

ORIGINAL ARTICLE

Clinical efficacy of TACE combined with Apatinib in the treatment of advanced hepatocellular carcinoma

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Summary

Purpose: To explore the therapeutic efficacy and clinical safety of transcatheter arterial chemoembolization (TACE) combined with Apatinib in patients with advanced hepatocellular carcinoma (HCC).

Methods: 88 patients with advanced HCC admitted to our hospital from March 2015 to March 2016 were randomly assigned into group A (TACE) or B (TACE combined with Apatinib). Therapeutic efficacy and adverse events were recorded by follow-up data every three months after treatment. Disease control rate (DCR) and objective response rate (ORR) in both groups were calculated based on 18-month follow-up records.

Results: Nine months after treatment, DCR and ORR in group A were 81.82% and 36.36%, respectively, and 95.45% and 63.64% in group B. Disease-free survival (DFS) in group

A and B was 11.15 and 16.5 months, respectively. No significant differences in the adverse event incidence (fever, abdominal pain, nausea and vomiting) after embolization were found between the two groups ($p > 0.05$). The incidence of hypertension, hand-foot syndrome, and proteinuria in group B was significantly higher than those in group A ($p < 0.05$). Adverse events were all alleviated after symptomatic treatment.

Conclusions: The therapeutic efficacy of TACE combined with Apatinib in HCC treatment is higher compared to TACE alone, which may be related to the inhibition of tumor angiogenesis. TACE combined with Apatinib can improve the prognosis and prolong the overall survival (OS) of HCC patients.

Key words: adverse events, apatinib, HCC, TACE

Introduction

Primary hepatocellular carcinoma (PHC) is the sixth most common cancer in the world, and more than 90% of PHC cases pathologically belong to hepatocellular carcinoma (HCC) [1]. China is a country with high incidence of HCC. Due to lack of early diagnosis and poor prognosis, HCC has become a major cause of cancer-related death. The mortality rate of HCC is very high worldwide. It is reported that less than 20% of HCC patients are eligible for surgical resection [2]. Therefore, local therapy is particularly important in the treatment of HCC.

Transcatheter arterial chemoembolization (TACE) is considered to be the first-line topical therapy for patients with advanced HCC who can not be operated. TACE has the advantages of safety, small trauma and good curative effect [3]. About 75% of blood supply in HCC is dependent on the hepatic artery. TACE controls tumor growth by injecting chemotherapy drugs and embolic agent into the blood supplying artery of HCC, further blocking the blood supply and inducing ischemia and hypoxia in the tumor site [4]. The microcatheter achieves super selection of the blood supplying artery, which

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significantly improves recovery of postoperative liver injury and complications with a good safety and efficacy [5]. The therapeutic efficacy of TACE may be affected by individual patient differences, liver function grading, lesion size, tumor number, vascular condition, blood supply, and portal vein tumor thrombus [6-8].

Apatinib mesylate (YN968D1) a novel small-molecule, highly selective VEGFR-2 inhibitor, can inhibit c-Kit and c-Src tyrosine kinases [9,10]. It can act on the ATP-binding site in VEGF receptors and block its downstream pathways, thereby inhibiting the migration and proliferation of vascular endothelial cells. Apatinib also exerts anti-tumor effects by inhibiting the phosphorylation of AKT and ERK1/2, as well as arresting cell cycle in G2/M phase [11,12]. The therapeutic dose of Apatinib induces apoptosis in tumors overexpressing VEGFR-2 [13-15]. Meanwhile, Apatinib can reverse multi-drug resistance and improve the efficacy of traditional chemotherapy drugs such as 5-FU, oxaliplatin, docetaxel and doxorubicin. Apatinib was first approved in China for gastric cancer treatment with definite curative effect, and researches on its efficacy of other tumors are ongoing as well [16-18].

Since Apatinib could selectively inhibit VEGFR-2, thereby preventing neovascularization, we speculated that the combination of Apatinib and TACE may inhibit the neovascularization of tumor tissue and improve the therapeutic efficacy of HCC treatment. A randomized controlled study was carried out to explore the efficacy and safety of TACE combined with Apatinib in treating HCC.

Methods

Subjects

A total of 88 patients with advanced HCC admitted to our hospital from March 2015 to March 2016 were enrolled. All patients were pathologically diagnosed as HCC by means of biopsy. Patients were randomly assigned into group A and B, with 44 patients in each group. Patients in group A received TACE alone and those in group B were treated with TACE combined with Apatinib. This study was approved by the ethics committee of the First Affiliated Hospital of Air Force Medical University. Signed written informed consents were obtained from all participants before the study entry.

Inclusion criteria were as follows: (1) Patients did not have dysfunctions in important organs and chemotherapy contraindications; (2) Patients with B-C stage of Barcelona Clinic Liver Cancer (BCLC); (3) Patients with Child-Pugh A or B, and Karnofsky performance status (KPS)>60; (4) Patients could not be operated on due to major surgical risk or refuse surgical resection; (5) Patients did not receive other treatments.

Exclusion criteria were as follows: (1) Patients with chemotherapy contraindications; (2) Patients with dys-

functions of heart, lung, liver or kidney; (3) Patients with severe coagulopathy (prothrombin time >18 s or bleeding tendency); (4) Drug withdrawal for longer than one month because of intolerance of adverse events or other reasons; (5) Intrahepatic single tumor or multiple tumors which were clustered together and those with portal vein tumor thrombus (PVTT) were directly connected with the primary tumor; (6) Large amount of ascites or refractory ascites; (7) Patients with distant metastasis.

Treatment methods

Patients in groups A and B underwent TACE under digital-subtraction angiography (DSA). The position and distribution of tumor and nutrient artery were determined by Seldinger method. Epirubicin, oxaliplatin, iodized oil and an equal amount of contrast agent mixed emulsifier were injected in tumor lesion. Blood supply artery was embolized with embosphere particles. At the end of embolization, blood supply was stagnant or blood flow slowed down significantly. Tumor staining was performed after embolization.

Patients in group B started taking Apatinib (Jiangsu hengrui Pharmaceuticals Co., Ltd, Lianyungan, China) orally 4 days after TACE treatment. The initial dose of Apatinib was 500 mg per day, which was adjusted according to the patient's tolerance after 1 to 2 weeks. The drug dose maintained if the patient showed good tolerance or had mild adverse events. Otherwise, drug dose decreased to 250 mg per day, which was gradually restored to the initial dose after the adverse events were alleviated. The withdrawal time was no more than 1 month. Apatinib was discontinued 4 days before TACE in the next course.

Follow-up and curative effect evaluation

All patients received regular examinations of CT/MRI, blood routine test, liver and kidney function test and serum AFP determination every 3 months after surgery. The therapeutic effects were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were recorded. The secondary endpoints observed in this study were progression-free survival (PFS), defined as the time from the first interventional therapy to the definite disease progression (PD) or death. The starting point of observation was the first treatment time, and the deadline was the time of PD or the last follow-up time. Disease control rate (DCR) and objective response rate (ORR) in both groups were calculated.

Adverse events

Adverse events were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [20].

Statistics

SPSS 20.0 statistical software (IBM, Armonk, NY, USA) was used for statistical analyses. The quantitative data were compared with Student's t-test. The categorical data were compared with Chi-square test or Fisher's

Exact test. Survival was analyzed with Kaplan-Meier method and the differences were compared by Log-rank test. $P < 0.05$ indicated that the difference was statistically significant.

Results

Basic characteristics

A total of 88 HCC patients were enrolled in this study and all of them were followed-up every 3 months after treatment for 18 months. There were 34 males and 10 females in group A, and the age ranged from 39 to 72 years, with an average age of 58.9 years. Among the 44 cases in group A, 36 were Child-Pugh grade A and 8 were grade B. KPS score was 70-90, with an average of 79.09. Thirty-four cases had hepatitis B, 4 had alcoholic liver and 6 had other causes. Based on the BCLC classification, 38 cases were stage B and 6 stage C. The mean tumor diameter in group A was 6.86 ± 2.12 cm.

In group B there were 32 males and 12 females, and the age was 34-79 years, with an average age

of 56.1 years. Thirty-eight cases were Child-Pugh grade A and 6 grade B. KPS score was 70-90, with an average of 78.67. By analyzing the basic diseases in group B, there were 36 cases of hepatitis B, 2 cases of alcoholic liver and 6 cases of other causes. Thirty-six cases were stage B and 8 stage C based on the BCLC classification. The mean tumor diameter in group B was 7.12 ± 2.15 cm. We did not observe significant differences in the age, gender, Child-Pugh classification, KPS score, etiology, and mean tumor diameter between the two groups ($p > 0.05$; Table 1).

Comparison of therapeutic efficacy

Nine months after treatment, there were 4 cases of CR, 12 cases of PR, 20 cases of SD and 8 cases of PD in group A. The DCR and ORR in group A were 81.82% and 36.36%, respectively.

In group B there were 8 cases of CR, 20 cases of PR, 14 cases of SD and 2 cases of PD. The DCR and ORR in group B were 95.45% and 63.64%, respectively. The therapeutic efficacy was statistically significant between the two groups ($p < 0.05$; Table 2).

Table 1. Comparison of general characteristics between the two groups of patients

Characteristics	A n=44	B n=44	p
Gender			0.372
Male	34	32	
Female	10	12	
Age, years			0.473
>60	19	15	
≤60	25	29	
Child-Pugh			0.516
A	36	38	
B	8	6	
KPS	79.09	78.67	0.625
AFP (μg/L)			0.318
>20	38	34	
≤20	6	10	
HBV-infected	34	36	0.251
Tumor diameter (mean±SD)	6.86 ± 2.12	7.12 ± 2.15	0.248
Number of tumors			0.386
Single	20	19	
Multiple	24	25	

Table 2. Comparison of therapeutic efficacy 9 months after treatment of the two groups of patients

Group	CR n (%)	PR n (%)	SD n (%)	PD n (%)	DCR n (%)	ORR n (%)
A group (n=44)	4 (9.09)	12 (27.27)	20 (46.45)	8 (18.18)	36 (81.82)	16 (36.36)
B group (n=44)	8 (18.18)	20 (45.45)	14 (31.82)	2 (4.55)	44 (95.45)	28 (63.64)
p					0.023	0.041

For abbreviations see text

Survival analyses

Based on the 18-month follow-up data, the disease-free survival (DFS) in group A and B were 11.15 months and 16.5 months, respectively, which was statistically significant ($p < 0.05$; Figure 1).

Comparison of PFS in patients with different liver function and tumor numbers in the combination treatment

We compared PFS in HCC patients undergoing TACE combined with Apatinib with different liver functions and tumor numbers. PFS in patients with Child-Pugh A and B was 16.3 and 16.0 months, respectively. The difference in PFS between patients with Child-Pugh A and B was not statistically significant ($p = 0.914$; Figure 2). PFS of HCC patients with single or multiple tumors was 16.4 and 16.15 months, respectively ($p = 0.692$; Figure 3).

Adverse events

According to the follow-up data, the main adverse events in group A were 34 (77.27%) cases with fever, 24 (54.55%) cases with abdominal pain, 20 (45.45%) cases with nausea and vomiting, and 10 (22.73%) cases with bone marrow suppression. In group B, there were 32 (72.73%) cases with hypertension, 22 (50%) cases of hand-foot syndrome, 18 (40.91%) cases with proteinuria, 5 (11.36%) cases with diarrhea, 6 (13.64%) cases with myelosuppression and 2 (4.55%) cases with refractory trigeminal neuralgia. No significant differences in the incidence of fever, abdominal pain, nausea and vomiting after embolization were found between the two groups ($p > 0.05$). The incidence of hypertension, hand-foot syndrome, and proteinuria in group B were higher than those in group A ($p < 0.05$). All the abovementioned adverse events subsided after symptomatic treatment.

Discussion

HCC treatments mainly include surgery, local minimally invasive surgery, chemotherapy drugs, radiotherapy, biological therapy and traditional Chinese medicine treatment [22]. HCC manifests as aggressive malignancy, with rapid development, frequent metastasis, poor prognosis, and occult symptoms. As a result, most HCC patients could not be operated due to the advanced stage when first diagnosed. The survival of patients with advanced HCC is very short, only 3-4 months [26].

TACE uses minimally invasive techniques to selectively insert a catheter into the blood supplying artery for injection of chemotherapeutic drugs

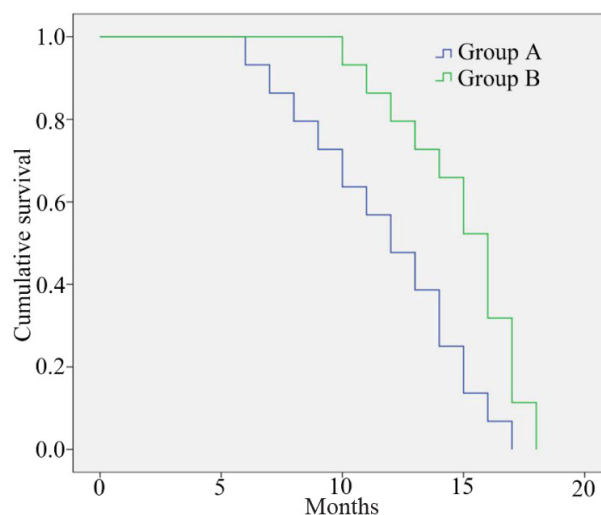


Figure 1. Comparison of DFS between the two groups ($p < 0.05$).

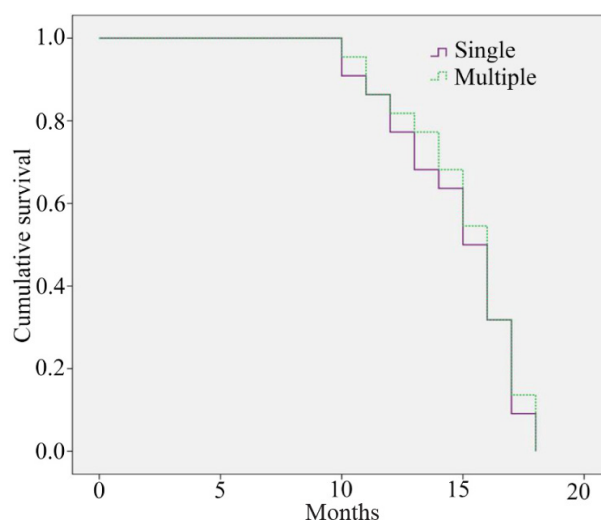


Figure 3. Comparison of DFS in patients with different numbers of tumors in group B ($p = 0.692$).

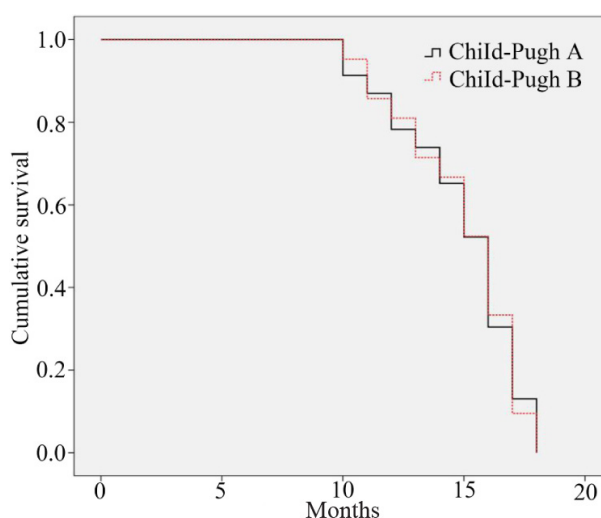


Figure 2. Comparison of DFS in patients with different Child-Pugh grade in group B ($p = 0.914$).

Table 3. Adverse events of enrolled patients

Adverse events	Group A	Group B	p
Fever	34	30	0.863
Abdominal pain	24	18	0.537
Nausea/Vomit	20	14	0.499
Myelosuppression	10	6	0.514
Hypertension	2	32	0.002
Hand-foot syndrome	0	22	0.014
Proteinuria	0	18	0.018
Diarrhea	2	5	0.134
Mouth ulcer	0	2	0.158
Trigeminal neuralgia	0	2	0.436

and embolic agents [27]. TACE can effectively prolong the survival of HCC patients with small trauma and fast recovery and is a safe and effective palliative treatment especially for advanced HCC. TACE efficiently inhibits tumor development [28]. However, some drawbacks with TACE treatment should be discussed. First, it requires multiple cycles in a short period of time. Second, TACE alone may not completely inactivate tumor lesions. Recent studies have confirmed that TACE can cause ischemia and hypoxia in embolized tissues, thereby triggering the secretion of multiple growth factors (such as VEGF) to promote tumor growth and metastasis. Angiogenesis is the most critical step in the development and progression of malignant tumors [29-31]. Previous studies have reported that sorafenib combined with TACE effectively prolongs the survival of patients with advanced HCC [32,33]. Therefore, TACE combined with targeting angiogenesis inhibitors can not only effectively inhibit angiogenesis around the tumor, but also delay tumor progression, thereby improving the therapeutic effect of the tumor treatment.

Apatinib is a small molecule VEGFR tyrosine kinase inhibitor, a derivative of PTK787, whose main target is VEGFR2/KDR. Apatinib inhibits VEGF-mediated VEGFR2 phosphorylation and downstream molecular activation and exerts its anti-tumor effect mainly by inhibiting proliferation, migration and lumen formation of tumor vascular endothelial cells [34]. Low-dose Apatinib could inhibit VEGFR2 phosphorylation and kinases, such as PDGFR, c-Kit and c-Src, are inhibited by high-dose Apatinib. It is reported that Apatinib inhibits the proliferation and migration of vascular endothelial cells by highly selective blockage of VEGFR2 receptor and reduction of tumor microvessel density [35]. Currently, Apatinib has been applied in the treatment of gastric cancer, colon cancer and non-small cell lung cancer, and exerts synergistic anti-

cancer effect with various chemotherapy drugs [36].

In this study, DCR was 81.82% and ORR 36.36% after 9 months of treatment in group A, which were 95.45% and 63.64% in group B, respectively. At 18 months of follow-up, the median PFS was 11.15 months in group A and 16.5 months in group B. This study confirmed that TACE combined with Apatinib is more advantageous for patients with advanced HCC than TACE alone. Most adverse events were tolerable and would not lead to treatment termination after symptomatic treatment. Besides, Apatinib did not aggravate the adverse events caused by chemoembolization. The adverse effects caused by Apatinib itself were mainly hypertension, hand-foot syndrome, proteinuria, diarrhea, etc. Most of them can be alleviated after symptomatic treatment, and some patients can be continually treated after dose reduction. Therefore, we confirmed the safety of Apatinib that could be widely applied in clinical practice.

The main limitations of this study were the limited number of the recruited patients. Further studies with more patients are needed in the future. Additionally, more basic characteristics, such as HBV activity status, HCV status, antivirals, diabetes, tumor distribution etc should be collected and analyzed.

Conclusions

The therapeutic efficacy of TACE combined with Apatinib in HCC treatment is better than that of TACE alone, which may be related to the inhibition of tumor angiogenesis. TACE combined with Apatinib can improve prognosis and prolong survival of HCC patients.

Conflict of interests

The authors declare no conflict of interests.

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