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ORIGINAL ARTICLE

Effects of TACE combined with microwave ablation on T lymphocyte subsets and prognosis in patients with liver cancer and analysis of safety

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Summary

Purpose: *To explore the influence of transcatheter hepatic arterial chemoembolization (TACE) combined with microwave ablation on T lymphocyte subsets and prognosis in patients with liver cancer and analyze the safety.*

Methods: *The clinical data of 160 patients were retrospectively analyzed. The patients in the control group underwent TACE, while those in the observation group were treated with microwave ablation in addition to TACE. Then, the changes in the levels of T lymphocyte subsets, liver function indexes and alpha-fetoprotein (AFP) before and after treatment were compared between the two groups.*

Results: *After treatment, the levels of cluster of differentiation 3$^+$ (CD3$^+$), CD4$^+$ and CD4$^+$/CD8$^+$ of patients were significantly increased in both groups, while the levels of CD8$^+$ and serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and AFP were overtly lowered, while the observation group had more obvious changes in the above-mentioned levels ($p<0.05$). The response rate and prognostic survival rate were evidently higher in the observation group than in the control group ($p<0.05$). The complications after treatment showed no significant difference between the two groups ($p>0.05$). Child-Pugh, tumor diameter and number of lesions were independent risk factors for the prognosis of survival of liver cancer patients undergoing TACE combined with microwave ablation ($p<0.05$).*

Conclusions: *TACE combined with microwave ablation has relatively high efficacy and safety in the treatment of liver cancer, which can improve liver function, immune function and prognostic survival.*

Key words: *TACE, microwave ablation, liver cancer, T lymphocyte subsets, safety, prognosis*

Introduction

Liver cancer, the most common malignancy in clinical practice [1], ranks top three in terms of morbidity and mortality rates, severely affecting human health and life [2]. As to the treatment of liver cancer, surgery is a preferred option, but the optimal timing of surgery is missed since patients tend to be at the middle or advanced disease stage and have tumor metastasis once the diagnosis is made due to its insidious early onset [3]. For the non-surgical palliative treatment methods for liver cancer in the clinic, transcatheter hepatic arterial chemoembolization (TACE) is the first choice at present, which achieves relatively poor therapeutic effect in treating multiple diffuse liver cancer and unresectable liver cancer caused by poor basic liver function [4]. However, TACE cannot completely kill tumor cells, and metastasis or relapse is easy to occur [5]. Besides, nowadays, a hot issue in clinical

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treatment is to seek combined treatment methods drawing on each other's strengths synergistically, to maximize the efficacy and improve the prognosis of patients. Therefore, in this study, the effects of TACE combined with microwave ablation on T lymphocyte subsets and prognosis of patients with liver cancer were investigated, and its safety was analyzed, so as to provide a reference for the diagnosis and treatment of liver cancer in the clinic.

Methods

General data

The clinical data of 160 patients treated in our hospital from February 2015 to February 2017 were retrospectively analyzed. In addition, these 160 patients were divided into control group (n=60) and observation group (n=100) based on different treatment methods. The general patient data showed no significant differences between the two groups, which were comparable ($p>0.05$) (Table 1). The patients in the observation group were subdivided into 12-month group (n=90) and 24-month group (n=67) in accordance with their prognostic survival to compare the factors influencing the prognostic survival of patients between the two groups. This study was approved by the Ethics Committee of our hospital. Signed written informed consents were obtained from all participants before the study entry.

Diagnostic criteria

The specific diagnostic criteria were [6]: 1) clinical manifestations of liver cancer and extrahepatic metastasis of cancer cells or visible bloody ascites; 2) alpha-fetoprotein (AFP) <400 μg/L, without metastatic liver cancer, active liver disease, reproductive embryonal tumor and pregnancy and with characteristics and at least two positive markers of liver cancer (CA19-9, AFU, GGTII, DCP, etc.) confirmed *via* one imaging examination or space-occupying lesions with characteristics of liver cancer verified through at least two imaging examinations; and 3) AFP >400 μg/L, without metastatic liver cancer, active liver disease, reproductive embryonal tumor and pregnancy, and with characteristics or space-occupying lesions with touchable large knots and hard and swollen masses of liver cancer. Liver cancer was graded as per the relevant criteria of the Child-Pugh classification [7].

Inclusion and exclusion criteria

Inclusion criteria: 1) patients meeting the above diagnostic criteria; 2) those without previous chemotherapy or radiotherapy; 3) those with an expected survival of no less than 3 months; and 4) those who signed the informed consent. Exclusion criteria: 1) patients with hematological disorders or immune system or infection; 2) those complicated by other tumors; or 3) those complicated by severe cardiopulmonary or renal dysfunction.

Methods

TACE was adopted for the patients in the control group. Under local anesthesia, the femoral artery was percutaneously punctured, followed by insertion and radiography of the superior mesenteric artery and celiac trunk using a digital subtraction angiography (ASI-2000, Guangzhou Aisui Technology Co., Ltd., Guangzhou, China) to analyze the blood supply to the liver of patients and

Table 1. Comparisons of baseline data between two groups of patients

	Control group (n=60)	*Observation group (n=100)*	*t/x²*	*p*
Age (years old)	40-75	41-75		
Average age (years old)	50.32±5.93	50.45±6.06	0.132	0.447
Male/female	49/11	85/15	0.306	0.580
BMI (kg/m²)	23.14±1.25	23.21±1.19	0.353	0.362
Tumor diameter, cm [n(%)]				
≤3	16 (26.67)	26 (26.00)	0.015	0.992
3-5	33 (55.00)	55 (55.00)		
≥5	11 (18.33)	19 (19.00)		
Tumor site [n(%)]				
Left lobe of liver	25 (41.67)	40 (40.00)	0.143	0.931
Right lobe of liver	21 (35.00)	34 (34.00)		
Left and right lobes of liver	14 (23.33)	26 (26.00)		
Number of lesions [n(%)]				
Single	43 (71.67)	69 (69.00)	0.127	0.722
Multiple	17 (28.33)	31 (31.00)		
Child-Pugh grade [n(%)]				
A	37 (61.67)	62 (62.00)	0.002	0.999
B	17 (28.33)	28 (28.00)		
C	6 (10.00)	10 (10.00)		

clarify the relevant tumor nourishing arteries. Next, the above-mentioned tumor nourishing arteries were selectively inserted, and 10 mL of gelatin sponge, 10 mL of fluid lipiodol and 100 mg of oxaliplatin (NMPN H20050962, specifications: 100 mL: 1 g, Hengrui Medicine, Lianyungang, China) were injected thereinto. After treatment, radiography was conducted again to evaluate the effect of embolization. Embolization was performed for about 2 times at an interval of 1 month according to the condition of the patients. The patients in the observation group were additionally treated with microwave ablation 7 days after TACE. Appropriate position was taken in accordance with the different sites of liver cancer, the puncture point was determined through computed tomography (CT), and puncture was carried out in the minimal path under the premise of avoiding the gastrointestinal tract, gallbladder and large blood vessels. The time and power of microwave (KY-2000 microwave ablation therapy instrument, Nanjing Kangyou Microwave Energy Application Research Institute, Nanjing, China) were adjusted based on diverse tumor sizes of patients with liver cancer. The microwave power was set to 40-60 W, and the action time was set to 5-8 min. Thereafter, normal saline was intermittently injected into the lesions of patients to maintain the ablation range at about 10 mm from the edge of the tumor. Additionally, the region of microwave ablation was kept spherical as far as possible. After microwave ablation, ablation therapy was employed for pin site to avoid the transfer of the pin site, and bed rest was needed.

Observation indicators

1) Determination of levels of T lymphocyte subsets: Fasting venous blood (5 mL) was sampled at 8 o'clock in the morning before and after treatment and centrifuged at 3000 r/min for 10 min, and the supernatant was collected and stored at -80°C for later use. Then, a flow cytometer was used to measure the levels of serum cluster of differentiation 3^+ ($CD3^+$), $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$. 2) Detection of liver function indexes: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured using an automatic biochemical analyzer (AU5800, Beckman Coulter, Miami, FL, USA). 3) Measurement of serum AFP: serum AFP level was determined *via* enzyme-linked immunosorbent assay (ELISA) using a kit (Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) in strict accordance with the instructions.

Criteria for efficacy evaluation

The efficacy was assessed based on the WHO Response Evaluation Criteria In Solid Tumors (RECIST) [8]. Overall response rate = (CR + PR) / total number ×100%.

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. Measurement data were expressed as mean±standard deviation and subjected to *t*-test. Enumeration data were expressed as n (%), and x^2 test or Fisher exact probability test were employed for the comparison. Log-rank test was utilized for univariate analysis. Survival curves were plotted according to Kaplan-Meier method, while log-rank test was used to compare survival differences between groups and the Cox proportional hazard model for multivariate analysis. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of changes in levels of T lymphocyte subsets before and after treatment between the two groups of patients

After treatment, the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were notably elevated, while the $CD8^+$level declined obviously in both groups of patients. Besides, the changes in the above levels were more pronounced in the observation group ($p<0.05$) (Table 2).

Comparisons of changes in liver function indexes and AFP between the two groups of patients before and after treatment

The levels of serum ALT, AST and AFP were remarkably lowered in both groups after treatment, and the decreases in the above indicators were more significant in the observation group ($p<0.05$) (Table 3).

Comparison of incidence rate of complications after treatment between the two groups of patients

The incidence rate of complications (abdominal pain & diarrhea, nausea & vomiting and fever)

Table 2. Comparisons of changes in T lymphocyte subset levels before and after treatment between two groups of patients

Group	*Time*	*$CD3^+$*	*$CD4^+$*	*$CD8^+$*	*$CD4^+/CD8^+$*
Control group (n=60)	Before treatment	61.32±10.61	27.32±10.15	31.98±12.63	1.14±0.69
	After treatment	65.63±11.35	32.08±11.20	27.66±11.32	1.48±0.72
Observation group (n=100)	Before treatment	60.98±10.66	27.06±10.33	32.15±12.74	1.26±0.74
	After treatment	69.82±11.69	38.69±11.43	23.45±9.68	1.96±0.92
$t/p_{\text{in control group}}$		1.861/0.033	2.113/0.019	1.709/0.046	2.287/0.012
$t/p_{\text{in observation group}}$		3.748/0.000	5.064/<0.001	3.648/0.000	3.977/<0.001
$t/p_{\text{between groups after treatment}}$		1.725/0.044	2.771/0.003	1.896/0.031	2.756/0.004

exhibited no statistically significant difference between the two groups of patients after treatment ($p>0.05$) (Table 4).

Comparison of clinical efficacy between the two groups of patients

The response rate was markedly higher in the observation group than that in the control group, showing a statistically significant difference (87.00% *vs.* 56.67%, $p<0.05$) (Table 5).

Comparison of prognostic survival rate between the two groups of patients

Compared with that in the control group, the survival rate of patients at 6 months, 12 months, 18 months and 24 months was prominently raised in the observation group, and the difference was statistically significant ($p<0.05$) (Table 6).

Univariate analysis of prognosis of patients in the observation group

According to Log-rank test performed for the univariate analysis of the prognosis of patients in the observation group, Child-Pugh grade, tumor diameter, number of lesions and AFP before treatment were dramatically related to prognostic survival ($p<0.05$) (Table 7).

Multivariate analysis of prognosis of patients in the observation group

Multivariate analysis by Cox regression revealed that Child-Pugh, tumor diameter and number of lesions were independent risk factors for the prognostic survival of patients with liver cancer receiving TACE combined with microwave ablation ($p<0.05$) (Table 8).

Discussion

For patients with liver cancer, the clinical treatment is generally limited by tumor size and site as well as liver function, and it is difficult to perform surgical resection. Moreover, the surgery is invasive, with few postoperative complications but a poor response rate [9]. TACE, a common method for the treatment of liver cancer in the clinic,

Table 3. Comparisons of changes in liver function indexes and AFP between two groups of patients before and after treatment

Group	*Time*	*ALT (U/L)*	*AST (U/L)*	*AFP (ng/L)*
Control group (n=60)	Before treatment	64.87±13.75	75.98±15.63	341.25±23.65
	After treatment	36.88±7.93	42.55±10.22	162.87±15.36
Observation group (n=100)	Before treatment	65.19±13.62	74.06±15.79	342.58±23.55
	After treatment	26.37±6.55	31.58±9.64	71.02±10.27
$t/p_{\text{in control group}}$		11.829/<0.001	13.455/<0.001	48.977/<0.001
$t/p_{\text{in observation group}}$		17.231/<0.001	15.403/<0.001	105.699/<0.001
$t/p_{\text{between groups after treatment}}$		6.855/<0.001	5.238/<0.001	45.297/<0.001

Table 4. Comparison of incidence rate of complications after treatment between two groups of patients

Group	*Abdominal pain & diarrhea n (%)*	*Nausea & vomiting n (%)*	*Fever n (%)*
Control group (n=60)	15 (25.00)	55 (91.67)	37 (61.67)
Observation group (n=100)	23 (23.00)	90 (90.00)	63 (63.0)
x^2	0.083	0.123	0.028
p	0.774	0.726	0.866

Table 5. Comparison of clinical efficacy between two groups of patients

Group	*PD n (%)*	*SD n (%)*	*PR n (%)*	*CR n (%)*	*Response rate n (%)*
Control group (n=60)	7 (11.67)	19 (31.67)	15 (25.00)	19 (31.67)	34 (56.67)
Observation group (n=100)	2 (2.00)	11 (11.00)	24 (24.00)	63 (63.00)	87 (87.00)
x^2					18.718
p					<0.001

Table 6. Comparison of prognostic survival rate between two groups of patients

Group	*At 6 months* *n (%)*	*At 12 months* *n (%)*	*At 18 months* *n (%)*	*At 24 months* *n (%)*
Control group (n=60)	53 (88.33)	46 (76.67)	40 (66.67)	24 (40.00)
Observation group (n=100)	98 (98.00)	90 (0.00)	82 (82.00)	67 (67.00)
x^2	4.906	5.229	4.869	11.146
p	0.027	0.022	0.027	0.001

Table 7. Univariate analysis of prognosis of patients in the observation group

Factor	*n*	*Survival rate (%)*		x^2	*p*
		12-month group (n=90)	*24-month group (n=67)*		
Child-Pugh grade					
A	62	62 (100.00)	57 (91.94)	6.750	0.034
B	28	24 (85.71)	10 (35.71)		
C	10	4 (40.00)	0 (0.00)		
Tumor diameter (cm)					
≤3	26	25 (96.15)	23 (88.46)	6.729	0.035
3-5	55	51 (92.73)	42 (76.36)		
≥5	19	14 (73.68)	2 (10.53)		
Tumor site, n (%)					
Left lobe of liver	40	36 (90.00)	26 (65.00)	0.035	0.983
Right lobe of liver	34	31 (91.18)	24 (70.59)		
Left and right lobes of liver	26	23 (88.46)	17 (65.38)		
Number of lesions, n (%)					
Single	69	64 (92.75)	60 (86.96)	7.868	0.005
Multiple	31	26 (83.87)	7 (22.58)		
AFP before treatment (ng/L)					
≤250	61	58 (95.08)	53 (86.89)	3.985	0.046
>250	39	32 (82.05)	14 (35.90)		

Table 8. Multivariate analysis of prognosis of patients in the observation group

Factor	*β*	*RR*	*Wald*	*95% CI*	*p*
Child-Pugh	2.524	9.869	4.253	1.315-76.842	0.004
Tumor diameter	3.748	8.069	3.310	1.023-35.869	0.016
Number of lesions	4.213	7.698	4.325	1.169-45.698	0.007
AFP before treatment	11.845	6.486	1.635	0.729-31.057	0.748

blocks the blood supply to the tumor and injects chemotherapy drugs to kill or inhibit tumor cells [10]. A study conducted by Wang et al [11] pointed out that TACE applied in treating patients with middle or advanced liver cancer achieves a relatively high tumor control rate, objective response rate and survival rate at early stage, but a downward response rate and control rate at late stage, with an average survival of about 11 months. The results of this study showed that the clinical efficacy and survival rate of patients in the control group treated with TACE alone were improved to some extent, but the effect was poor. This may be because the TACE alone cannot completely block the blood vessels supplying the tumor, easily promoting the formation of collateral circulation, and, moreover, vascular occlusion, tumor blood deficiency, intra-arteriovenous fistula and other factors will accelerate the loss of chemotherapy drugs, leading to residual lesions and reducing the therapeutic effect [12].

ALT and AST, liver function indexes, effectively reflect the severity of liver injury in patients with liver cancer, and there is a certain relationship between the level of liver function indicators and liver injury [13]. Cellular immunity is the important anti-tumor immunity in the immune system of the body. $CD4^+$ is able to activate NK cells and macrophages by releasing the corresponding cytokines, thus exerting the effect of anti-tumor immunity. $CD3^+$, a membrane molecule on the surface of mature T lymphocytes, is capable of effectively reflecting the total amount of T lymphocytes in the peripheral blood. $CD8^+$ can directly kill tumor cells through apoptosis and cell lysis, and $CD4^+/CD8^+$ plays a vital role in maintaining body immune function and regulating cellular immunity [14]. The level of AFP, a substance formed during fetal development, is low in normal human body, and has a certain association with tumor size, which is one of the important markers for clinical screening of tumors [15]. In this study, the observation group treated with combination therapy had more pronounced improvements in the levels of T lymphocyte subsets, liver function indexes and AFP, and a relatively high prognostic survival rate and response rate. This is mainly because TACE effectively blocks the arteries supplying blood to the tumor and effectually ameliorates the "thermal precipitation" generated during microwave ablation, thereby greatly widening the range of microwave ablation. TACE has a good effect in treating liver cancer at early stage, which is able to efficaciously control the blood supply to tumor lesions, kill tumor cells and reduce tumor diameter. TACE provides a good foundation for microwave ablation and indirectly improves the range and effect of ablation. Certain interactive branches are detected between the hepatic artery system and the portal system, through which lipiodol flows into the corresponding portal veins after embolization, effectively relieving the "thermal precipitation" caused by the portal system [16]. TACE combined with microwave ablation can effectually eradicate tumors, eliminate the inhibition of the immune status of the body and produce heat shock proteins (HSPs) like HSP70, thereby efficaciously triggering the cellular immunity and improving the immune function. Furthermore, liver cancer cells have an iodophilic effect, and high-intensity microwaves have a strong reflection effect on iodine and generate high temperature, thus indirectly expanding the ablation range [17]. Edema, hypoxia and ischemic symptoms are found in the lesions of liver cancer after TACE that can enhance the sensitivity of tumor cells to heat and the efficient killing of tumor cells. In addition, the heat generated by microwave can also increase the uptake of chemotherapy drugs administered in TACE by tumor cells [18]. For the treatment of patients with liver cancer, microwave ablation combined with TACE is also able to reduce the number of treatments with TACE, effectively protect the liver function, and improve the quality of life and survival.

In this study, multivariate analysis of prognosis of patients with liver cancer was carried out, and it was revealed that Child-Pugh, tumor diameter and number of lesions were independent risk factors for liver cancer. Child-Pugh is a comprehensive system for the evaluation of liver cancer stage. The later the stage, the severer the condition of patients and the lower the prognostic survival rate, which is in line with the findings of research by Qian et al [18]. Tumor diameter and number of lesions are independent risk factors affecting survival. The larger the lesion and the larger the number of lesions, the more complicated the treatment process and the poorer the prognosis, which is consistent with the findings of Huang et al study [19]. AFP level is one of the important laboratory indicators for the diagnosis of liver cancer. Multivariate analysis showed that AFP level is not a risk factor affecting survival. Therefore, judging the prognosis based on the serum AFP level in clinical practice is a certain limitation, which is in accordance with the findings of Wang et al study [20].

Conclusions

In conclusion, TACE combined with microwave ablation applied in the treatment of liver cancer can effectively improve liver function, immune function and survival and enhance efficacy and safety, which has certain value in clinical practice. Besides, Child-Pugh, tumor diameter and number of lesions are independent risk factors affecting the survival of liver cancer patients undergoing TACE combined with microwave ablation.

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Conflict of interests

The authors declare no conflict of interests.

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