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Review Article

Application of apatinib combined with TACE in patients with liver cancer complicated with portal vein tumor thrombosis

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Abstract: To investigate the application value of apatinib combined with transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) complicated with portal vein tumor thrombus (PVTT). According to the different treatment methods, the collected patients with HCC complicated with PVTT were divided into a joint group (JG) and a control group (CG). The CG was treated with TACE (n = 116), and the JG was treated with apatinib (n = 131) in addition to the treatment in the CG. The expression of immune and angiogenesis related factors after different treatments were analyzed. There was no remarkable difference in clinical efficacy between the two groups after treatment (P>0.05). The levels angiogenic factors (VEGF and HIF-1α) in the two groups were compared. The levels of the two factors improved in both groups after receiving different treatment methods, with more obvious effect in the JG (P<0.05). By examining the immune-related factors of all the subjects, it was found that the immune function of both groups was notably improved after treatment; and CD3+, CD4+ and CD4+/CD8+ levels in the JG were higher than that in the CG, while CD8+ level was lower than that in the CG (P<0.05). Further comparison indicated that there was no considerable difference in hepatic function index between the two groups after treatment (P>0.05). The incidence of diarrhea, hypertension, hand-foot syndrome and proteinuria in the JG was higher than that in the CG (P<0.05). The results of the follow-up investigation revealed that the overall survival rate of the JG was higher than that of the CG (P<0.05). Apatinib combined with TACE can significantly inhibit tumor angiogenesis and improve patients' immunity in patients with HCC complicated with PVTT, and has high safety.

Keywords: Apatinib, hepatocellular carcinoma with portal vein tumor thrombus, transcatheter arterial chemoembolization, angiogenesis, immune function

Introduction

Hepatocellular carcinoma (HCC) is a common cause of death from tumor-related diseases [1]. HCC is characterized by fast and hidden onset, with high malignant degree [2]. For the past few years, with the continuous development of ultrasound, CT and other imaging technologies, the diagnosis rate of early HCC is constantly improving, and the tumor-related mortality rate is also constantly decreasing [3, 4]. In China, however, patients diagnosed with advanced liver cancer still account for about 70%-80% [4]. Due to the anatomical and biological characteristics of liver HCC, the disease has a high probability of invading the intrahepatic vessels, especially the portal vein system [5]. Therefore, about 10-40% of patients are found to have portal vein tumor thrombosis (PVTT), resulting in increased treatment difficulty, especially in radical surgical treatment. Some studies also show that patients with HCC complicated with PVTT have poor prognosis, which seriously threatens the life and health of the patients [6].

Transcatheter arterial chemoembolization (TACE) is widely recognized as an effective treatment in clinical practice, which can effectively inhibit the development of HCC. But TACE alone does not have an ideal long-term efficacy [7]. At

present, the literature reveals the effect of TACE combined therapy. For example, the research of Yuan [8] suggests that sorafenib combined with TACE can improve the curative effect and appropriately prolong the survival time in patients with HCC complicated with PVTT. Moreover, literature shows that radiotherapy combined with TACE can achieve better results [9]. Apatinib is a novel receptor tyrosine kinase inhibitor with high selectivity, and its binding affinity is more than 10 times that of sorafenib [10]. At present, apatinib has shown good clinical results in treating various solid tumors, and it can selectively bind and effectively inhibit VEGF receptor (VEGFR-2), and then block VEGFR-2 mediated angiogenesis [11]. Previous study has shown that apatinib alone can be used for intervention in patients with HCC complicated with PVTT, and good results are shown [12]. However, there are few studies on the combination of apatinib and TACE at present, and whether this treatment has any effect on tumor angiogenesis and immune function in patients with HCC complicated with PVTT remains to be further demonstrated.

Previous studies have explored the efficacy of apatinib combined with TACE treatment for hepatocellular carcinoma [13], but their study only explored the treatment efficiency and survival of patients, and has certain limitations. Dysregulation of angiogenesis and abnormal immune function have been identified as key factors in numerous pathological conditions including cancer [14, 15]. Therefore, our study explored the effects from multiple aspects (such as tumor angiogenesis, immune function, etc.) and comprehensively described the application value of apatinib combined with TACE, so as to provide good reference and help for clinical treatment.

Methods

General data

A total of 247 patients with HCC complicated with PVTT admitted to The Second Hospital of Shanxi Medical University were collected as research subjects. Among them, 116 patients who received TACE alone were enrolled in the CG, male: female = 67:49, with a mean age of (54.27±7.13) years. Another 131 patients who received apatinib combined with TACE were enrolled in the JG, male: female = 77:54, with a mean age of (54.45±7.09) years. The study was conducted with the approval of the Ethics Committee of The Second Hospital of Shanxi Medical University and this study is in line with the Declaration of Helsinki. The contents of the experiment were described to the patients, all of whom agreed and signed the informed consent.

Inclusion criteria: Patients who's HCC was confirmed by pathological diagnosis, and clear tumor thrombus was found in the portal vein by imaging examination. Patients had complete clinical data. Patients were accompanied by family members upon admission. Patients did not receive surgical treatment, biological targeted therapy or radiotherapy or chemotherapy in the 3 months prior to this treatment.

Exclusion criteria: Patients who were in Child-Pugh grade C. Patients complicated with coagulation disorders or other malignant tumors. Patients who were unable to actively receive treatment. Patients who were unwilling to be followed-up.

Therapies

CG: Patients were treated with TACE. Patients were intubated by puncture with Seldinger, and a 5F catheter sheath (Terumo, Japan) was inserted. Arteriography and indirect portal vein angiography were performed by injecting contrast agent to preliminarily determine the tumor blood supply and portal vein thrombus. Then super selective catheterization was performed to make the catheter as close to the tumor as possible. After confirming the tumor supply artery, 1.0 g 5-FU (Ningbo Dahongying Pharmaceutical Co., Ltd., with SFDA approval number of H33022622), 150 mg oxaliplatin (Hainan Jinrui Pharmaceutical Co., Ltd., SFDA approval number: H20143023) and 0.3 g calcium folinate (Jiangsu Hengrui Medicine Co., Ltd., with SFDA approval number of H2002-3636) were injected. Under fluoroscopy, 7-25 mL of ultra-liquid iodized oil (Yantai Luyin Pharmaceutical Co., Ltd., SFDA approval number: H37022398) was injected slowly, and at the same time, the arterial vessels supplied by the tumor were embolized by microspheres. The interval of TACE treatment was 3-4 weeks, and the total treatment was for 2-3 times. Postoperative routine antiemetic, anti-acid, liver protection and other symptomatic treat-

Table 1. Comparison of clinical general data between the two groups n [%]/(x±sd)

	Control group (n = 116)	Joint group (n = 131)	X^2/t	P
Gender			0.026	0.871
Male	67 (57.76)	77 (58.78)		
Female	49 (42.24)	54 (41.22)		
Average age (years)	54.27±7.13	54.45±7.09	0.199	0.843
Average body weight (kg)	54.32±6.79	55.12±6.56	0.941	0.348
Child-Pugh classification			0.005	0.943
Grade A	65 (56.03)	74 (56.49)		
Grade B	51 (43.97)	57 (43.51)		
Diameter of tumor (cm)	7.94±2.67	8.02±2.55	0.241	0.810
Location of tumor thrombus involvement			0.019	0.991
Portal vein trunk	61 (52.59)	68 (51.91)		
Branch of portal vein	38 (32.76)	44 (33.59)		
Simultaneous involvement	17 (14.65)	19 (14.50)		

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

	CR	PR	SD	PD	Disease control rate
Control group (n = 116)	13 (11.21)	56 (48.27)	22 (18.97)	25 (21.55)	78.45%
Joint group (n = 131)	30 (22.90)	61 (46.56)	23 (17.56)	17 (12.98)	87.02%
X^2					3.205
P					0.073

ment were conducted. JG: Patients received treatment of TACE combined with apatinib, of which TACE was the same as the CG. Apatinib was taken 3 days after TACE treatment (Jiangsu Hengrui Medicine Co., Ltd., SFDA approval number: H20140103) at a daily dose of 500 mg, once a day. If intolerable side effects occurred, the dosage was reduced to 250 mg or the drug was stopped. When the side effects were resolved, patients resumed medication. According to imaging, liver function and physical strength scores, the overall condition of the patients was comprehensively evaluated at intervals to determine whether the patient required TACE treatment again or not.

Detection of indicators

Fasting venous blood of patients in both groups after 1 month of treatment was collected and centrifuged at 3000gehe corresponding test tube for g. Vascular endothelial growth factor (VEGF) and hypoxia-induced factor-1α (HIF-1α) were detected with the help of ELISA. The kits for VEGF and HIF-1α were provided by Shanghai Zhenyu Biotechnology Co., Ltd. (with batch numbers of CSB-e111718h-1, CSB-e112-112h-1). The enzyme label analyzer (BS-1101) was from Beijing Linmao Technology Co., Ltd. The procedures were carried out strictly in accordance with the instructions. FACSCalibur full-automatic flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA) was applied to measure the immune function indexes (CD3+, CD4+, CD8+, CD4+/CD8+) of the two groups of patients after surgery. Fluorescent conjugated monoclonal antibodies (CD3+, CD4+, CD8+) were used for surface analysis. Extracellular staining was conducted according to the manufacturer's instructions. Conjugated fluorescent antibodies (different combinations of surface markers) were added to each plasma free peripheral blood sample and then incubated for 15 min in dark. After that, erythrocyte lysate was added, placed at room temperature for 10 min, and centrifuged for 10 min at 350 temperature fo The upper liquid was discarded to terminate cell lysis. Finally, the cell staining buffer was added and centrifuged for 5 min at 350 × g for washing, twice, and the supernatant was discarded. The sample was re-suspended in the staining buffer for flow cytometry analysis preparation. The procedures were conducted according to the instructions.

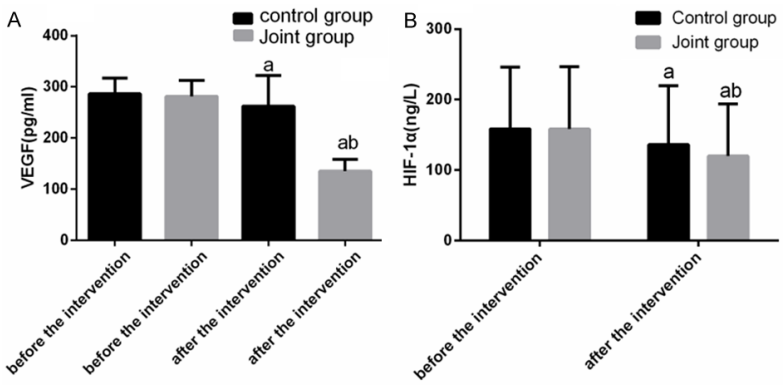

Figure 1. Comparison of tumor angiogenesis related factors before and after treatment between the two groups. A. Comparison of VEGF levels before and after treatment between the two groups. B. Comparison of HIF-1α levels before and after treatment between the two groups. Notes: a means comparison with the same group before treatment, [a]P<0.05. b means comparison with the control group after treatment, [b]P<0.05.

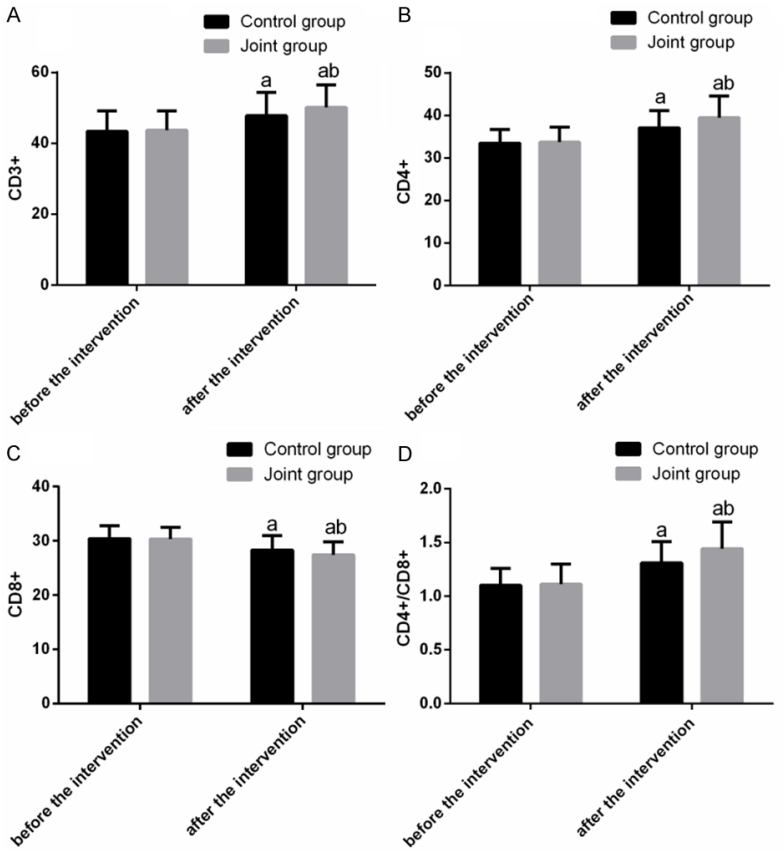

Figure 2. Comparison of immune function between the two groups before and after treatment. A. Comparison of CD3+ levels between the two groups before and after treatment. B. Comparison of CD4+ levels between the two groups before and after treatment. C. Comparison of CD8+ levels between the two groups before and after treatment. D. Comparison of CD4+/CD8+ levels between the two groups before and after treatment. Notes: a means comparison with the same group before treatment, [a]P<0.05. b means comparison with the control group after treatment, [b]P<0.05.

Outcome measures

According to the result of MRI review after 1 month of treatment, the tumor status was assessed in line with the evaluation criteria for the therapeutic effect of solid tumor (RECIST). ① Complete response (CR): no arterial phase enhancement in the lesion. ② Partial response (PR): a reduction of at least 30% of the arterial enhancement area. ③ Stable disease (SD): the reduction of lesion diameter did not meet the criteria of PR or the increase did not meet the criteria of PD. ④ Progressive disease (PD): an increase in the total diameter of the lesion more than 20% or the appearance of new lesions. Disease control rate = CR+PR+SD/total cases.

The levels of angiogenic factors, immune factors and liver function indexes before and 1 month after treatment were observed.

Adverse reactions after treatment in the two groups were observed.

The subjects were followed up by telephone or review, and the survival status of the two groups was counted.

Statistical treatment

Statistical analysis was performed by the aid of SPSS 20.0 (IBM Corp, Armonk, NY, USA). The counting data was represented by [n (%)]. Chi-square test was applied for inter-group comparison. The measurement data was expressed by mean standard deviation (x±sd). The

Table 3. Comparison of liver function indexes between the two groups before and after treatment

	CD3+	CD4+	CD8+	CD4+/CD8+
Control group (n = 116)				
Before the intervention	43.37±5.77	33.47±3.24	30.43±2.37	1.10±0.16
After the intervention	47.77±6.58	37.09±4.02	28.31±2.65	1.31±0.20
T	5.523	6.800	6.714	7.846
P	<0.05	<0.05	<0.05	<0.05
Joint group (n = 131)				
Before the intervention	43.65±5.54	33.68±3.56	30.34±2.17	1.11±0.19
After the intervention	50.14±6.35*	39.47±5.14*	27.41±2.43*	1.44±0.25*
T	8.657	10.880	9.861	13.100
P	<0.05	<0.05	<0.05	<0.05

Note: *denotes comparison with the control group after treatment, *P<0.05.

comparison between the two groups was conducted by t test. The comparison among groups was conducted by repeated measurement analysis of variance. LSD-t test was utilized for back testing. Kaplan-Meier was applied for survival analysis, and Log-rank test was used for detection. Differences in data were statistically significant as P<0.05.

Results

General clinical data

In **Table 1**, we show that there was no remarkable difference in gender, average age, average body weight, Child-Pugh classification, tumor diameter and tumor thrombus involvement location between the two groups (P>0.05), showing group comparability.

Comparison of efficacy between the two groups

According to the statistics of the efficacy of the two groups (**Table 2**), the disease control rate of the CG was slightly lower than that of the JG (78.45% VS 87.02%), but not statistically significant (P>0.05).

Comparison of tumor angiogenesis related factors before and after treatment between two groups

According to the comparison of the levels of angiogenic factors (VEGF, HIF-1α) between the two groups, as shown in **Figure 1**, no difference existed between the two groups before treatment. After treatment, the levels of VEGF, HIF-1α in both groups were lower than those before treatment, and the levels of the two in the JG were lower than those in the CG (P<0.05).

Changes in immune-related factors during treatment

The changes of immune cytokines in the two groups treated with different methods were compared. **Figure 2** and **Table 3** show that there was no considerable difference in the comparison of immune cytokines between the two groups before treatment (P>0.05). While CD3+, CD4+, CD4+/CD8+ after treatment in both groups were higher than those before treatment, and CD8+ was lower than that before treatment (P<0.05). After treatment, CD8+ in the JG was lower than that in the CG, and CD3+, CD4+ and CD4+/CD8+ were all higher than those in the CG (P<0.05).

Comparison of liver function indexes

Indexes of liver function were detected at the time of review (1 month after treatment), as shown in **Figure 3**. We found that there was no difference in liver function between the two groups before treatment, but slight changes had taken place after different treatment interventions, in which ALT and TBIL levels in both groups were slightly up-regulated over before treatment (P<0.05), while no remarkable difference was found in ALT, ALB and TBIL between the two groups after treatment (P>0.05).

Adverse effects during treatment

The occurrence of adverse reactions during the treatment of the two groups was statistically analyzed, as shown in **Tables 4** and **5**. There was no remarkable difference in adverse reactions of fatigue, nausea and vomiting, thrombocytopenia and other aspects related to TACE treatment between the two groups (P>0.05). The incidence of diarrhea, hypertension, hand-foot syndrome and proteinuria in the JG was

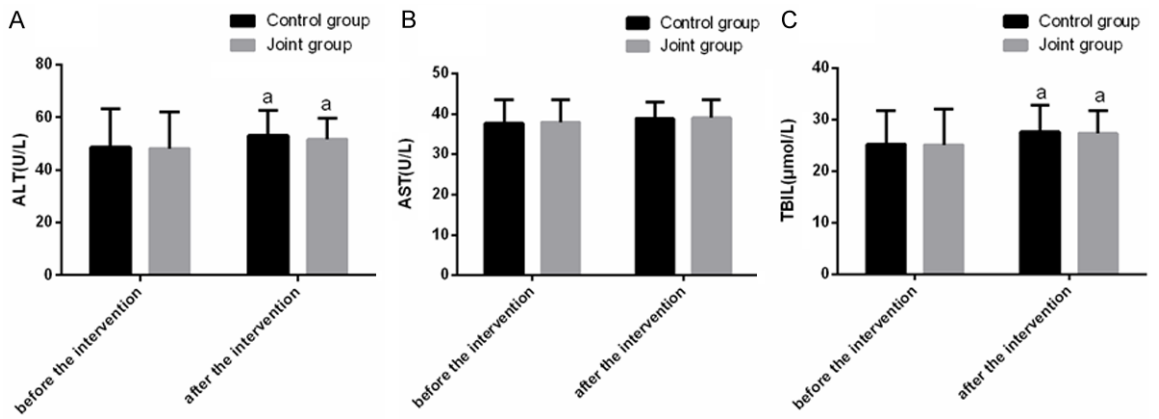

Figure 3. Comparison of liver function indexes between the two groups before and after treatment. A. Comparison of ALT levels between the two groups before and after treatment. B. Comparison of AST levels between the two groups before and after treatment. C. Comparison of TBIL levels between the two groups before and after treatment. Note: a indicates comparison with the same group before treatment, $^{a}P<0.05$.

Table 4. Comparison of adverse reactions related to TACE treatment between two groups in treatment process n [%]

Group	Number of cases	Gastrointestinal hemorrhage	Inguinal hematoma	Spontaneous bacterial peritonitis	Liver function impairment	Hepatorenal syndrome	Ischemic cholecystitis	Pleural effusion
Control group	116	2 (1.72)	5 (4.31)	6 (5.17)	9 (7.76)	2 (1.72)	5 (4.31)	3 (2.59)
Joint group	131	4 (3.05)	6 (4.58)	7 (5.34)	10 (7.63)	1 (0.76)	5 (3.82)	2 (1.53)
X^2		0.459	0.011	0.004	0.001	0.473	0.039	0.348
P		0.498	0.918	0.952	0.971	0.492	0.844	0.555

higher than that in the CG (P<0.05). The adverse reactions in most patients could be controlled after symptomatic treatment, dose reduction and suspension of administration.

Comparison of survival rate between two groups after treatment

The survival rate of the two groups was observed through follow-up, as shown in **Figure 4**. In which the one-year survival rate and the two-year survival rate of the patients in the CG were 26.72% and 9.48%, respectively, and the two of the patients in the JG were 50.38% and 27.48%, respectively. The overall survival rate of the JG was higher than that of the CG (P<0.05).

Discussion

Generally, in the case of PVTT, HCC patients have poor prognosis and an overall survival of only 2-4 months [16]. It is difficult for patients with this disease to undergo surgical resection. Hence, TACE has become the first option of treatment, which can effectively relieve blockage, relieve portal hypertension, and reduce the occurrence of complications such as hepatic encephalopathy and gastrointestinal hemorrhage. In general, it has notable short-term effect, but the long-term effect is not ideal [17-19]. Molecular targeted drugs are more and more widely used in clinic due to their precise therapeutic effects. Apatinib, as a newly applied broad-spectrum anti-tumor targeted drug, has the effect of inhibiting the proliferation of vascular endothelial cells. Meanwhile, it can also change the multidrug resistance of tumor cells, thus improving the efficacy of traditional chemotherapy drugs, especially platinum drugs [20]. However, the combination of TACE and apatinib has not been sufficiently studied in the application of HCC and PVTT.

Relevant studies have supported that in treating liver cancer patients, apatinib combined with TACE showed better objective remission rates and disease control rates in the first and third months compared with TACE alone [21].

Table 5. Other adverse reactions during treatment n [%]

Group	Number of cases	Nausea and vomiting	Thrombocytopenia	Diarrhea	Fatigue	Hypertension	Hand-foot syndrome	Proteinuria
Control group	116	28 (24.14)	3 (2.59)	4 (3.45)	6 (5.17)	3 (2.59)	0 (0.00)	0 (0.00)
Joint group	131	35 (26.72)	10 (7.63)	15 (11.45)	15 (11.45)	25 (19.08)	30 (22.90)	27 (20.61)
X^2		0.132	3.143	5.548	3.117	4.082	30.240	4.963
P		0.716	0.076	0.019	0.078	<0.001	<0.001	<0.001

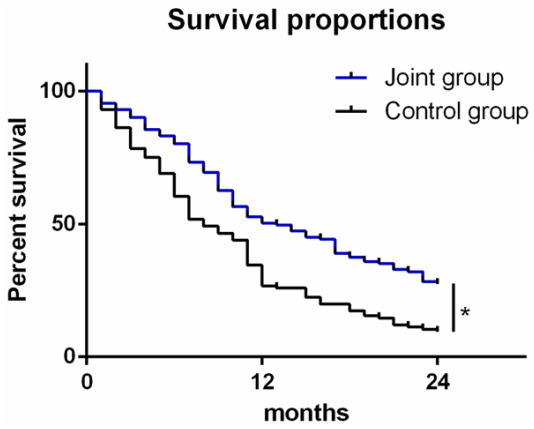

Figure 4. Comparison of survival of the two groups. The one-year survival rate and the two-year survival rate of the patients in the control group were 26.72% and 9.48%, respectively. The one-year survival rate and the two-year survival rate of the patients in the joint group were 50.38% and 27.48%, respectively.

However, the research of team of Lu [13] showed that there is no notable difference between the effective rate of apatinib combined with TACE in treating advanced HCC patients and TACE alone. In this study, the disease control rate of the two groups was compared. The group with combined use of apatinib had higher disease control than that of the TACE group alone, and there was no remarkable difference after statistical comparison. The result may be due to the fact that only the short-term efficacy of the two groups were detected this time, without comparing the efficacy of the patients treated for a long time. At present, angiogenesis disorder has been identified as a key factor in multiple pathological conditions including cancer [22]. Previous studies have proved that angiogenesis produces a marked effect on the occurrence and progression of HCC [23]. Since tumor vasculature produces a marked effect on carcinogenesis, the use of angiogenesis as a target for cancer therapy has become a recognized and effective method [24]. VEGF and its related receptors are highly expressed in most cancers and are powerful angiogenic factors, which are involved in the occurrence, neovascularization, invasiveness and metastatic potential of HCC [25]. HIF-1α is also one of the angiogenic factors, which is decreased in HCC and is correlated with poor prognosis of HCC [26]. The results of this study indicated that VEGF and HIF-1α levels reduced clearly after treatment with TACE alone and TACE combined with apatinib, and the latter one was more significant. Previous studies have shown that after 1 month of TACE treatment in primary liver cancer, the serum VEGF and hif-1 levels of the patient decrease [27], which is similar to the results in this paper. Combined with the results of this study, it could be seen that the anti-angiogenic ability of apatinib combined with TACE is improved. It is speculated that apatinib plays an anticancer role via inhibiting the activity of VEGFR-2 tyrosine kinase, cutting off the signal transduction of VEGF-receptor binding and inhibiting tumor angiogenesis.

The T lymphocyte cells subpopulation are part of the human immune response and are an important component of the body's immune system. Among them, CD3+ is the total T lymphocyte, and T cells are divided into two subsets, which respectively express CD4+ and CD8+, and CD4+/CD8+ can reflect the cellular immune dysfunction. Therefore, the detection of T cell subsets can largely reflect the immune function and disease development in the body [28-30]. Recent studies show that recombinant human endostatin combined with apatinib mesylate can considerably improve the immune function factors of non-small cell lung cancer patients, and increase CD3+, CD4+, and CD4+/CD8+ levels [31]. Therefore, we speculate that apatinib may have the same effect in patients with HCC complicated with PVTT. Previous studies have proved that TACE can improve the immunity of patients with advanced HCC [32]. However, in the results of this study, the

immune function factors of the two groups of patients with HCC complicated with PVTT improved after treatment, which is similar to the previous results. The following results showed that CD3+, CD4+, and CD4+/CD8+ levels were higher than those of TACE alone, and CD8+ was lower than those of TACE alone, suggesting that TACE combined with apatinib could enhance the therapeutic effect of TACE and remarkably improve the immunity of patients with HCC complicated with PVTT. After TACE treatment, because of the absorption of necrotic substances and the application of chemotherapeutic drugs in the embolism and other factors, adverse reactions such as liver function damage and hemorrhage will occur [33]. Moreover, some studies have reported that TACE has certain influence on liver function of HCC patients, which will lead to the elevation of ALT level after treatment [34]. Therefore, we have detected the liver function indexes of patients and found that ALT and TBIL were slightly increased after TACE treatment in the two groups, while no difference was found in AST level. There was no remarkable difference in AST, TBIL and ALT levels between the two groups. The findings indicate that the combined administration of apatinib will not trigger aggravation of liver function damage caused by TACE in patients with HCC complicated with PVTT. Then, we compared the complications in the two groups and found that there was no remarkable difference in the incidence of TACE-related adverse events between the two groups. At present, various anti-tumor therapies combined with apatinib have become hot research topics, and previous literature shows that the application of apatinib in gastric cancer can remarkably improve the survival of patients [35]. Due to certain toxic side effects of apatinib, however, there are certain restrictions in application. Adverse reactions of patients after using apatinib in this study are mainly diarrhea, hypertension, hand-foot syndrome, proteinuria and other aspects, which is consistent with the previous reported results [36]. However, there are no cases of patients dying from side effects of treatment in this study, and the adverse reactions can be relieved after corresponding treatment, which proves that the treatment scheme is safe and feasible. At present, there are reports that TACE treatment can improve the survival rate of HCC patients complicated with PVTT in some degree [37], but the efficacy is limited. The research of Liu's team [4] shows that the combined treatment of apatinib and TACE improves the progression-free survival rate and overall survival rate of patients with HCC complicated with PVTT. Since there is no CG in this study, as well as the sample size, whether it is the result of combined use remains to be further explored. After follow-up investigation in this study, it was found that the survival rate of patients treated with apatinib combined with TACE was remarkably higher than that of patients treated with TACE alone, and the survival rate of patients with HCC combined with PVTT was prolonged.

This study mainly explores the effect of apatinib combined with TACE on tumor angiogenesis, immune function and safety of patients with HCC combined with PVTT. However, there are still some limitations in this study. For example, no comparison has been made on the clinical efficacy of long-term recovery at multiple stages, and only patients in Child-Pugh grade A and grade B were selected. Therefore, we will strengthen the research in this direction in the future, so as to provide a better direction for clinical treatment.

Conclusion

The application of apatinib combined with TACE in patients with HCC combined with PVTT can notably inhibit tumor angiogenesis, improve the immunity of patients, and it has a high safety.

Disclosure of conflict of interest

None.

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