JBUON 2018; 23(3): 629-634
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Comparison of the effects of postoperative prophylactic transcatheter arterial chemoembolization (TACE) and transhepatic arterial infusion (TAI) after hepatectomy for primary liver cancer

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Summary

Purpose: *To explore the impact of transcatheter arterial chemoembolization (TACE) and transhepatic arterial infusion (TAI) on the therapeutic effect of postoperative prophylactic hepatic artery interventional therapy after hepatectomy for primary liver cancer (PLC).*

Methods: *This study was conducted on 93 patients who had undergone hepatectomy for PLC and received prophylactic interventional treatment within 1 to 3 months after hepatectomy. These patients were divided into two groups: TACE (n=50) and TAI (n=43). The TACE group was treated with lipiodol-chemotherapy drug emulsion, and the TAI group received chemotherapeutics infusion only. The differences of postoperative tumor recurrence and impact on liver function were compared between the two groups.*

Results: *There were no significant differences between the two groups with regard to sex, age, liver function Child-Pugh score, preoperative tumor size, preoperative serum alpha-fetoprotein (AFP) and other factors. Clinical overall remission rates (82 vs 76%), recurrence rates (12.2 vs 16.2%) and mean hospital stay (6.31±1.98 vs 5.98±2.02 days) of the TACE group and TAI group showed no obvious differences. However, the disease-free survival (DFS) of the TACE group was remarkably higher than that of the TAI group (23.60±3.56 vs 16.95±2.67 months). Both TACE and TAI caused transient liver dysfunction, but compared with TAI, TACE resulted in more severe liver function injury.*

Conclusions: *No significant differences between TACE and TAI groups were noticed in overall remission and recurrence rate, but TACE showed a better performance in prolonging DFS than TAI. Compared with TAI, TACE leads to more serious but transient liver dysfunction. Concerning the impact of TACE and TAI on recurrence after PLC operation, further studies are needed to reach more reliable conclusions.*

Key words: *hepatic artery interventional therapy, primary liver cancer, transcatheter arterial chemoembolization, transhepatic arterial infusion*

Introduction

Primary liver cancer (PLC) is one of the most common malignancies, ranking second in cancer-related death [1]. Each year there are globally about 550,000 new cases of PLC and about 600,000 deaths [2]. At present, hepatectomy-based surgical treatment is the preferred method for PLC treatment. However, high recurrence rate is the main factor affecting the survival of patients with PLC [3,4]. After hepatic resection, 2-year recurrence rate is 35-50% and 5-year recurrence rate is up to 61.8% [5]. For now, how to delay postoperative recurrence is one of the focuses of the combined therapy in treating PLC [6].

Transcatheter hepatic artery interventional therapy is considered to be the first choice for PLC patients who are not fit for operation and can sig-

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Received: 11/10/2017; Accepted: 05/11/2017

nificantly improve the 2-year survival rate [7,8]. At present, the proportion of patients treated with interventional therapy accounts for 61.9% of patients with hepatic carcinoma in China, and interventional therapy is the most important treatment method for patients with middle and advanced liver cancer [9]. Relevant literature shows that prophylactic hepatic artery interventional therapy can clearly help reduce the risk of recurrence after resection of PLC. Also, it can detect some small lesions that are not detected by imaging methods or during surgery via radiography, improving consequently the postoperative DFS rate [10,11]. Currently, prophylactic hepatic artery interventional therapy includes TACE and TAI [12]. However, there is still no definite conclusion about the difference between the two groups concerning the therapeutic effect after PLC resection.

This study was designed to investigate any differences between TACE and TAI on the efficacy of prophylactic hepatic arterial intervention after PLC resection so as to guide clinical treatment.

Methods

Patients

Patients with PLC who were subjected to hepatectomy and postoperative prophylactic interventional treatment at the Third Affiliated Hospital of Soochow University between June 2014 and June 2015 were enrolled. Inclusion criteria: (1) Patients aged 18-75 years, with no distant metastasis found in the preoperative imaging examinations; (2) Patients with the liver cancer lesion completely removed via surgery; (3) PLC confirmed by surgical and histopathological examination, without residual tumor cells in the surgical margins; (4) Patients that underwent prophylactic hepatic artery interventional therapy within 1-3 months after tumor resection; (5) Patients with Child-Pugh score A or B (Table 1); (6) Patients with no serious heart, lung, kidney or other organ diseases; (7) Patients with complete follow-up data, voluntarily participating in the study and providing signed informed consent. This study was approved by the ethics committee of the Third Affiliated Hospital of Soochow University.

Therapeutic methods

Prophylactic hepatic arterial interventional therapy was scheduled to be carried out within 1-3 months after the PLC surgical resection. Seldinger technique with percutaneous femoral artery puncture was adopted. Firstly, hepatic duct (Cook Company, Bloomington, IN, USA) intubation was inserted to the arteria hepatica propria to conduct conventional radiographies in order to detect possible hepatic artery variations, superior mesenteric artery, renal artery, and left gastric artery. Then, 2-3 experienced interventional radiologists repeatedly confirmed that there were no tumor blood vessels and tumor lesions (if necessary, super-selective arteriography would be applied to further determine whether there were abnormal blood vessels, and last, transcatheter hepatic artery interventional treatment was carried out. In the TACE group administered were 50-100 mg oxaliplatin and 10-20 mg epirubicin mixed with 2-4 mL lipiodol to produce the chemoembolization emulsion which was then injected via the catheter. For the TAI group, the hepatic duct was detained in the arteria hepatica propria, and TAI (50-100 mg oxaliplatin + 50 mL 5% glucose, 10-20 mg epirubicin + 50mL normal saline, 50 mL/hr) was performed by micro-pump. Postoperative management: if postoperative fever, vomiting, abdominal pain and other embolization symptoms developed, conventional symptomatic treatment such as anti-vomit drugs, analgesic drugs, anti-febrile drugs, hydrochloric acid suppression and nutritional support could be applied. Routine blood tests, liver function, blood coagulation and other examinations were repeated on the third postoperative day.

Follow up and research index

The follow-up period ended in September 2016. World Health Organization's Response Evaluation Criteria in Solid Tumors (RECIST) were used in the postoperative assessment of treatment: complete remission (CR) was defined as disappearance of arterial phase-enhanced imaging lesions plus no new lesion appearance. Partial remission (PR) was defined as reduction of arterial phase-enhanced imaging lesions diameter >30%. Clinical overall remission (OR) was the sum of CR+PR.

Confirmation of recurrence of intrahepatic lesions detected during the follow-up period and the occurrence of distant metastasis were deemed as an end event. Diagnostic criteria confirming recurrence were: B-scan

Table 1. Child-Pugh class of liver function

Tests	*1 point*	*2 points*	*3 points*
Total bilirubin (μmol/L)	<34	34–51	>51
Serum albumin (g/L)	>35	28-35	<28
Prothrombin time prolongation (s)	<4.0	4.0–6.0	>6.0
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

5-6 points define Child-Pugh A grade, 7-9 points Child-Pugh B grade, 10-15 points Child-Pugh C grade

ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), hepatic arteriography or any other imaging examination showing features of focal hepatic lesions consistent with the characteristics of PLC. If no imaging examination showed focal hepatic lesions, but the postoperative serum alpha-fetoprotein (AFP) increased again and was more than 200μg/L, recurrence after hepatectomy was also considered after excluding active liver disease or pregnancy. Furthermore, DFS was defined as the period from recurrence to surgical removal.

The differences in length of stay and DFS between the two groups were compared. At the same time, liver function tests were performed on the 3rd day before and after the operation and at the 4th week after operation. Specific tests included AST, ALT, total bilirubin (TBIL), albumin (ALB) and prothrombin time (PT).

Statistics

SPSS 22.0 software was used for statistical analyses. All quantitative data were expressed as mean±standard deviation, using independent t-test samples. Paired t-test was applied for changes in various liver function indicators before and after interventional therapy. Percents were used to express the numerical data and x^2 test to assess and compare differences. Kaplan-Meier method was used for plotting survival curves and Log-rank test was employed to compare survival between the two groups. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of baseline characteristics of patients between the two groups before the interventional therapy

A total of 93 patients met the inclusion criteria, including 75 males and 18 females, aged 26-73 years. These patients were distributed into the TACE group (n=50) and the TAI group (n=43) based on the drugs used in the intervention. There were no significant differences between the groups in age, sex, preoperative liver function Child-Pugh score, AFP level, number of lesions, tumor diameter, vessel cancer embolus and grade of tumor differentiation (Table 2).

Table 2. Preoperative baseline data of patients in the two groups (mean±SD)

Data	*Number of cases*	*TACE group*	*TAI group*	*p value*
Age, years				0.507
≤50	55	28	27	
>50	38	22	16	
Gender				0.486
Male	75	39	36	
Female	18	11	7	
Child-Pugh classification				0.114
A	81	41	40	
B	12	9	3	
AFP, ng/ml				0.954
≤200	30	16	14	
>200	63	34	29	
Number of tumor lesions				0.883
1	62	33	29	
>1	31	17	14	
Tumor capsule				0.726
Complete	58	32	26	
Incomplete	35	18	17	
Tumor diameter, cm				0.911
≤5	46	25	21	
>5	47	25	22	
Cancer vessel embolus				0.713
Yes	50	26	24	
No	43	24	19	
Tumor differentiation				0.563
I	19	12	7	
II	27	15	12	
III	47	23	24	

Effects of the two ways of intervention on the therapeutic effect and recurrence of disease

The clinical OR rate was 82.0% in the TACE group and 76% in the TAI group (p>0.05). During follow-up, 13 cases recurred, of which, 8 were intrahepatic recurrences and another 5 cases were intrahepatic recurrences plus distant metastases. Six cases (12.20%) of recurrence were found in the TACE group within 1 year after the operation and 7 cases (16.2%) of recurrence were found in the TAI group (p>0.05) (Table 3).

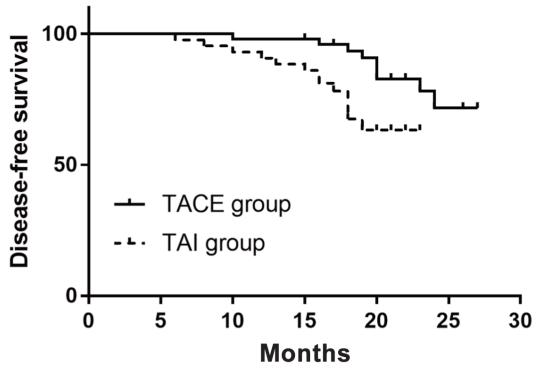

Figure 1. Kaplan-Meier disease-free survival of patients in the TACE group and TAI group (p=0.026).

The mean hospital stay of the TACE group was 6.31±1.98 days and of the TAI group 5.98±2.02 days (p>0.05) (Table 4). The mean DFS was 23.60±3.56 months in the TACE group and 16.95±2.67 months in the TAI group, favoring significantly the TACE group (p=0.034; Figure 1; Table 4).

Results of comparisons on liver function between the two groups

There were no significant differences between the two groups regarding the preoperative levels of AST, ALT, TBIL, ALB and PT. In the TACE group, the levels of AST, ALT, TBIL and PT were significantly increased 3 days after the operation. All tests returned to preoperative levels after 4 weeks. Similarly, after 3 postoperative days, the levels of AST, ALT and TBIL levels in the TAI group were clearly higher than those before the operation, ALB level was significantly lower than that before

Table 3. Comparison of clinical effects between the two groups

Group	*Number of cases*	*Overall remission, n (%)*	*Recurrence, n (%)*
TACE	50	41 (82.0)	6 (12.0)
TAI	43	33 (76.7)	7 (16.2)
p value	-	0.531	0.553

Table 4. Comparison of hospital stay and disease-free survival between the two groups (mean±SD)

Group	*Number of cases*	*Hospital stay (days)*	*Disease-free survival (months)*
TACE	50	6.31±1.98	23.60±3.56
TAI	43	5.98±2.02	16.95±2.67
p value	-	0.531	0.026

Table 5. Comparison of postoperative liver function data between the two groups (mean±SD)

Parameters	*Time*	*TACE*	*TAI*	*p value*
AST (U/L)	3 days preoperative	43.59±14.14	45.33±15.79	>0.05
	3 days postoperative	118.94±93.46	68.26±40.69	<0.05
	4 weeks postoperative	36.31±12.72	40.11±13.09	>0.05
ALT (U/L)	3 days preoperative	42.83±19.65	45.22±22.47	>0.05
	3 days postoperative	106.69±68.76	90.28±48.50	<0.05
	4 weeks postoperative	43.26±25.51	48.73±20.38	>0.05
TBIL (μmol/L)	3 days preoperative	23.42±12.53	20.46±10.05	>0.05
	3 days postoperative	37.11±18.25	25.51±9.36	<0.05
	4 weeks postoperative	23.65±13.81	19.06±10.30	>0.05
ALB (g/l)	3 days preoperative	38.55±6.29	39.25±6.93	>0.05
	3 days postoperative	34.26±5.06	35.63±5.89	>0.05
	4 weeks postoperative	39.58±6.75	39.95±5.76	>0.05
PT (s)	3 days preoperative	14.98±1.27	14.63±1.06	>0.05
	3 days postoperative	15.26±1.49	14.79±1.93	<0.05
	4 weeks postoperative	14.12±1.19	14.46±1.08	>0.05

the operation, and there was no significant difference in PT level; after 4 weeks, all tests returned to preoperative levels. In addition, compared with TAI, TACE had a greater impact on liver function, mainly represented by increased AST, ALT and TBIL. In summary, both interventional therapies caused transient liver dysfunction, but TACE led to more severe liver damage than TAI. However, liver function recovered to normal range within 4 weeks after liver operation (Table 5).

Discussion

Surgical resection is an effective method for the treatment of early liver cancer, but its long-term effect is not satisfactory [13], especially with regard to recurrences. The causes of postoperative recurrences are connected with the disease biological characteristics [14]. Cellular adhesion molecules are secreted confinuously by tumor cells and enter the blood circulation and the surrounding organs, thus leading to tumor recurrence [15]. In order to reduce the recurrence rate, authors recommend to carry out the preoperative interventional therapy, but some others believe that this will delay the time to operation, and may offer a chance for tumor cell for shedding and dissemination although tumor necrosis is achieved [16]. How to inhibit or kill these small intrahepatic foci is an important issue to improve the postoperative DFS rate and to also improve the efficacy of surgery, especially the long-term efficacy.

A meta-analysis evaluated 4 modes of treatment after hepatectomy for liver cancer: preoperative TACE, postoperative TACE, systemic chemotherapy and systemic chemotherapy plus TACE. The results showed that only postoperative TACE can significantly improve the 1-, 2- and 3-year survival rates and reduce the recurrence rate [17].

Two postoperative preventive hepatic artery interventional treatments were compared in this study, and the results showed that TACE and TAI contributed to the improvement of long-term efficacy after hepatectomy for liver cancer and no clear differences existed between TACE and TAI over clinical OR rate, recurrence rate and postoperative hospital stay. However, DFS in the TACE group was significantly better than that of the TAI group, and the hospital stay between the two groups showed no statistical significance, indicating that TACE did not increase the hospital stay while improving the postoperative therapeutic effect.

Some reports have indicated that postoperative prophylactic hepatic artery intervention may lead to different degrees of liver dysfunction of patients with liver cancer, but death caused by liver function injury due to TACE or TAI is rare [18]. AST, ALT, ALB, TBIL and PT reflect the degree of liver function damage to a certain extent. The results of this study showed that AST, ALT and TBIL were significantly increased in both TACE and TAI groups and ALB decreased significantly compared with that before operation and 3 days after the operation, but there was no obvious difference in PT level between TACE group 3 days after operation, and all tests returned to preoperative levels after 4 weeks. Compared with TAI, TACE had a greater damaging effect on liver function, mostly showing increase in AST, ALT and TBIL. There are many reports on changes in short-term liver function after hepatic artery intervention therapies in China and abroad, and the main trends are: 1) After treatment, serum ALT and AST are significantly raised in 1-3 days, start to decline after 1 week, and become normal in 2-3 weeks; 2) After treatment, serum TBIL raises in 24 hrs, reaches the peak in 10-14 days, and return to preoperative levels within 30 days [19,20]. The results of this study are approximately identical with the above change rules.

The limitations of our study are as follows: 1) This study included a small number of patients and risk factors for recurrence after liver cancer resection were not analyzed (i.e. impact of liver function Child-Pugh score, preoperative tumor diameter, preoperative AFP level, number of tumor lesions, cancer vessel embolus and grade of tissue differentiation). 2) The follow-up time was short and therefore further long-term follow-up studies of the effects of TACE and TAI on recurrence after hepatectomy for liver cancer are needed.

Conclusions

DFS of patients may be prolonged by performing transcatheter hepatic artery interventional treatment within 1-3 months after the surgical removal of PLC. OR and recurrence rates in the TACE and TAI groups do not differ significantly, but TACE is better in prolonging DFS than TAI. TACE causes more serious transient liver damage to patients when compared with TAI. Comparison of the influence of TACE and TAI on the recurrence after liver cancer operation needs to be further studied.

Acknowledgement

This study was supported by Changzhou High-Level Medical Talents, Training Project (No 2016CZBJ044).

Conflict of interests

The authors declare no conflict of interests.

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