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Assessment of the feasibility of TACE combined with intratumoral injection of cisplatin in hepatocellular carcinoma

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Abstract: The feasibility of transcatheter arterial chemoembolization (TACE) combined with intratumoral injection of cisplatin as treatment for hepatocellular carcinoma. 30 cases receiving TACE were denoted the TACE group, another 30 cases receiving TACE combined with an intratumoral multi-point injection of cisplatin were denoted the TACE/cisplatin group. Cases with partial remission/complete remission (PR/CR) were analyzed using 2 tests; alpha fetoprotein (AFP), aspartate amino transferase (AST), total bilirubin (TBIL), erythrocyte, and platelet levels were detected and the differences between two groups were analyzed using the Student's t-test; cases with complications, including intrahepatic metastasis (IM), upper gastrointestinal bleeding (UGB), and liver failure were also counted. The correlation of clinical parameters with PR/CR was analyzed using multifactorial correlation analysis. Cases with PR/CR in the TACE/cisplatin group were significantly more than in TACE group, accompanied by significant declination in FAP. There were no significant differences of AST, ALT, TBIL, blood urea nitrogen (BUN), white blood cells (WBC), red blood cells (RBC), and platelets (PLT) between two groups; 3 cases with IM, one case with UGB and one case with LF were found in the TACE group, but only 1 case with IM was found in the TACE/cisplatin group. In addition, tumor stage was correlated with PR/CR. We concluded that TACE combined with intratumoral injection of cisplatin was more effective than TACE, and with fewer complications and side effects.

Keywords: Transcatheter arterial chemoembolization (TACE), intratumoral injection of cisplatin, alpha fetoprotein (AFP)

1 Introduction

In recent years, transcatheter arterial chemoembolization (TACE) has been extensively used to treat hepatocellular carcinoma and has provideds a good short-term therapeutic effect, but the 3- and 5-year survival rates are still not ideal [1]. Several prospective randomized controlled studies reported that limitations in inhibiting relapse and also metastases and severe complications of TACE were found in many cases in spite of its tumoricidal ability [2-4]. Hence, it is necessary to find a treatment that can not only function by killing tumor cells, but also can enhance the safety of TACE.

As a broad spectrum anticancer drug, cisplatin can kill tumor cells by directly destroying DNA duplication and stimulating an immune reaction [5]. At present, as an improved method of interventional therapy, TACE combined with intratumoral injection of cisplatin, has been applied clinically and has produced good therapeutic outcomes. In this paper, we compare TACE combined with intratumoral injection of cisplatin with conventional TACE, analyze the differences in partial remission/complete remission (PR/CR,) liver function, kidney function, bone marrow haematopoietic function, and complications between the two groups: one with TACE alone, one with TACE plus cisplatin. In addition, we also analyze the correlation of clinical parameters with PR/CR. According to these results, the effectiveness and safety of TACE combined with intratumoral injection of cisplatin was further confirmed.

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2 Materials and methods

2.1 Clinical documents

After being diagnosed by pathology combined with ultrasonic examination, enhanced CT and enhanced MRI, 60 non-diffuse primary hepatocellular carcinoma patients without previous treatment were selected for this research. All patients had evaluable tumors, were without distant metastasis and dysfunction of heart, lung, and kidney, had a Karnosky score >70, and a Child A grade. Other clinical information is shown in Table 1.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.
Informed consent: Informed consent has been obtained from all individuals included in this study.

Table 1: Patient parameters

Clinical parameters	Groups	
	TACE group (n)	TACE/cisplatin group (n)
Gender		
Male	17	18
Female	13	12
Age		
≤55	12	16
>55	18	14
Clinical stage		
I	10	11
II	18	21
Tumor diameter		
≤5cm	13	11
>5cm	17	19

2.2 Equipment for research

An interventional therapy machine was supplied by Zhuhai Hejia Medical Equipment Co., Ltd (Guangzhou, China); a digital subtraction angiography system (model number SMC-III) was purchased from Beijing Chi Matt Image Technology Co Ltd (Beijing, China); a multi-detector–row computed tomographymodel number definition AS+was purchased from the Siemens company (Munich, Germany); a puncture guiding system (model number HGGR-2000) was also purchased from Zhuhai Hejia Medical Equipment Co., Ltd (Guangzhou, China).

2.3 Therapy methods and effectiveness assessment

Three weeks after TACE in the control group, tumor volume was measured by CT and lipiodol deposition was confirmed. Three weeks after TACE in the TACE/cisplatin group, tumor volume was measured by CT and lipiodol deposition was similarly confirmed, then multi-point intratumoral injection of cisplatin guided by CT was performed. The dosage of cisplatin (from 10 mg to 30 mg) was adjusted according to tumor volume. Criteria for a therapeutic effect were as follows: 1, complete remission [6] (tumor vanished completely); 2, partial remission [7] (tumor image reduced); 3, no change [8] (tumor image did not show significant changes); 4, progression of disease (PD). Tumor low density image expanded or new lesions were found by imaging examination. CR and PR were considered effective outcomes.

2.4 Statistical analysis

SPSS 13.0 was used and all data were expressed as means±SD. The difference of effective outcome in the two groups was analyzed using a χ^2 test; the difference between the two groups was analyzed using Student's *t*-test; the correlation of clinical parameters with CR/PR was analyzed using correlation analysis of multiple factors.

3 Results

3.1 TACE combined with intratumoral multi-point injection of cisplatin resulted in more patients in CR/PR and reduced blood AFP

6 months after treatment in the two groups, the outcome was evaluated; the result is shown in Figure 1. No complete recovery (CR) was achieved in either of the two groups, but the proportion of PR in the TACE/cisplatin group was 87% and greater than 60% in the TACE group. In addition, the proportion of NC and PD in the TACE/cisplatin group was 10% and 3%, respectively, much smaller than the respective 20% and 20% in the TACE group. Moreover, as shown in Table 2, 26 cases achieved CR/PR in the TACE/cisplatin group, but only 18 cases in TACE group; 4 cases achieved NC/PD in TACE/cisplatin group, but 12 cases in TACE group; the difference was significant (p<0.05). Furthermore, blood AFP was 73.23±22.44 ug/L in the TACE/cisplatin group, nearly half that in the TACE group (143.7±22.23 ug/L) (Figure 2, p=0.000). The results suggest that the therapeutic outcome of TACE combined with intratumoral injection of cisplatin is much more effective than TACE alone.

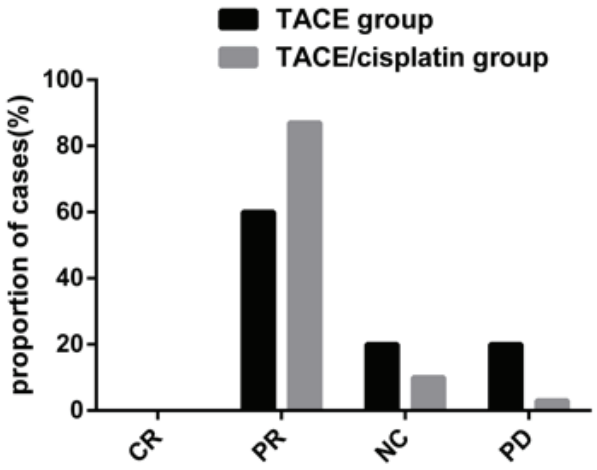

Figure 1: Proportion of cases with different therapeutic outcomes in TACE group and TACE/cisplatin group

Table 2: The difference of effective outcome in two groups

	TACE group	TACE/cisplatin group	χ^2	p
	Cases (n)	Cases (n)		
CR/PR	18	26	5.455	0.02*
NC/PD	12	4		

*p <0.05 was significant

3.2 Fewer complications and no increase in side effects occurred in patients of TACE/cisplatin group compared with the TACE group

As shown in Figure 3, only one case with upper gastrointestinal bleeding (UGB) was found in TACE/cisplatin group; however, in the TACE group, one case with UGB, 3 cases with intrahepatic metastasis (IM), and one case with liver failure (LF) were found in control group, suggesting

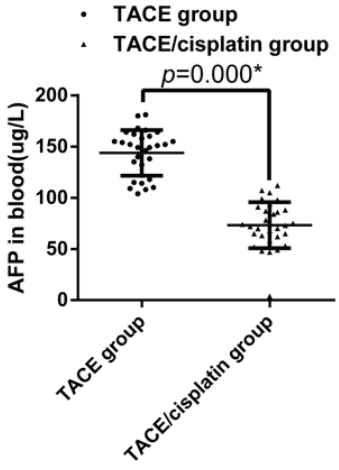

Figure 2: Difference in blood AFP in TACE group and TACE/cisplatin group

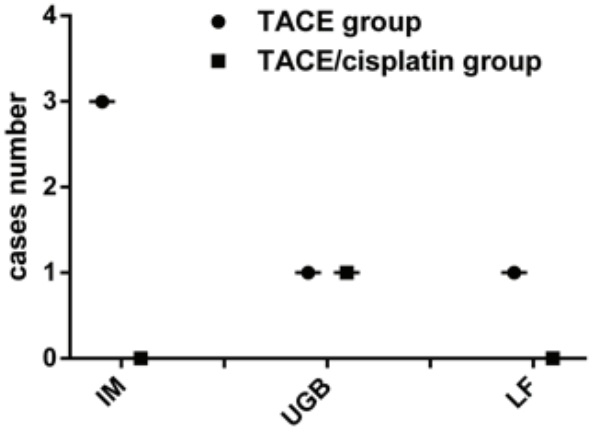

Figure 3 Number of cases with IM (intrahepatic metastasis), UGB (upper gastrointestinal bleeding) and LF (liver failure) in the TACE group and the TACE/cisplatin group

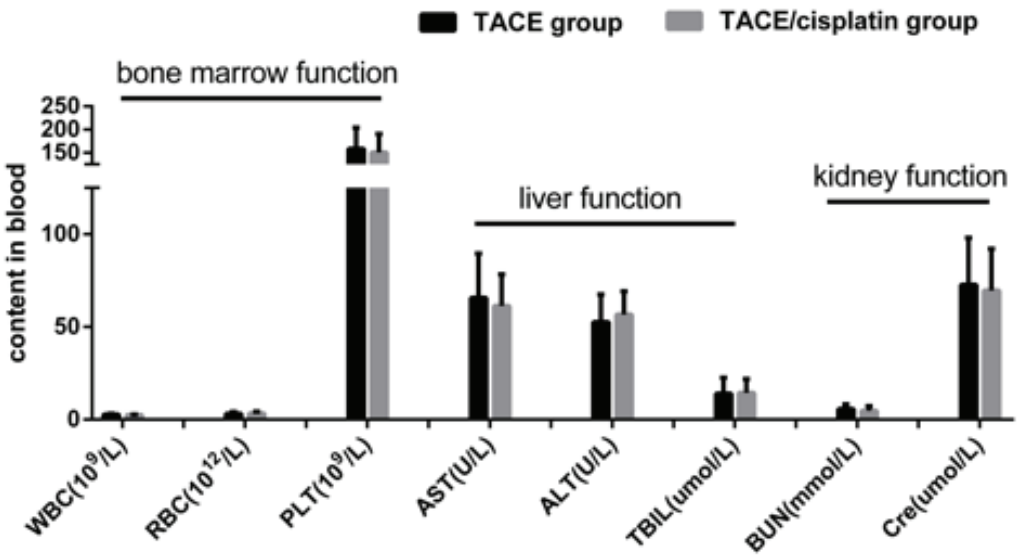

Figure 4: Blood detection of WBC (leukocyte), RBC (erythrocytes), PLT (platelets), AST (aspartate aminotransferase), ALT (alanine aminotransferase), TBIL (total bilirubin), BUN (Urea nitrogen) and Cre (creatinine) in the TACE group and the TACE/cisplatin group

that fewer complications occurred in the TACE/cisplatin group. In addition, as shown in Figure 4, the white blood cell count (WBC) in TACE group and TACE/cisplatin group was 2.77±0.41×10^9/L and 2.48±0.32×10^9/L, red blood cell count (RBC) was 3.21±0.99×10^{12}/L and 3.33±1.00×10^{12}/L, platelet count (PLT) was 158.53±45.80×10^9/L and 150.77±39.6×10^9/L, all without a significant difference; the kidney function indexes blood urea nitrogen (BUN) and creatinine (Cre) were 5.67±2.52 mmol/L and 72.67±25.32 umol/L, respectively, in the TACE group, 4.67±2.54 mmol/L and 69.67±22.48 umol/L, respectively, in the TACE/cisplatin group, all without a significant difference between two groups; the liver function index aspartate amino transferase (AST), alanine transfaminase (ALT), and total bilirubin (TBIL) were 65.63±24.01U/L, 52.57±14.94U/L, and 14.07±8.56umol/L, respectively, in the TACE group, 61.27±17.01U/L, 56.7±12.50U/L, and 14.37±7.55umol/L, respectively, in the TACE/cisplatin group, all without a significant difference between the two groups; All the data demonstrate that TACE combined with intratumoral injection of cisplatin can induce fewer complications and no further damage to liver function, kidney function, and bone marrow hematopoietic function compared to TACE. This proves the safety of TACE combined with intratumoral injection of cisplatin.

3.3 Patients at clinical stage I showed better therapy outcome than those at stage II

To further confirm whether therapy outcome was also affected by other clinical parameters, correlation analysis was performed and found that clinical stage was significantly correlated with PR/CR (hazard ratio=0.284, 95%CI=0.079–0.47, p=0.028, Table 3), but there was no correlation between gender, age, tumor diameter, and PR/CR.

Table 3: Correlation of clinical parameters with effective outcome (PR/CR)

Variable	Hazard ratio	95%CI	p
Gender (male vs female)	-0.051	-0.301–0.217	0.699
Age (≤55 vs >55)	-0.111	-0.354–0.154	0.399
Clinical stage (I vs II)	0.284	0.079–0.47	0.028*
Tumor diameter (≤5cm vs >5cm)	0.185	0.049–0.406	0.158

*p <0.05 was significant

4 Discussion

Lipiodol injected into the liver via hepatic artery using TACE deposits mainly in tumor vessels, hepatic sinus, and surrounding liver tissue [9]. Because of a low clearance rate in tumors, lipiodol is stranded in local tumor for a very long time and induces ischemia and hypoxia in the tumor, and finally, coagulation necrosis; the more lipiodol deposits in the tumor, the higher the degree of

necrosis [10]. However, tumor cells remaining in the local area with little lipiodol or without lipiodol makes relapse easy. One research reported that, after TACE, even though 50% of tumor tissue necrosis happened in 73% of hepatocellular carcinoma patients, only 5% produced complete necrosis, and the remaining cancer cells exhibited stronger proliferation and invasion capacity. For example, multiple intrahepatic metastases or pulmonary metastases were found in some patients a short time after TACE [11]. Moreover, rapid establishment of the peripheral collateral blood supply provides sufficient nutrition for the remaining tumor tissue and thereby induces proliferation [12]. Multiple intratumor injections of cisplatin can not only kill microcarcinoma lesions in tumors and vessels, but can also kill tumor cells that moved into the surrounding area; this can continue to kill tumor cells surviving from lipiodol and make for a better prognosis [13]. In this paper, more cases with PR/CR and fewer cases with NC/PD were found in the TACE/cisplatin group; Blood FAP also significantly declined in the TACE/cisplatin group. These results suggest the high effectiveness of TACE combined with intratumoral injection of cisplatin.

Complications and side effects of therapy in hepatocellular carcinoma, which greatly affect quality of life and prognosis, have attracted more and more attention in recent years [14]. It has been reported that after TACE, liver function damage occurred in most cases, and UGB and LF also occurred in some cases. Several series of TACE could even induce liver atrophy and severe liver function decompensation, which causes a change for the worse [15]. In the present paper, we found only one case with UGB in the TACE/cisplatin group, but one case with UGB, one case with LF, and three cases with portal vein tumor thrombus were found in the TACE group. Moreover, to evaluate the side effecfs of chemotherapy, we compared liver function, kidney function, and bone marrow hematopoietic function between the two groups and found no significant difference. These results fullly confium the safety of TACE combined with intratumor injection of cisplatin.

Two studies have reported that the therapeutic effect of embolism treatment could be influenced by many factors, including tumor blood supply, tumor stage, tumor size, and liver functions, among others [16, 17]. In the present paper, correlation analysis of multiple factors showed that clinical stage was significantly correlated with prognosis, but that gender, age, and tumor size showed no correlation with prognosis. This supplies further clinical evidence for predicting prognosis of hepatocellular carcinoma after embolism treatment.

In conclusion, this study further confirmed the effectiveness and safety of TACE combined with an intratumoral injection of cisplatin in hepatocellular carcinoma, supplying evidential support for further expanded clinical application.

Conflict of interest statement: Authors state no conflict of interest

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