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Transarterial chemoembolization combined with Huaier granule for the treatment of primary hepatic carcinoma

Safety and efficacy

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Abstract

To evaluate the safety and efficacy of transarterial arterial chemoembolization (TACE) with gelatin sponge particles (GSPs-TACE) and Huaier granule to treat primary hepatic carcinoma (PHC).

A series of 62 patients with PHC were included between June 2009 and December 2011, and randomly assigned to a control (n = 31) or an experimental group (n = 31). The control patients received TACE with 350 to 560 μm GSPs plus lobaplatin chemotherapy. Patients in the experimental group received TACE plus Huaier granule. Treatment safety and mid-to-long-term efficacy were evaluated.

Follow-up ranged from 12 to 24 months with a mean of 28.7 months. The 6- and 12-month overall survivals were 100% and 93.5% in the experimental group and 90.3% and 80.6% in control group, respectively. The difference in overall survival at 12 months was significant ($\chi^2 = 5.213$, $P < .05$), but the difference in median survival in the experimental group (20.6 months) and control group (17.1 months) patients was not significant ($\chi^2 = 0.745$, $P > .05$). The number of TACE procedures in the experimental group (2.9 ± 8.7) and control group (4.1 ± 7.3) patients was significantly different ($\chi^2 = 7.262$, $P < .05$). The 6-month (87.1% vs. 73.3%, $\chi^2 = 5.945$) and 12-month (72.4% vs. 64.3%, $\chi^2 = 6.384$) tumor objective response rates in the experimental and control groups were significantly different ($P < .05$). There were no statistically significant differences in the occurrence of treatment-related adverse reactions in the 2 groups.

Transarterial chemoembolization with GSPs and Huaier granule was safe and effective for treating PHC patients.

Abbreviations: CT = computed tomography, GSPs-TACE = transarterial arterial chemoembolization with gelatin sponge particles, HCC = hepatocellular carcinoma, PHC = primary hepatic carcinoma, TACE = transarterial arterial chemoembolization.

Keywords: gelatin sponge particles, hepatic carcinoma, Huaier granule, transcatheter arterial chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is the 6th most common malignant tumor worldwide. With approximately 748,000 new cases and 696,000 deaths annually, HCC ranks 3rd among the frequently diagnosed malignancies. More than 50% of the HCC patients diagnosed each year are in China.[1] Currently, surgical resection, radiofrequency ablation, and liver transplantation are considered curative treatments of early HCC.[2] However, more than 70% of HCC patients are diagnosed with advanced disease and are no longer indicated for curative treatment.[3]

Evidence from randomized-controlled clinical trials shows that transcatheter arterial chemoembolization (TACE) improves survival in HCC patients.[4,5] Currently, particle embolization with DC-drug eluting beads or gelatin sponge particles (GSPs) is used in the treatment of HCC. Drugs delivered directly by the microspheres increase tumor necrosis and response rate.[6,7] The domestically produced 350 to 560 μm GSPs used in this study have previously been used for regional embolization in the treatment of HCC. Treatment resulted in tumor necrosis and shrinking, rapid recovery of liver function, and good short-term effectiveness.[8]

Huaier granules are obtained from the fruiting bodies of parasitic fungi growing on aging Chinese cassia trees. They contain a variety of organic components and more than 10 minerals. The structures include a protein composed of 6 heteropolysaccharides and 18 amino acids, polysaccharide protein is the active ingredient.[9] The clinical effectiveness of Huaier granule in the treatment of primary HCC has previously been shown.[10,11] The study aim was to evaluate the mid-to-long-term efficacy and safety of TACE combined with Huaier granules in a series of HCC patients.

Editor: Durga Tripathi.

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The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:29(e7589)

Received: 10 April 2017 / Received in final form: 1 June 2017 / Accepted: 30 June 2017

http://dx.doi.org/10.1097/MD.0000000000007589

2. Materials and methods

2.1. Patient selection

Men and women diagnosed with primary hepatic carcinoma (PHC), <80 years of age, and indicated for TACE but not curative resection surgery, or did not consent to surgery, were eligible and were included between June 2009 and December 2011. Inclusion criteria were Child–Pugh A–B and Barcelona Clinic Liver Cancer A–C liver function and expected survival >3 months. Patients with anticancer therapy before study treatment, histories of allergy to contrast agents, chemotherapy drugs, or adverse reactions to Huaier granules, or evidence of heart, kidney, or brain dysfunction were excluded. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. All patients gave written informed consent before participation.

2.2. TACE procedure and Huaier granule administration

The patients were randomly assigned to treatment with TACE and lobaplatin or with TACE and lobaplatin plus Huaier granule using a digital table of random numbers. The Seldinger technique was used to puncture the right femoral artery, and a 5F-RH catheter was inserted for celiac and hepatic artery angiography. Angiography of ectopic arteries including the phrenic, superior mesenteric, left gastric, and right renal arteries was performed, depending on tumor location, size, and completion of tumor staining, to clear all the tumor feeding arteries. The procedure was the same as for conventional TACE with administration of a suspension of 100 mg 350 to 560 μm diameter GSPs (Hangzhou Yili Kang Pharmaceutical Technology Co., China) and 10 to 20 mg lobaplatin (Hainan Chang'an International pharmaceutical Co., Ltd., China). The volume was chosen based on the tumor size and slowly injected via the catheter into the arteries supplying the tumor under fluoroscopic guidance. The TACE procedure was stopped when tumor staining completely disappeared and regional arterial blood flow stopped. Embolization was monitored by intraoperative radiography or DynaCT contrast angiography.

Patients in the experimental group were given Huaier granule (Gold Grams; Qidong Gai Tianli Pharmaceutical Co. Ltd., China; State Food and Drug Administration (Trial) standard YBZ04202003), 20 g orally 3 times/d beginning 3 days before TACE and continuing after surgery unless discontinued because of intolerance or death.

2.3. Treatment efficacy and monitoring adverse reactions

The first post-treatment computed tomography (CT) scan was performed 4 days after TACE, and lesion size, necrosis, and the presence of new lesions were evaluated monthly thereafter by enhanced CT imaging. Tumor response was evaluated by the modified Response Evaluation Criteria in Solid Tumors (mRECIST 1.1) criteria. Blood was collected for alpha-fetoprotein and evaluation of liver function at 4 and 7 days and 1 month after treatment. The need for repeated intervention was determined by comprehensive assessment of the response to treatment. Adverse reactions were evaluated following the 2010 Drug Adverse Reaction Evaluation Criteria.

2.4. Statistical analysis

SPSS 13.0 software (SPSS Inc., Chicago, IL) was used for the statistical analysis. Categorical data were evaluated using the chi-squared test; $P<.05$ was considered statistically significant. Survival rates were estimated by the Kaplan–Meier method.

Table 1

General information of the patients in 2 groups.

Indicators	Experimental group	Control group	χ^2	*P*
N	31	31	0.000	1.00
Average age	64.9	62.7	0.054	.53
Gender			0.422	.61
Male	27	29		
Female	4	2		
History of hepatitis				
HBV	22	23	0.071	.42
HCV	4	3		
Alcoholic liver disease	2	0		
None	3	5		
Child–Pugh grading				
A	24	26	0.899	.22
B	7	5		
C	0	0		
BCLC grading				
A	6	4	0.812	.23
B	20	23		
C	5	4		
Tumor thrombus	5	4	0.182	.37
Portal vein thrombosis	4	4		
Inferior vena cava Tumor thrombus	1	0		
Tumor average maximum diameter, cm	6.7	7.1	0.745	.27
Tumor size, cm				
<5	3	2	0.069	.43
5–10	18	17		
>10	10	12		
AFP			2.046	.18
≤400	22	20		
>400	9	11		

AFP = alpha fetal protein, BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, HCV = hepatitis C virus.

3. Results

The study included 62 patients with PHC, 56 men and 6 women from 36 to 79 (average of 53.7) years of age. All patients were treated by TACE. There were no statistically significant differences of age, gender, and tumor size in the 2 groups (Table 1). In both groups, postoperative body temperature fluctuated between 37.2 and 39.1°C, which may have been related to tumor necrosis and absorption. There were no cases of acute liver injury or surgery- or chemotherapy-related deaths in either group. There were no statistically significant differences in the adverse events that occurred in the 2 groups (Table 2).

When the study concluded in December 2012, patient follow-up ranged from 12 to 42 (average 28.7) months. Eleven of 31 patients (35.5%) in the experimental group died; no patients were lost to follow-up. Sixteen of 31 control group patients (51.5%) died; 2 patients were lost to follow-up. The 6- and 12-month survivals were 100% and 93.5% in the experimental group and 90.3% and 80.6% in the control group, respectively. The difference in 12-month survival was significant ($\chi^2=5.213$, $P=.02$). Median survival was 20.6 months in the experimental group and 17.1 months in the control group, but the 3.5-month difference was not significant ($\chi^2=0.745$, $P=.27$, Fig. 1). The difference in the number of TACE procedures, 4.1 ± 7.3 in the experimental group and 2.9 ± 8.7 in the control group, was

Table 2

Comparison of adverse reaction indicators between 2 groups during treatment.

		Leucopenia		Thrombocytopenia		Diarrhea		Anorexia and fatigue		Stomach discomfort	
Groups	n	n	%	n	%	n	%	n	%	n	%
Experimental	31	3	9.7	3	9.7	10	32.3	3	9.7	5	16.1
Control	31	5	16.1	4	12.9	8	25.8	8	25.8	7	22.6
χ^2			0.435		0.485		2.037		0.137		0.325
P			.54		.49		.18		.72		.34

Table 3

Comparison of the effects in the treatment of primary liver cancer between 2 groups.

		6 mo survival		12 mo survival			
Groups	n	n	%	n	%	Median survival time	Treatment number
Experimental	31	31	100.0	29	93.5	20.6	2.9±8.7
Control	31	28	90.3	25	80.6	17.1	4.1±7.3
χ^2			2.437		5.213	0.745	7.262
P			.14		.02	.27	.01

Table 4

Tumor response according to modified Response Evaluation Criteria in Solid Tumors in 1 mo, 6 mo, and 12 mo after TACE or TACE combined with Huaier granule.

		Complete remission		Partial remission		Disease stabilization		Disease progression		Objective response rate	
Time after treatment	Groups	n	%	n	%	n	%	n	%	n	%
1 mo after treatment	Experimental	13	41.9	15	48.4	2	6.5	1	3.2	28	90.3*
	Control	12	38.7	16	51.6	3	9.6	0	0	280	90.3*
6 mo after treatment	Experimental	13	41.9	14	45.2	2	6.5	2	6.5	27	87.1**
	Control	10	33.3	12	40.0	4	13.3	4	13.3	22	73.3**
1 y after treatment	Experimental	12	41.4	9	31.0	4	13.8	4	13.8	21	72.4**
	Control	9	32.1	9	32.1	3	10.7	7	25	18	64.3**

TACE = transarterial arterial chemoembolization.
*$P > .05$ and **$P < .05$, comparison between groups.

statistically significant, suggesting that combining TACE with oral administration of Huaier particles reduced the number of interventional treatments (Table 3).

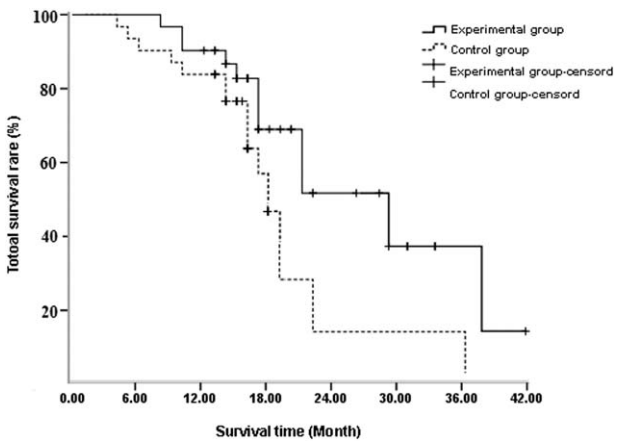

Figure 1. Kaplan–Meier survival curves comparing survival in patients who received TACE combined with 350 to 560 μm gelatin sponge particles and single chemotherapy drugs lobaplatin (control group), and the patients treated by TACE combined with Huaier granule (experimental group). TACE = transarterial arterial chemoembolization.

The 6-month objective tumor response rates were 87.1% in the experimental group and 73.3% in the control group ($\chi^2 = 5.945$, $P < .05$) and the 1-year response rates were 72.4% and 64.3%, respectively ($\chi^2 = 6.384$, $P < .05$). The between-group differences were significant (Table 4).

4. Discussion

The study results showed that GSPs-TACE combined with Huaier particles was effective for the treatment of HCC, and during follow-up, the tumor response rate, number of interventions, and survival were found to be better in the experimental group than in the control group. Median survival in the experimental group was 20.6 months, which was 3.5 months longer than in the control group. Overall, combination treatment improved clinical efficacy.

Vascular endothelial growth factor increases in the peripheral blood of HCC patients after TACE, and promotes development of the microvascular environment that favors recurrence of liver tumors.[12] Huaier particles have been shown to inhibit angiogenesis in HCC tissue, reduce levels of vascular endothelial growth factor, and inhibit proliferation, migration, and differentiation of vascular endothelial cells.[13] These molecular events may have been involved in the combined treatment of HCC in this study. The in vivo necrosis of liver tumors that begins shortly after TACE may

result in antigen exposure that promotes an immune response and activates specific antitumor activity.[14] Huaier particles can enhance macrophage activity, increase p53 "housekeeping gene" expression, and downregulate Bcl-2 expression, thus improving immune function.[15] The treatment response to GSPs-TACE plus Huaier particles may reflect enhanced immune function. TACE destroys liver tumors primarily by "starvation," and with treatment including Huaier particles, resistant tumor cells that escape the liver[16] would be under immune surveillance. Huaier particles can directly inhibit tumor growth, thus promoting tumor cell apoptosis and necrosis.[17] Continuing "mopping up" after TACE might allow complete elimination of tumor cells by combined regimens like that used in this study.

More than 90% of HCC patients develop primary liver cancer against a background of hepatitis B-related cirrhosis, and the extent of cirrhosis and decreased liver function affect long-term prognosis in patients treated with TACE.[12] However, the use of iodized oil in TACE procedures can promote liver fibrosis and the liver toxicity of chemotherapy drugs.[18] The effects of the particles used as embolization agents on liver cirrhosis are not known, but repeated TACE may have an impact on liver function. Huaier particles have potential antiviral activity and promote recovery from injury to liver cells and repair of liver function. So the Huaier particles may have a supportive effect that reduces the long-term effect of GSPs-TACE in HCC patients after surgery, but there was no significant difference in the occurrence of adverse reactions in the study groups.

Limitations of this prospective study include possible group and follow-up bias despite random group allocation. Other limitations include the limited number of patients in each groups, short follow-up, and the single-center design. Large multicenter randomized-controlled trials are warranted to confirm the safety and effectiveness of this treatment regimen.

5. Conclusion

Combining 350 to 560 μm GSPs-TACE with traditional Chinese Huaier particles improved the treatment response of HCC patients, and improved the mid-to-long-term survival. The addition of Huaier particles was well tolerated.

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