Therapeutic effect of transcatheter arterial chemoembolization and percutaneous injection of acetic acids on primary liver cancer

Hong-Bin Chen, Yue Huang, Dong-Ling Dai, Xia Zhang, Zhong-Wen Huang, Qi-Kai Zhang, Hui-Hua Wang, Jun-Su Zhang and Ge Pan

Sanming, China

BACKGROUND: **The resection rate of primary liver tumor in China is only about 20%. A lot of patients with moderate and advanced liver tumor may lose the chance of operation. The objective of present research was to study the efficacy of transcatheter arterial chemoembolization (TACE) combined with percutaneous injection of chemical agents and acetic acids in the treatment of patients with primary liver cancer (PLC).**

METHODS: **Thirty-three patients with middle and advanced stage of PLC were divided into two groups: percutaneous injection of chemical agents and acetic acids (15 patients, group A) and TACE (18 patients, group B).**

RESULTS: **Tumor diameter and serum AFP level reduced to 86.6% and 83.3% in group A, and 55.5% and 40% in group B, respectively. There was significant difference between the two groups ($P<0.01$). The 1-, 2-, 3-, 4-year survival rates of group A were 96.7%, 86.6%, 51.3%, 33.3%, respectively and in group B were 66.7%, 44.4%, 16.7%, 0%, respectively ($P<0.01$).**

CONCLUSION: **TACE combined with percutaneous injection of chemical agents and acetic acids is efficacious to increase the survival rate of patients with PLC.**

(*Hepatobiliary Pancreat Dis Int 2004; 3: 55-57*)

KEY WORDS: **primary liver cancer; liver artery; chemoembolization; chemical drug injection; acetic acid**

Author Affiliations: Departments of Gastroenterology (Chen HB and Huang Y), Interventional Therapy (Huang ZW, Zhang QK and Wang HH), Ultrasonography (Zhang JS) and CT (Pan G), Sanming Municipal First Hospital, Sanming 365000, China; Department of Gastroenterology, Second Affiliated Hospital, Chongqing Medical University, Chongqing 400000, China (Dai DL and Zhang X)

Corresponding Author: Hong-Bin Chen, MD, Department of Gastroenterology, Sanming Municipal First Hospital, Sanming 365000, China (Tel: 86-598-8222574; Email: smchb@yahoo.com.cn)

Introduction

Primary liver cancer (PLC) is a common malignancy in China. Once confirmed, most cases are at the middle or advanced stage of the disease and lost the chance of operation. Presently, transcatheter arterial chemoembolization (TACE) is assumed to be one of the first-line treatments for PLC,[1-3] but its effect is not well elucidated because of frequent recurrence after a short period of amelioration.

We treated 15 patients with PLC by TACE combined with percutaneous injection of chemical agents and acetic acids (group A), and 18 patients by TACE alone (group B) at our hospital from February 1998 to December 2001. The therapeutic effects in the two groups were compared.

Methods

Patients

Thirty-three PLC patients (23 men and 10 women; mean age 42±23 years) were confirmed by ultrasound B, CT, alpha fetoprotein (AFP), angiography, clinical and laboratory examination (Table 1). Patients with diffuse liver carcinoma or those associated with severe jaundice, ascites, portosystemic thrombosis or metastasis were excluded. The patients were classified according to the criteria for Liver Tumor Staging and Classification published in the *Chinese Journal of Liver Diseases* in 1999. All patients on admission were randomly divided into comprehensive treatment group (group A) and TACE treatment group (group B). Those with tumor diameter ranging from 6 cm to 20 cm were thought to lose the opportunity of operation. In group A the tumor diameter was 15±5 cm and in group B 13±6 cm. The data from the two groups were compared.

Table 1. Clinical and laboratory results of the two groups

Group	Cases (n)	M/F	Age (y)	AFP (p/n)	Tumor type		Stage of tumor				Diameter (cm)
					Simple	Cirrhosis	Ⅰ	Ⅱ	Ⅲ	Ⅳ	
A	15	10/5	46±21	12/3	8	7	0	10	5	0	15±5
B	18	13/5	41±22	15/3	10	8	0	11	7	0	13±6

Treatment

TACE (group B)

The femoral artery was perforated by Seldinger technique and the catheter was introduced by superselection into the proper hepatic artery or the blood supply artery for injection of chemical agents. Fluorouracil (1000 mg), mytomycin (10-20 mg), carboplatin (100 mg) or hydroxy-camptothecine (10-20 mg) were emulsified with 10-20 ml of 40% iodized oil, and were injected slowly under regular surveillance. Subsequently, the accumulation of iodized oil was observed. After the iodized oil deposited fully, gelatin particles were embolized to slow the blood down. Further, 5-10 mg of dexamethasone was injected through the catheter. Such embolization was repeated 1-6 times under the normal conditions of liver function, hemogram and others 30-40 days after each intervention.

Comprehensive treatment (group A)

Percutaneous injection of acetic acid was given 7-14 days after TACE. After the tumor was localized and measured by CT or ultrasound B, 36% acetic acid was injected at multiple spots along the tumor edge. Ten-60 ml of acetic acid was given according to the formula: $V=4\pi/3(R+0.5)^3$ (V: total volume of acetic acid; R: radius; 0.5: extension of intervention). 250-500 mg of fluorouracil was injected subsequently. 36% acetic acid and fluorouracil were injected after 7-10 days repeatedly. Each treatment course included TACE once and 36% acetic acid and injection of chemotherapeutic agents for 3-4 times. Times of treatment courses were determined by general condition, tolerance and tumor size.

Criteria for therapeutic evaluation

Ultrasound B, CT and angiography were performed to see changes of tumor size, serum AFP level, blood routine, and liver function regularly before and after treatment. Furthermore, the survival rates of patients were monitored. Tumor size and serum AFP level reduced after 2-3 treatments in all patients, but fluctuation of AFP level was seen in some patients who could receive repeated interventions.

Statistical analysis

The data were treated using the χ^2 test. A P value less than 0.01 was considered significant.

Table 2. Changes of tumor size after imaging evaluation before and after treatment (%)

Group	Significantly effective[a]	Effective[b]	Ineffective[c]
A	60.0(9/15)	86.6(13/15)	13.3(2/15) *
B	16.7(3/18)	55.5(10/18)	44.4(8/18)

*: $P<0.01$. a: tumor contraction >50%; b: tumor contraction 10%-50%; c: tumor contraction <10%.

Table 3. Changes of serum AFP level before and after treatment (%)

Group	Significantly effective[a]	Effective[b]	Ineffective[c]
A	50.0(6/12)	83.3(10/12)	16.7(2/12) *
B	13.3(2/15)	40.0(6/15)	60.0(9/15)

*: $P<0.01$. a: AFP <20 μg/L; b: AFP <20-400 μg/L; c: AFP≥400 μg/L.

Table 4. Survival rates of the 2 groups after treatment (%)

Group	1-y	2-y	3-y	4-y
A	96.7(14/15)	86.6(13/15)	51.3(8/15)	33.3(5/15) *
B	66.7(12/18)	44.4(8/18)	16.7(3/18)	0(0/18)

*: $P<0.01$.

Results

The reduction rates of tumor size and serum AFP level were 86.6% and 83.3% in group A, and 55.5% and 40.0% in group B, respectively. There was a significant difference between the two groups ($P<0.01$, Tables 2-4). The 1-, 2-, 3-, 4-year survival rates in group A were significantly different from those in group B ($P<0.01$, Tables 2-4).

Discussion

The natural history of PLC is about one to four months, and surgery is almost impossible for most cases.[4] Because 95% of blood supply for liver tumor is from the hepatic artery and 75% of blood supply for normal liver tissue comes from the portosystemic vein, selective block of the hepatic artery may result in tumor ischemia and necrosis; but there is no effect on normal liver tissue, so TACE has become the first-line treatment among non-surgical managements. Actually TACE alone does not bring about complete tumor necrosis. Palmad[5] report-

ed in 1998 that in patients having Ⅱ-stage surgery after TACE, only 22%-72% tumors developed complete coagulative necrosis. Some scholars speculated that peripheral tumor tissues are most active[6] since there are double blood supply, branch blood supply, and multiple arteries blood supply, especially the compensatory blood supply by the portal vein. Studies have shown that TACE combined with percutaneous injection of acetic acid could enhance therapeutic effect because acetic acid is potent to kill local tissues and cells, causing dehydration and fixation of tumor cells, coagulation and degeneration of proteins, degeneration, necrosis and thrombosis of endothelial cells. Finally ischemic necrosis, especially the destruction of tumor fibrous tissues after TACE, facilitates diffusion of acetic acid in tumor tissues. Moreover, the block of tumor blood supply could prevent acetic acid from blood washing. Many studies focused on percutaneous injection of dehydrated alcohol, but few on injection of acetic acid. Similarly New Zealand rabbits with PLC were injected percutaneously 50% acetic acid or dehydrated alcohol into tumor tissues, resulting in a superficial necrotic area in tumor: 1.79 ± 0.6 cm in the acetic acid group and 1.48 ± 0.54 cm in the dehydrated alcohol group, respectively ($P\leqslant0.05$).[7] Pathologically, there was a distinct boundary between normal and necrotic tissues in which hepatic lobule outlines, karyorrhexis, nuclei disapperance or a central necrotic zone existed. Clinical studies[7] showed that all 25 patients with PLC were injected 50% acetic acid and their survival rate was over 6 months (90% survived over a year), without complications caused by puncture. Ohnishi et al[8] reported 2-year survival rates of 92% and 63% after injection of acetic acid and alcohol respectively. The specificity of acetic acid concentration from 10% to 75% needs further study. In our study 36% acetic acid was used with the following side effects: (1) transient blood pressure elevation, return to normal level within 6-7 hours automatically without special treatment; (2) dull pain in the epigastric region, particularly exacerbated in patients with peptic ulcer, which is possibly related to the stimulation of acetic acid to the gastric mucosa, and it can be alleviated by proton pump inhibitor, H-2 receptor blocker or mucosa protectant; (3) transient pain in the right upper abdomen even reactive pleural effusion for liver envelope stimulated by acetic acid exudated from liver tumor.

Few studies have focused on the treatment of PLC via percutaneous injection of chemical agents.[9] Recent investigations have suggested that the precedant 5-Fu such as capecitabine (Xelodu) could transform to cytotoxic 5-Fu on the surface of tumor cells with positive expression of platelets derived growth factor (PD-GF).[10] Moreover, PD-GF is always highly expressed in aggressive liver tumor. The present study provides the in vivo evidence that injection of 250-500 mg of 5-Fu percutaneously into the tumor once each week for 3-4 times one month after TACE combined with injection of 36% acetic acid could reduce tumor size, and serum AFP level but increase the survival rates of patients. Furthermore, no antagonism was observed between the two chemical agents. We consider that the three managements in combination is helpful in the treatment of middle and advanced stage PLC.

Competing interest

The author or authors do not choose to response to the statements listed in Instructions for Authors.

References

1 Ye SL. Present status and evaluation of interventional therapy for primary hepatocellular carcinoma. Chin J Liver Dis 2002; 10:165.

2 Xu GH, Wen HC, Li ZW, Wu HX, Chen ZZ, Chen XH, et al. Investigation on the liver treatment with transcatheter arterial chemoembolization and percutaneous acetic acid injection. Clin Radio 2002;21:66-68.

3 Zhou GL, Wang JH, Zhou KR, Yuan ZP. Intratumoral microvessel density and expression of vascular endothelial growth factor in hepatocellular carcinoma after chemoembolization. Chin J Liver Dis 2002;10:170-173.

4 Shiina S, Tagawa K, Unuma T. Percutaneous ethanol injection therapy of hepatocellular carcinoma: analysis of 77 patients. JAR 1990;15:1221-1226.

5 Palma LD. Diagnostic imaging and interventional therapy of hepatocellular carcinoma. Br J Radio 1998;71:808-818.

6 Li Q. Clinical progression of the interventional therapy of primary liver cancer. Chin Clin Dig Dis 2001;13:95-96.

7 Li SL, Lu GR, Li XF. Experimental research and clinical application on the new treatment of liver cancer – acetic acid or hot saline injection into tumor led by ultrasound. Fujian Yiyao Zazhi 2000;22:195.

8 Ohnishi K, Yoshioka H, Ito S, Fujiwara K. Prospective randomized controlled trial comparing percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma. Hepatology 1998;27:67-72.

9 Aguayo A, Patt YZ. Nonsurgical treatment of hepatocellular carcinoma. Semin Oncol 2001;28:503-513.

10 Fujieda S, Sunaga H, Tsuzuki H, Tanka N, Saito H. Expression of platelet-derived endothelial cell growth factor in oral and oropharyngeal carcinoma. Clin Cancer Res 1998; 4: 1583-1590.

Received May 6, 2003
Accepted after revision November 25, 2003