² (Child-Pugh A, 1.5 g/m² and Child-Pugh B, 1 g/m²)] intra-arterially administered for 4-24 h.

After the treatment was completed in both groups, the indwelling catheter in the artery was removed, and the pressure hemostasis was regulated at the puncture point. All patients were given a fluid infusion to support and protect the liver treatment.

Observed clinical data

During and after the arterial chemotherapy treatment, any development of pain, fever, nausea, vomiting and anxiety was recorded. Then, 5-7 d later, laboratory tests were performed, including a routine blood test and thrombotest, blood ammonia and liver and kidney function tests. These tests were repeated after 4-6 wk to observe any adverse reactions in the patients. Contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT) examinations were performed every 4-6 wk to evaluate the treatment (mRECIST) efficacy.

The original treatment protocol was stopped, and the PFS time was recorded if any of the following developments occurred: (1) the patient died or there were extrahepatic metastases or intrahepatic lesion

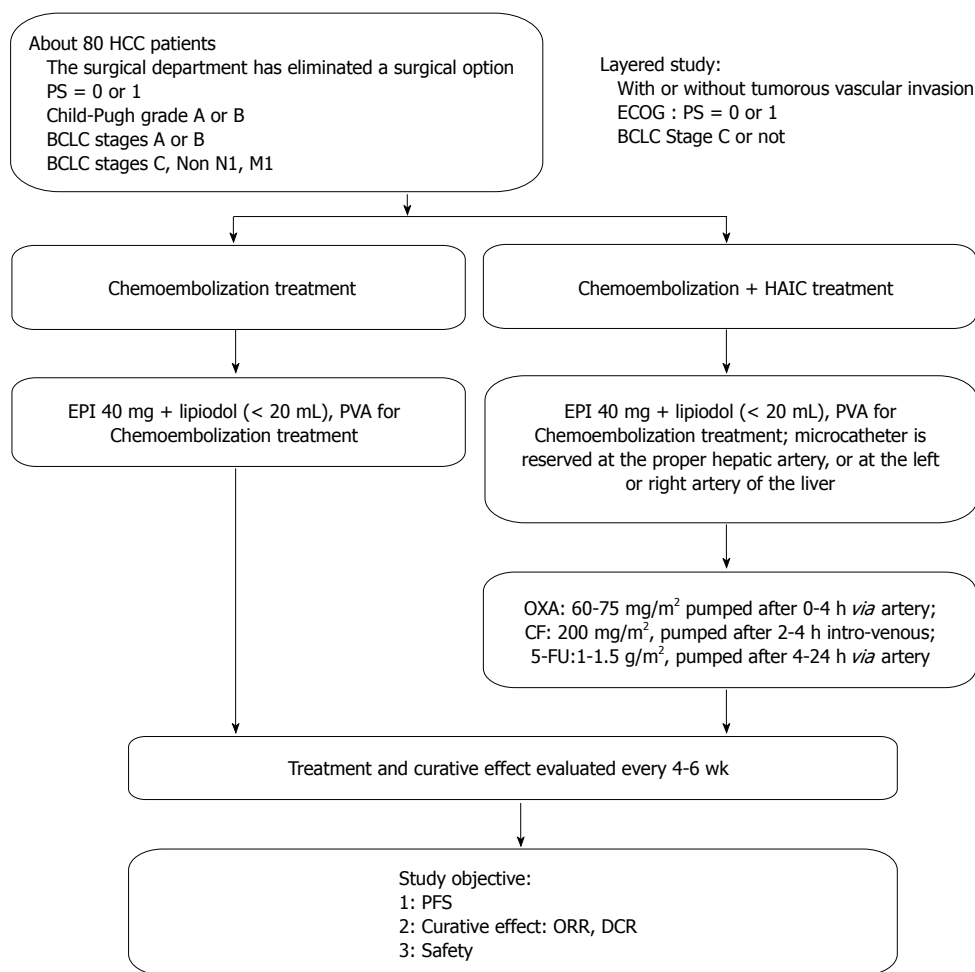


Figure 1 Flow chart of the treatment scheme. PFS: Progression free survival; ORR: Objective response rate; DCR: Disease control rate; HAIC: Hepatic arterial infusion chemotherapy; PVA: Polyvinyl alcohol particles; BCLC: Barcelona Clinic Liver Cancer staging.

development; (2) there were intolerable grade IV adverse reactions (NCI-CTCAE v3.0 criteria); or (3) a Child-Pugh class of C and an ECOG > 2 were recorded.

The following supplementary descriptions were also recorded in our study: (1) if the patients demonstrated stable conditions with complete response (CR), an alpha-fetoprotein (AFP) recheck was performed every 3 mo at the clinic or ward, and contrast enhanced MRI or CT evaluations were conducted; (2) if there were any new tumor nodes (> 5 mm) in the liver, the progressive disease (PD) was evaluated, and the PFS was recorded. The original protocol could be administered for continuous treatment. When PD was identified twice consecutively, the patient was excluded from the study and received regular follow-ups; and (3) the HCC patients who received stage-II resection or ablation after these interventional treatments were excluded. Only the curative effect and safety were evaluated; no PFS rates were recorded.

Follow-up analysis

All patients received chemoembolization alone or combined treatment at least once; then, the efficacy and safety of the two protocols were evaluated:

(1) The curative effect, according to the mRECIST, was analyzed and evaluated, including the objective response rate (ORR) of the tumor/disease control rate (DCR): ORR = CR + partial response (PR); DCR = CR + PR + C (SD); and (2) The median progression free survival (mPFS) was analyzed. Any adverse reactions were recorded, and the safety of this treatment was evaluated (NCI-CTCAE v3.0; Levi special grading standard for sensory nerve toxicity)^[18].

Statistical analysis

All data were analyzed using SPSS Version 15.0 (SPSS Inc., 2006, Chicago IL, United States). The end point of this clinical study was mPFS. When the patients died, or if the tumors progressed, the PFS time was recorded for the survival analysis. If the treatment was terminated due to the loss of follow-up information, if the patient underwent surgery after the interventional treatment, if the patient's general condition deteriorated (PS > 2), if the patient's liver function deteriorated (Child-Pugh C), or if the patient experienced intolerable adverse reactions, then the last examination and evaluation time or the resection time of the patient was recorded and designated as

Table 1 Baseline clinical characteristics of patients enrolled *n* (%)

	Chemoembolization group (<i>n</i> = 39)	Chemoembolization + HAIC group (<i>n</i> = 45)	<i>P</i> -value
Age (yr)	59.69 ± 13.13	57.16 ± 10.34	0.325
Gender			0.832
Male	35 (89.7)	41 (91.1)	
Female	4 (10.3)	4 (8.9)	
Hepatitis condition			0.309
Hepatitis B	32 (82.1)	39 (86.7)	
Hepatitis C	3 (7.7)	3 (6.7)	
Hepatitis B + hepatitis C	1 (2.6)	3 (6.7)	
Non-hepatitis	3 (7.7)	0	
Grading of physical condition			0.393
PS = 0	18 (46.2)	24 (53.3)	
PS = 1	21 (53.8)	21 (46.7)	
Ascites			0.900
Yes	10 (25.6)	11 (24.4)	
No	29 (82.4)	34 (75.6)	
Liver function Child-Pugh			0.075
Grade A	36 (92.3)	41 (91.1)	
Grade B	3 (7.7)	4 (8.9)	
Diameter of tumor target lesion (cm)			0.347
≤ 10	19 (48.7)	29 (64.4)	
> 10	20 (51.3)	16 (35.6)	
Number of tumor			0.149
> 3	22 (56.4)	31 (68.9)	
≤ 3	17 (43.6)	14 (31.1)	
Blood vessel invasion			1.000
No	26 (66.7)	30 (66.7)	
Yes	13 (33.3)	15 (33.3)	
BCLC stage			0.860
Stage A	4 (10.3)	3 (6.7)	
Stage B	9 (23.1)	15 (33.3)	
Stage C	22 (56.4)	21 (44.1)	
Relapse after surgical resection	4 (10.3)	6 (13.3)	
Follow-up time, median (mo)	7.2 (1.3-15.2)	9.3 (3.8-14.6)	0.169

censored data for the survival analysis. The curative effect, ORR and DCR of the two groups were compared using the Pearson correlation coefficient and the Chi-squared test. The mPFS time (Kaplan-Meier method) was assessed for all enrolled HCC patients. Log-rank tests were used to perform the univariate analysis for the PS status, liver function (Child-Pugh grading)^[19], vascular invasion, AFP value, total bilirubin value, tumor quantity and the diameter of the tumorous target lesion. Multivariate analysis was performed using the Cox proportional hazards regression model. The Pearson method or the Fisher's exact test and the Chi-square test were used to compare the rate of adverse reactions in the two groups, with $P < 0.05$ indicating statistical significance.

RESULTS

Comparison of baseline clinical characteristics of the enrolled patients

As shown in Table 1, the baseline clinical characteristics of the enrolled patients showed no significant difference between the two groups. Clinical characteristics, including age, gender, hepatitis conditions, physical condition grading, ascites, Child-Pugh grade, diameter of tumor target lesion, number of tumors, blood

vessel invasion, Barcelona stage and follow-up time, showed no significant differences between the two groups ($P > 0.05$). The blood test indicators, including white blood cell count, hemoglobin value, platelet count, glutamate pyruvate transaminase, glutamic-oxaloacetic transaminase, total bilirubin, serum albumin, prothrombin time, creatinine and AFP, also showed no significant difference between the two groups ($P > 0.05$), as shown in Supplementary Table 1.

Overall therapeutic evaluation

As shown in Table 2, excluding the two patients in the chemoembolization treatment group who were lost to follow-up, the ORR was 45.9%. The ORR in the chemoembolization + HAIC treatment group was 68.9%. There were statistically significant differences between the two groups ($P = 0.036$). In the chemoembolization + HAIC treatment group, the DCR was 86.7%, which was higher than that in the chemoembolization group; however, there was no statistically significant difference between the two groups ($P = 0.068$).

Univariate and multivariate analyses of prognosis of inoperable HCC patients

As shown in Table 3, two patients were excluded from

Table 2 Overall curative effect based on mRECIST criteria *n*

	Chemoembolization group (<i>n</i> = 39)	Chemoembolization + HAIC group (<i>n</i> = 45)	<i>P</i> -value
CR	5	12	
PR	12	19	
SD	9	8	
PD	11	6	
Not evaluated	2 (lost)	0	
ORR	17/37 (45.9%)	31/45 (68.9%)	0.036
DCR	26/37 (70.3%)	39/45 (86.7%)	0.068

DCR = CR + PR + SD; ORR = CR + PR; *P* value: Pearson method, χ^2 test. DCR: Disease control rate; PR: Partial response; SD: Partial response; ORR: Objective response rate.

group A: one patient experienced a reduced lesion size after treatment, and based on the PR benchmark, this patient received surgical resection; and one patient received the combined RF treatment after three chemoembolization treatments. Three patients were excluded from group B: one patient received resection after experiencing a lesion size reduction and reduced tumor thrombosis located in the portal vein left branch, based on the PR benchmark; and two patients received the combined RF treatment after chemoembolization + HAIC treatment. After Kaplan-Meier univariate analysis, the following conditions, which showed significant differences in terms of mPFS between the two groups, were associated with a better prognosis and longer mPFS: chemoembolization combined with HAIC ($P = 0.00049$), ECOG grading PS = 0 ($P = 0.00014$), BCLC stage A or B ($P = 0.00051$), no vascular tumor invasion ($P = 0.00047$), AFP < 400 ng/mL ($P = 0.03$), a target lesion diameter sum ≤ 10 cm ($P = 0.00011$), and albumin (Alb) ≥ 35 g/L ($P = 0.027$). The other factors showed no significant differences in terms of MPFS between the two groups, as shown in Supplementary Table 2.

Then, a Cox proportional hazards regression model was used to conduct the multivariate analysis of the patients in terms of interventional therapy proposal, ECOG grade, BCLC stage, vascular tumor invasion, AFP, sum of tumor target lesion diameter and Alb. The model demonstrated that the chemoembolization + HAIC treatment ($P = 0.00048$) was an independent good prognostic factor, but BCLC stage C ($P = 0.003$) and vascular tumor invasion ($P = 0.050$) were independent poor prognostic factors for inoperable HCC patients.

Survival analysis

After the univariate and multivariate analyses, a survival analysis of the three factors was performed, including the interventional therapy proposal, BCLC stage, and vascular tumor invasion. As shown in Figure 2, the mPFS in the chemoembolization + HAIC treatment group (8.0 mo, 95%CI: 7.2-8.8 mo) was significantly better than that in the chemoembolization-

only treatment group (4.5 mo, 95%CI: 3.3-5.7 mo). As shown in Figure 3A, for patients with BCLC stage A/B disease, the mPFS was prolonged in group B (9.7 mo, 95%CI: 4.6-14.9 mo) compared with group A (6.9 mo, 95%CI: 4.5-9.2 mo); however, there were no statistically significant differences between the two groups ($P = 0.170$). As shown in Figure 3B, for the BCLC Stage C patients, group B (4.5 mo, 95%CI: 0.1-9.6 mo) had better mPFS than group A (3.6 mo, 95%CI: 2.6-4.5 mo), and there was a statistically significant difference between the two groups ($P = 0.004$). As shown in Figure 3C, for patients with no vessel invasion, the mPFS rate in group B (9.9 mo, 95%CI: 7.1-12.7 mo) was significantly better compared with that of patients in group A (5.6 mo, 95%CI: 3.8-7.4 mo) ($P = 0.001$). As shown in Figure 3D, for patients with vessel invasion, group B (4.2 mo, 95%CI: 2.8-5.6 mo) also had significantly better mPFS than group A (3.0 mo, 95%CI: 1.2-4.8 mo) ($P = 0.044$).

Adverse reactions

The patients in group A received a total of 92 treatments, and the patients in group B received a total of 137 treatments. As shown in Table 4, when grades I and II adverse reactions were compared between the two groups (χ^2 test), we found that the chemoembolization group had fewer reactions. The adverse reactions, including low platelets ($P = 0.001$), nausea ($P = 0.030$), and vomiting ($P = 0.025$) demonstrated significant differences. When grades III and IV adverse reactions were compared between the two groups, there was a significant difference in pain ($P = 0.008$).

DISCUSSION

According to clinical meta-analysis for a number of international HCC interventional treatments, chemoembolization has not demonstrated a better curative effect or greater survival benefits compared with embolization treatment^[20-23], and the effect of perfusion chemotherapy through the hepatic artery is questionable^[16]. This finding may be related to the following factors: there are significant differences in terms of the enrolled patients and treatment methods for chemoembolization in each clinical study; there is no standard for the selection of chemotherapeutic drugs and doses; and no high-level evidence-based studies have been proposed^[21]. In addition, the perfusion time through the hepatic artery is short and does not consider the metabolism of the chemotherapeutic drug in the liver and tumor.

In our study, we selected a small dose of OXA (60-75 mg/m²) combined with 5-FU for the continuous HAIC treatment administered to the patients. CF was given to increase the response rate of 5-FU through chemical biological tuning. Compared to the previous

Table 3 Univariate and multivariate prognostic analyses of the patients (*n* = 79)

Correlative factor	Number of cases	Kaplan-Meier univariate analysis			Cox multivariate analysis		
		mPFS (mo)	95%CI	P-value	Sig	EXP(B)	95%CI
Interventional therapy				0.00049	0.00048	0.26	0.174-0.612
Chemoembolization	37	4.5	3.3-5.7				
Chemoembolization combined with HAIC	42	8.0	7.2-8.8				
Grading of physical condition				0.00014	0.312	1.525	0.674-3.452
PS = 0	40	8.9	6.2-11.5				
PS = 1	39	4.5	3.7-5.2				
Vascular invasion ¹				0.00047	0.050	1.963	0.989-3.898
No	52	7.9	7.3-8.5				
Yes	27	3.8	2.7-4.8				
BCLC Stage ²				0.00051	0.003	3.083	1.479-6.426
Stage C	30	3.8	3.0-4.6				
Stage A or B	39	9.3	6.7-11.9				
AFP (ng/mL)				0.03	0.488	1.255	0.660-2.386
< 400	52	7.3	5.8-8.8				
≥ 400	27	4.5	2.1-7.0				
Sum of tumor target lesion diameter (cm)				0.00011	0.326	1.449	0.691-3.338
≤ 10	45	7.8	6.1-9.5				
> 10	34	4.3	3.2-5.3				
Serum albumin (g/L)				0.027	0.27	0.628	0.275-1.434
< 35	7	4.3	3.0-5.6				
≥ 35	72	7.3	5.9-8.6				

¹Venous invasion refers to portal vein or hepatic vein tumor thrombosis, APVS; ²BCLC staging did not include patients who relapsed after surgery. PFS: Progression free survival; mPFS: Median progression free survival; AFP: Alpha-fetoprotein; HAIC: Hepatic arterial infusion chemotherapy; BCLC: Barcelona Clinic Liver Cancer staging.

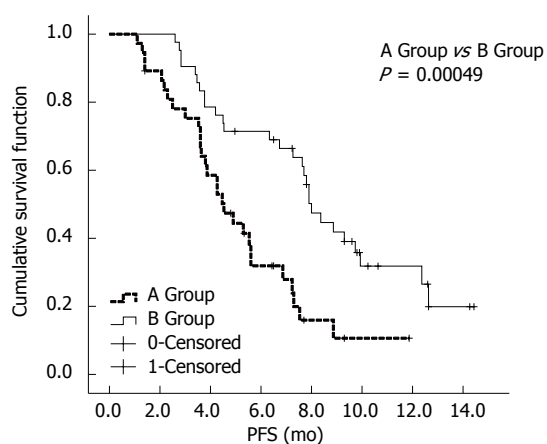


Figure 2 Comparison of the median progression free survival in the chemoembolization + hepatic arterial infusion chemotherapy treatment group (group B) and chemoembolization alone treatment group (group A). HAIC: Hepatic arterial infusion chemotherapy.

studies, we designated the chemoembolization treatment group as the control group to ensure that we could better observe the effects of HAIC. The mRECIST criteria that introduced the concept of the “active lesion” were used for the analysis, which may more objectively and accurately reflect the curative effect compared with the original RECIST criteria for HCC^[24-26]. Our study results demonstrated that chemoembolization + HAIC treatment is significantly better than chemoembolization treatment alone in terms of DCR, and our findings also support the use

of ORR compared with chemoembolization treatment alone. Data from the integrated study show that the chemoembolization + HAIC combined treatment may significantly increase the short-term effect of the treatment for the HCC patients who have no metastasis or unresectable tumors, and it may extend the mPFS.

In addition, the chemoembolization + HAIC treatment demonstrated a better prognosis than the chemoembolization treatment alone. The survival analysis results also showed that for patients with or without vascular invasion, the mPFS between the chemoembolization + HAIC treatment and chemoembolization treatment showed a statistically significant difference. For the BCLC stage C patients, the mPFS for the chemoembolization + HAIC group was significantly prolonged, with a better curative effect. The following may explain this improvement: chemoembolization caused tumor ischemia, and the induced transmembrane ion pump failed, which, to some extent, had a synergistic effect combined with the high-concentration chemotherapy and enabled the tumor cells to absorb more chemotherapeutic drugs^[27]; and after the chemoembolization treatment, HAIC had a therapeutic effect on the portal vein, hepatic vein tumor thrombosis, and the tumor, evidenced by the lack of obvious feeding vessels in the angiography^[28,29]. For the HCC patients with BCLC stage A or B disease, the mPFS rate was prolonged in the chemoembolization + HAIC treatment compared

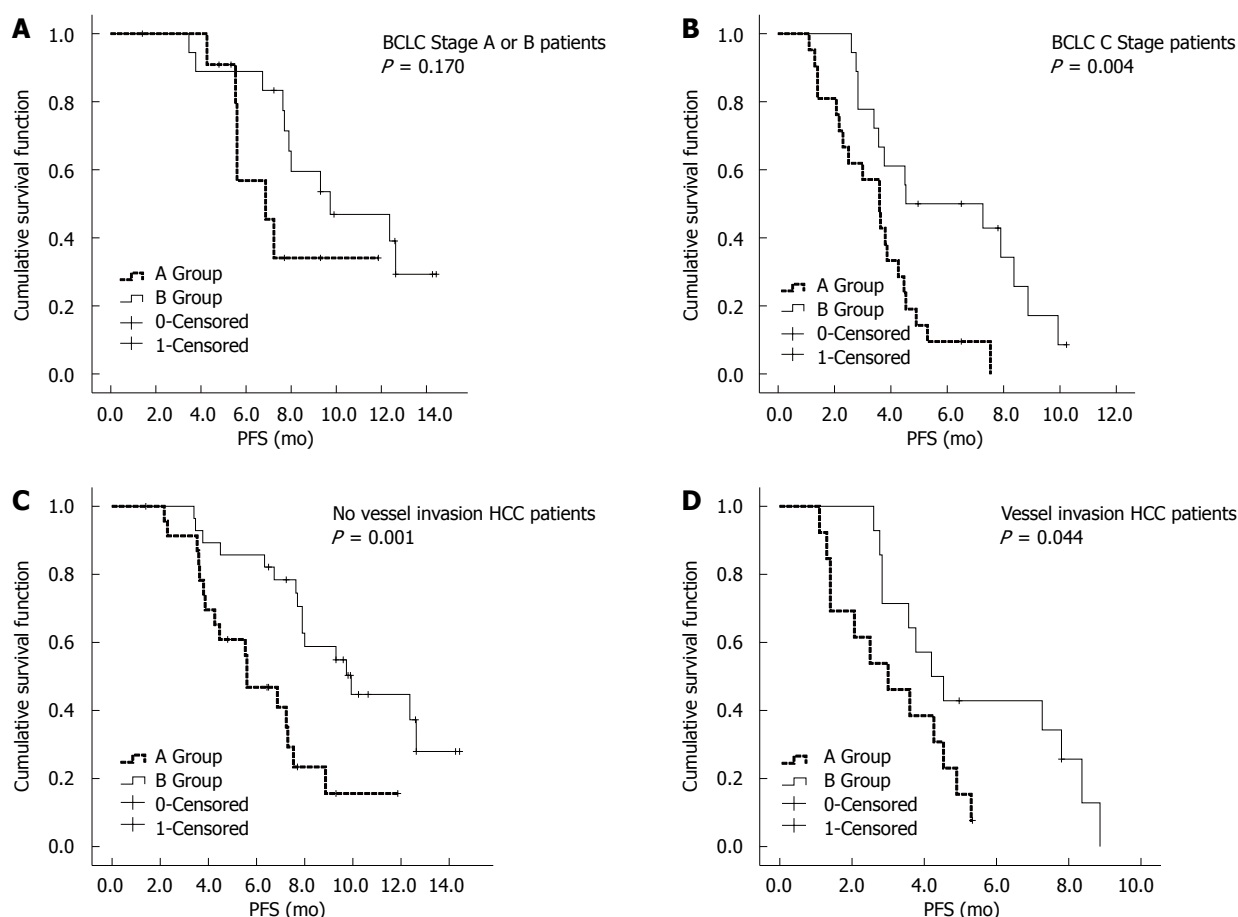


Figure 3 Comparison of the median progression free survival in patients with different BCLC stages and patient state in the chemoembolization + hepatic arterial infusion chemotherapy treatment group (group B) and chemoembolization alone treatment group (group A). A: Hepatocellular carcinoma (HCC) patients with BCLC stage A/B disease; B: HCC patients with BCLC stage C disease; C: HCC patients without vessel invasion; D: HCC patients with vessel invasion. HAIC: Hepatic arterial infusion chemotherapy.

Table 4 Adverse reactions of patients enrolled in our study *n* (%)

Adverse reaction	Chemoembolization (<i>n</i> = 92)		Chemoembolization + HAIC (<i>n</i> = 137)		<i>P</i> ₁	<i>P</i> ₂
	I + II	III + IV	I + II	III + IV		
Hematologic toxicity						
Reduction of white cells	13 (14.1)	0	21 (15.3)	2 (1.4)	0.803	-
Reduction of hemoglobin	17 (18.5)	3 (3.3)	21 (15.3)	2 (1.4)	0.530	0.393
Reduction of thrombocyte	19 (20.7)	7 (7.6)	57 (41.6)	5 (3.6)	0.001	0.231
Non-hematologic toxicity						
Increase of total bilirubin	38 (41.3)	4 (4.3)	74 (54.0)	5 (3.6)	0.059	0.744
Increase of glutamate pyruvate transaminase	55 (59.8)	5 (5.4)	78 (56.9)	11 (8.0)	0.668	0.450
Increase of glutamic-oxaloacetic transaminase	50 (54.3)	8 (8.7)	82 (59.8)	9 (6.5)	0.408	0.547
Fever	55 (59.8)	11 (12.0)	64 (46.7)	12 (8.8)	0.052	0.430
Pain ¹	40 (43.5)	3 (3.3)	63 (46.0)	19 (13.9)	0.708	0.008
Nausea	47 (51.1)	3 (3.3)	91 (66.4)	5 (3.6)	0.030	0.875
Vomit	19 (20.7)	0	47 (34.3)	3 (2.2)	0.025	-
Diarrhea	1 (1.1)	0	4 (3.0)	0	0.768	-
Constipation	18 (19.6)	1 (1.1)	29 (21.2)	0	0.651 ³	-
Neurotoxicity ²	-	-	13 (6.8)	0	-	-

¹Pain was evaluated according to the grading standards for acute and subacute toxicity reactions for anti-cancer drugs issued by the WHO; ²Neurotoxicity was evaluated according to the Levi special grading standard for sensory nerve toxicity; ³Fisher's exact testing method, χ^2 test (*P*₁ value: comparison of grades I + II adverse reactions between the two groups; *P*₂ value: comparison of grades III + IV adverse reactions between the two groups). Statistics for adverse events: Evaluation based on the NCI - CTCAE v3.0 criteria. *P*-values: Pearson method, χ^2 test.

with that in the chemoembolization-only treatment group, although there was no statistically significant difference between the two groups, which may be related to the small number of enrolled patients. Although the tumor vessels were already embolized with chemoembolization, the vessels may recur and the HAIC treatment may have a therapeutic effect on the tumor mass if it was completely embolized.

In terms of adverse reactions, our study results showed that the chemoembolization + HAIC treatment demonstrated good safety and tolerance. The chemoembolization + HAIC treatment increased the occurrence of adverse reactions, including grades I - II low platelet count, nausea and vomiting. However, in terms of grades III-IV adverse reactions, statistically significant differences were only found for pain. Meanwhile, during the chemoembolization + HAIC treatment in this study, no bleeding, thrombus, infection or other related complications caused by the indwelling catheter were found. Note that in group B, OXA caused sharp pain (VAS: Grade 8-10) in six different patients at the midsection during the administration of HAIC (most of which occurred in 2-4 hours after the chemotherapy). The HAIC treatment was complemented with lidocaine given at intervals during the infusion treatment. The specific cause and mechanism of the sharp pain experienced by the patient may be related to the local administration of the high-concentration chemotherapy drugs^[30]. This side effect should be further observed in future clinical studies.

There were also some limitations to our study. First, the patients were not enrolled on a randomized basis, and the data may be affected by a selection bias. Most of the enrolled HCC patients had Child-Pugh grade A, PS = 0 or 1, and whether the patients with Child-Pugh grade B and PS = 2 can benefit from chemoembolization + HAIC treatment must be assessed in our future study. Second, the therapy endpoints of chemoembolization were not completely consistent. Some patients were treated with PVA particles, which may affect the study result. Third, the number of enrolled patients for this study was small, and a multi-center analysis is needed.

In conclusion, chemoembolization combined with HAIC with OXA/5-FU/CF may be a generally safe treatment, and it is more effective than chemoembolization alone for patients with unresectable HCC without distant metastasis. Based on these promising results, a large-scale, multicenter, randomized, controlled study should be conducted in the future.

COMMENTS

Background

Clinical studies of hepatic arterial infusion chemotherapy (HAIC) with oxaliplatin (OXA) used to treat hepatic metastasis for colon or rectal cancer have illustrated its good curative effects, however, few high-level evidence-based clinical studies of HAIC with OXA for the treatment of hepatocellular carcinoma

(HCC) have been reported.

Research frontiers

We conducted a phase II, prospective, non-randomized clinical study in inoperable HCC patients without extra-hepatic metastases. The curative effect and safety of the combination of chemoembolization and HAIC with OXA/5-fluorouracil (5-Fu)/folinic acid (CF) were investigated.

Innovations and breakthroughs

Chemoembolization combined with HAIC with OXA/5-Fu/CF may be a generally safe treatment.

Applications

Chemoembolization combined with HAIC with OXA/5-Fu/CF may be more effective than chemoembolization alone for patients with unresectable HCC without distant metastasis.

Terminology

Chemoembolization combined with HAIC with OXA/5-Fu/CF should be taken into consideration for the therapy for patients with unresectable HCC without distant metastasis, and more evidence should be used to demonstrate the therapy effect.

Peer-review

This study found that chemoembolization combined with HAIC with OXA/5-Fu/CF may be safe and more effective than chemoembolization alone for inoperable HCC patients without distant metastasis. Over all, this study is well designed, and the manuscript is interesting.

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