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Uninfluenced alpha-fetoprotein and treatment of liver primary carcinoma by lobaplatin in combination with 5-fluorouracil and doxorubicin via chemoembolization and transarterial chemoembolization

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Abstract: Alpha-fetoprotein (AFP) is a protein encoded by the *AFP* gene and normally produced by the fetus. The purpose of this study is to investigate the efficacy of lobaplatin in combination with 5-fluorouracil (5-FU) and doxorubicin on AFP and treatment of primary carcinoma of the liver by transhepatic arterial chemotherapy and embolization (TACE). Patients with primary carcinoma of the liver who took the TACE for treatment were enrolled in this study and divided randomly into the research group and the control group. Patients in the research group adopted the TACE in combination with lobaplatin, while those in the control group took cisplatin instead in combination with TACE. We compared the baseline data, hepatic indicators before treatment and after 1 month of treatment, efficacy and the incidence rates of adverse events after TACE between two groups. Differences in the baseline data, including Child-pugh grade, type of liver cirrhosis, KPS scores and AFP showed no statistical significance (P >0.05). Before the treatment, we identified no significant differences in the comparison of ALT, AST, TBiL and ALB between two groups (P >0.05), while significant differences emerged after treatment (P <0.05). Also, efficacy comparison revealed the significant difference between the two groups (P <0.05). After TACE, patients in the research group reported 1 case of nausea, 1 of vomiting and 1 of necrotic absorption fever, and those in the control group reported 3 cases of nausea, 5 of vomiting and 4 of necrotic absorption fever, with a significant difference in comparison of the incidence rates (P <0.05). TACE is a promising strategy for the treatment of primary carcinoma of the liver, while lobaplatin, as the 3rd generation of anti-tumor platinum-based drugs, is less toxic than cisplatin, but excels in efficacy.

Key words: Lobaplatin; TACE; Liver cancer; Clinical efficacy.

Introduction

Alpha-fetoprotein or alfa fetal protein (AFP) is a protein encoded by the *AFP* gene and normally produced by the fetus. It is normal for adults to have AFP levels below 10 ng/mL. High levels of AFP in the blood (greater than 500 ng / mL) may be a sign of liver tumors. High levels of AFP may mean other cancers, including Hodgkin's disease, lymphoma, and renal cell carcinoma (1, 2).

Primary carcinoma liver is the most common malignancy in China. According to the latest survey report, the annual mortality rate of patients with primary carcinoma of the liver in China has attained 20.37/100,000, occupying the second place in malignancy-led death, only secondary to the lung cancer in the urban region, and gastric cancer in the rural region (3, 4). Conventionally, surgical resection is preferred in the treatment of liver cancer, but only suitable for the patients in the good status of heart and lung functions, limited range of tumor and with no metastasis, instead of all patients. Moreover, prior to the primary carcinoma of the liver, the majority of patients in China reported a history of hepatitis or liver cirrhosis. Therefore, about 80% of patients are not eligible for surgical resection (5, 6). As such, various non-surgical treatment methods have been developed, whereas the selection of methods should be based on the condition of patients. Currently, TACE, as the widely-accepted non-surgical method for treatment of primary carcinoma of the liver (7), can induce the thrombosis in the hepatic artery that nourishes the tumors, resulting in the local ischemic necrosis of tumor nodes, or suppressing the growth of tumors; blocking the blood supply to the tumors also deteriorates the blood supply to the healthy liver tissues (8, 9). Cisplatin, as the traditional platinum-based drug, excels in killing tumor cells but gives rise to a variety of problems, including the side effect. Lobaplatin is the 3rd generation platinum-based anti-tumor drugs, with a wider anti-tumor spectrum, better solubility and lower toxicity (10, 11).

Thus, we aimed to elucidate the therapeutic value

of lobaplatin by analyzing the data of patients with primary carcinoma of patients who took TACE between February 2017 and January 2019, and detailed information is reported as follows. In addition, the AFP level has been evaluated else.

Materials and Methods

Data and methods

General data

A retrospective analysis was conducted with the data collected from the patients with primary carcinoma of the liver who underwent TACE in this hospital between February 2017 and January 2019. The diagnosis was further validated by the enhanced liver CT and laboratory test of AFT, and all patients were classified into the Stage II or III by TNM staging criteria, conforming to the indications of TACE. They were then randomized into the research group (lobaplatin + TACE) and control group (cisplatin + TACE), with 60 patients in each group. In the research group, there were 35 males and 25 females, with an average age of (60.25±5.74) years; among them, there were 22 with bulky tumors, 26 with nodular tumors and 12 with diffusive tumors. In the control group, there were 32 males and 28 females, with an average age of (61.72±6.25) years; among them, there were 24 with bulky tumors, 25 with nodular tumors and 11 with diffusive tumors. Differences between the baseline data showed no statistical significance (P >0.05).

Inclusive and exclusive criteria

Inclusive criteria: 1) Patients with tumor diameter smaller than 8 cm as indicated by imaging examination; 2) Patients with the pathological examination result; 3) Patients with estimated survival period for 3 months or longer.

Exclusive criteria: 1) Patients with severe dysfunction in key organs, like heart, brain, liver and kidney; 2) Patients with poor tolerance of TACE.

Treatment

Prior to the TACE, patients underwent the skin test of iodine sensitivity, with muscle injection of atropine, phenobarbital and pethidine. Under the local anesthesia, modified Seldingger was performed for percutaneous puncture of femoral artery, followed by the arteriography of celiac artery, or mesenterium if necessary to observe the distribution of aorta abdominal branches and the blood supply to the tumor tissues, and guide the insertion of the catheter tip into the target arteries. Thereafter, TACE was performed: Patients in the control group took cisplatin (60mg/m^2), 5-fluorouracil (1.5 g/m^2) and doxorubicin (50 mg/m^2) in combination with iodinated oil (10 to 30 mL); those in the research group took lobaplatin (50mg/m^2), 5-fluorouracil (1.5g/m^2) and doxorubicin (50mg/m^2) in combination with iodinated oil (10 to 30 mL). Following TACE, patients received the corresponding therapies for anti-inflammation, anti-infection, liver protection, stomach-settling and painkilling.

Observation indexes

Observation indexes included the baseline clinical data, hepatic indicators before treatment and after 1 month of treatment, and the incidence of adverse reactions after TACE.

Clinical data

Clinical data included the Child-pugh grade, type of liver cirrhosis, KPS score and AFP level.

Hepatic indicators

Hepatic indicators included the levels of ALT, AST, TBiL and ALB.

Efficacy evaluation

As per the Response Evaluation Criteria in Solid Tumors (RECIST) (8), patients were categorized into the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). CR: No targeted lesions; PR: Longitudinallength of baseline lesion was shortened by 30%; SD: Shrinkage of baseline lesions was found but not reached the criteria of PD; PD: Increase in the longitudinal length of baseline lesion by 20% or the emergence of new lesions.

Statistical methods

Statistical analysis of data was performed by the use of SPSS 19.0 software. Measurement and enumeration data were compared by t-test or chi-square test, respectively. The difference at P <0.05 was thought statistically significant.

Results

Comparison of the AFP level and baseline clinical data between two groups

No statistical significance was shown in differences of the baseline clinical data of patients between two groups, including Child-Pugh grades, type of liver cirrhosis, KPS scores and AFP (P >0.05; Table 1).

Comparison of the hepatic indicators before treatment and after 1 month of treatment between two groups

Statistical significance of the differences in levels of ALT, AST, TBiL and ALB were only found after treatment (P <0.05), but not identified before treatment (P

Table 1. Comparison of the baseline clinical data between two groups (mean ± standard deviation)

Group	Child-pugh grades		Type of liver cirrhosis		KPS score	AFP (μg/L)
	Grade A	Grade B	Hepatitis B	Schistosomiasis		
Research group	52	2	40	4	76.36±12.55	658.33±128.53
Control group	50	5	37	2	77.03±12.38	679.39±133.59
t/χ^2	0.94		0.66		0.48	0.15
P	>0.05		>0.05		>0.05	>0.05

Table 2. Comparison of the hepatic indicators before treatment and after 1 month of treatment between two groups (mean ± standard deviation).

Group	ALT(U/L)		AST (U/L)		TBiL (μmol/L)		ALB (g/L)	
	Before treatment	At 14 d after treatment	Before treatment	At 14 d after treatment	Before treatment	At 14 d after treatment	Before treatment	At 14 d after treatment
Research group	32.4±2.6	42.4±3.5	67.4±5.0	45.0±2.0	28.2±2.6	17.4±3.0	31.1±3.1	37.3±4.4
Control group	32.8±3.0	35.7±3.4*#	68.0±5.1	51.4±3.7*#	28.0±2.4	23.6±2.6*#	32.2±3.2	33.5±4.0*#

Note: *P <0.05 *vs.* the levels before treatment; #P <0.05 *vs.* the control group at the same time point.

Table 3. Comparison of the efficacy between two groups [n (%)].

Group	CR	PR	SD	PD	Total effectiveness rate
Research group	4(6.67)	35(58.33)	12(20.00)	9(15.00)	39(65.00)
Control group	0	18(30.00)	24(40.00)	18(30.00)	18(30.00)
t/χ^2					5.76
P					<0.05

>0.05; Table 2).

Comparison of the efficacy between two groups

The difference in comparison of the efficacy between the two groups showed statistical significance (P <0.05; Table 3).

Comparison of the incidence rates of post-TACE adverse reactions between two groups

After TACE, patients in the research group reported 1 case of nausea, 1 of vomiting and 1 of necrotic absorption fever, and those in the control group reported 3 cases of nausea, 5 of vomiting and 4 of necrotic absorption fever, with a significant difference in comparison of the incidence rates (P <0.05).

Discussion

Primary carcinoma of the liver is the fifth most common malignancy in the world and also the most common malignancy in China. In China, almost 80% of patients with primary carcinoma of the liver have progressed into the middle or advanced stage, gaining no opportunity for surgical resection (9). Previously, radical resection of liver tumors dominated the treatment of liver cancer, which, however, resulted in a high 2-year recurrence rate of 35% to 50% as indicated by the in-depth research. Thus, TACE is gradually promoted in clinical practice (10).

The first use of TACE in the treatment of liver cancer was firstly reported in 1975 and has gradually applied as the most common method for interventional therapy of primary carcinoma of the liver, especially suitable for the elder patients in the middle or advanced stage. Generally, TACE is performed by intubation via femoral artery puncture to inject the chemotherapeutics directly towards the tumors, thereby blocking the arteries responsible for blood supply to the tumors (11, 12). Traditional drugs used in TACE include cisplatin-based drugs, doxorubicin and 5-FU, which, however, make patients more susceptible to adverse reactions, like hematotoxicity or responses of the gastrointestinal tract (13).

Modern technique benefits the lobaplatin by lowering the toxicity. In this study, after TACE, patients in the research group reported 1 case of nausea, 1 of vomiting and 1 of necrotic absorption fever, and those in the control group reported 3 cases of nausea, 5 of vomiting and 4 of necrotic absorption fever, with the significant difference in comparison of the incidence rates (P <0.05). Likewise, it is reported (14) that in 40 patients, TACE in combination with lobaplatin manifested efficacy superior to that of the traditional strategies, with lower incidence rates of responses in gastrointestinal tract and damages to liver and kidney. Meanwhile, the statistical significance of the differences in levels of ALT, AST, TBiL and ALB were only found after treatment (P <0.05), but not identified before treatment (P >0.05). The difference in comparison of the efficacy between the two groups showed statistical significance (P <0.05). Thus, the administration of lobaplatin can enhance the anti-tumor efficacy, while alleviating the general toxic or side-effect. Besides, it is demonstrated that lobaplatin can prevent the recurrence of minimal lesions. Overall, cancer is a multi-faceted issue (15-20).

In conclusion, TACE is a promising strategy for the treatment of primary carcinoma of the liver, while lobaplatin, as the 3rd generation of anti-tumor platinum-based drugs, is less toxic than cisplatin, but excels in efficacy.

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