Apatinib Combined With Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombus: A Multicenter Retrospective Study

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ABSTRACT

Purpose: Studies focusing on the effects of combined transcatheter arterial chemoembolization (TACE) + the tyrosine kinase inhibitor apatinib in the treatment of patients with hepatocellular carcinoma (HCC), with the location and extent of portal vein tumor thrombus (PVTT) assessed as the main variable, are rare. This multicenter, retrospective, controlled study was performed to compare the efficacy and tolerability of TACE + apatinib and TACE alone in patients with HCC and PVTT.

Methods: We retrospectively analyzed data from patients with nonresectable HCC and PVTT who underwent treatment with TACE + apatinib or TACE alone between January 2015 and January 2016. Outcomes in patients who underwent TACE + apatinib were compared with the outcomes of patients who underwent TACE alone, by using the Kaplan–Meier method, according to PVTT type: PVTT in the main portal vein (type A), PVTT in the first-order portal vein branch (type B), and PVTT in second- or lower-order portal vein branches (type C).

Findings: One hundred eighty-eight patients were included in the analysis; 85 underwent treatment with TACE + apatinib and 103 underwent treatment with TACE. TACE + apatinib was associated with a significantly greater median survival compared with TACE alone in patients with PVTT type B (12.2 vs 7.5 months; $P < 0.001$) or type C (13.7 vs 7.2 months; $P = 0.006$). Along with treatment strategies and α-fetoprotein, the absence of main PVTT was an independent factor predictive of survival on uni- and multivariate analysis. Apatinib-related grade 3 adverse events occurred in 27 patients (31.8%).

Implications: TACE + apatinib can be of potential benefit to patients with advanced HCC with tumor thrombus in the first- and lower-order portal vein branches. Adverse events with apatinib need to be monitored during application, despite the manageable appearance. (*Clin Ther*. 2019;41:1463–1476) © 2019 Published by Elsevier Inc.

Key words: apatinib, hepatocellular carcinoma, overall survival, transarterial chemoembolization.

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INTRODUCTION

According to the 2018 Global Cancer Statistics report, liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide.[1] Due to rapid proliferation, increased intrahepatic spreading, and metastasis, the survival rate in patients with nonresectable hepatocellular carcinoma (HCC) is typically poor, especially in those with portal vein tumor thrombus (PVTT).[2-7] Moreover, the treatment options in patients with HCC and PVTT are limited, and PVTT usually indicates a poor prognosis, with a very short median survival time (2–4 months) if left untreated.[8-10] According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) and sorafenib are recommended as standard therapies in patients with HCC of BCLC stages B and C, respectively.[11] Although Xue et al,[12] Zhang et al,[13] and Luo et al[14] have reported that TACE was well tolerated and might improve OS in patients with HCC and PVTT, its efficacy remained unsatisfactory. Meanwhile, sorafenib was not associated with better survival in patients with HCC and PVTT in the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol[15]) trial. Another multicenter study revealed that TACE combined with sorafenib could prolong median time to progression by nearly 2 months versus TACE alone, but the difference was not statistically significant.[16] Therefore, the immediate establishment of a new treatment strategy is necessary.

Apatinib, a selective inhibitor of vascular endothelial growth factor receptor (VEGFR)-2, with a binding affinity 10-fold that of vatalanib or sorafenib, has shown encouraging results in the treatment of a variety of solid tumors.[17-19] Apatinib* was approved in China as a subsequent-line therapy in patients with advanced gastric cancer.[20,21] Promising efficacy and tolerability profiles have been reported with apatinib as the first-line therapy in a Phase II multicenter, randomized trial conducted in China involving patients with treatment-refractory gastric cancer.[22] Based on the findings from those studies, it can be assumed that a combination of delayed intrahepatic tumor progression using TACE and targeting systemic disease (eg, vascular invasion or extrahepatic metastasis) with apatinib may offer a greater survival benefit to patients with HCC and PVTT than TACE alone. Moreover, only 2 reports have focused on the effects of combined TACE + apatinib in the treatment of patients with HCC,[23,24] and although the retrospective study by Liu[24] assessed the efficacy and tolerability of the above treatment in patients with PVTT, it included a rather small number of patients. We conducted this multicenter, retrospective, controlled study in 4 hospitals to compare the efficacy and tolerability profile of TACE + apatinib and TACE alone in patients with HCC and PVTT.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the medical records of cirrhotic patients with unresectable HCC and PVTT who underwent TACE + apatinib or TACE alone between January 2015 and January 2016 at 1 of 4 institutions in China: the First Affiliated Hospital of Sun Yat-Sen University, Nanfang Hospital, Southern Medical University, Dongguan People's Hospital, and Gaozhou People's Hospital.

Approval of the protocol of this study was obtained from the the first affiliated hospital of Sun Yat-Sen University, and written informed consent was obtained from each patient before the procedures.

Inclusion and Exclusion Criteria

Inclusion criteria included: (1) cirrhosis diagnosed based on transient elastography (≥14.6 kPa), ultrasonography, and MR imaging findings (eg, signs of portal hypertension, ascites, heterogeneous echotexture, and surface nodularity); (2) HCC diagnosed by 2 imaging modalities, or biopsy[25]; (3) stage B or C according to the BCLC staging system[26] who could not tolerate surgical resection or who refused surgical resection; (4) Child-Pugh A or B liver function; (5) lack of heart, lung, or kidney dysfunction; (6) an Eastern Cooperative Group Performance Status score of 0–2 points; and (7) presence of PVTT on 3-phase dynamic computed tomography obtained within 7 days before treatment.[27]

Patients were excluded from this study if they: (1) had main portal vein obstruction; (2) had undergone

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* Developed by Jiangsu Hengrui Medicine Co Ltd, Lianyungang, People's Republic of China.

surgery, local-regional therapies (radiofrequency ablation), or liver transplantation; (3) had undergone sorafenib therapy, systemic chemotherapy, intra-arterial chemo-infusion, or TACE; (4) had a history or presence of a malignant tumor in addition to HCC; (5) underwent treatment with a method (radiofrequency ablation, percutaneous ethanol injection, or iodine-125 seed implantation) other than TACE during this study.

Classification of PVTT

The criteria for PVTT classification were used as reported previously,[28–31] and PVTT was classified into 1 of 3 subgroups: (1) type A, defined as PVTT in the main portal vein; (2) type B, defined as PVTT in the first-order portal vein branch (the right or left portal vein); and (3) type C, defined as PVTT in the second- or lower-order portal vein branch (segmental branches of portal vein or higher).

Therapeutic Methods

TACE Procedures

TACE was performed by 1 of 2 experienced radiologists (JY Y and JP L) with 8 years of experience in interventional therapy according to previous literature.[32] A selective catheter was inserted into the tumor-feeding arteries after an evaluation of the arterial blood supply of the liver and confirmation of the patency of the portal vein by visceral angiography.

Hepatic artery infusion chemotherapy was performed using 300 mg of carboplatin.[†] Subsequently, chemoembolization was performed using an emulsion consisting of 50 mg of epirubicin[‡] and 5 mL of ethiodized oil.[§] The same chemotherapeutic agents at the same dosages were used throughout this study, regardless of the tumor number and size. If residual flow remained after infusion of these agents, additional lipiodol was injected. Embolization was finally performed using gelatin sponge particles (Gelfoam; Hangzhou Bi-

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† Bristol-Myers Squibb, New York, New York.

‡ Trademark: Pharmorubicin (Pfizer Inc, New York, New York).

§ Trademark: Lipiodol Ultra-Fluide (Guerbet Laboratories, Aulnay-sous-Bois, France).

Trumed Biotech Co Ltd, Hangzhou, Zhejiang, People's Republic of China) 350–560 μm in diameter.

Apatinib Administration

Patients treated with apatinib received therapy at a daily metronomic oral dosage of 500 mg on days 3–5 after the TACE session. Grades 3/4 adverse events (AEs) led to dosage modification (250 mg daily) or temporary interruption until symptoms resolved to grade ≤2. Treatment continued until disease progression as defined by the Modified Response Evaluation Criteria in Solid Tumor (mRECIST), clinical progression (defined as an Eastern Cooperative Group Performance Status score of ≥3 or symptomatic deterioration, including increased levels on liver function tests), unacceptable toxicity, withdrawal of consent by the patient, a decision by the treating physician that discontinuation would be in the patient's best interest, or death. Patients were followed up for tumor assessments every month during the treatment, which was allowed to continue beyond progression on the investigator's judgment of patient benefit.

Clinical and Laboratory Evaluation

Clinical and laboratory data were collected from all patients prior to TACE. Clinical data included age, sex, BCLC stage, and Child-Pugh score. In addition, imaging data including tumor size and vascular invasion were collected using abdominal computed tomography or MR imaging. Laboratory data included α-fetoprotein (AFP), alanine and aspartate aminotransferase, albumin, total bilirubin, hepatitis B surface antigen, and prothrombin time.

The patients underwent computed tomography or MR imaging every 4–12 weeks. Efficacy was measured as time to tumor progression (TTP; defined as the number of months from the start of the first TACE procedure until the date that tumor progression was confirmed radiologically) and overall survival (OS; defined as the number of months between the first TACE procedure until death or the last follow-up). AEs were reported according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, and the severities of the AEs were recorded.

Tumor response was evaluated according to mRECIST,[33] which has 4 levels: *complete response* (CR), the disappearance of all of the target lesions in

the arterial phase in enhanced imaging; *partial response* (PR), in which the total reduction of the diameter of the target lesions (enhanced arterial phase) was ≥30% compared with the baseline value; *stable disease* (SD), in which the diameter of the target lesion was reduced by <30% or increased by <20%; and *progressive disease* (PD), in which the diameter of the target lesion was increased by ≥ 20% or new lesions appeared.

Statistical Analysis

All statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois). To determine significant differences between groups, the continuity correction and independent-samples t test, Pearson χ^2 test, and Fisher exact test were used. Survival curves were calculated for both groups by using the Kaplan−Meier method. Univariate analysis was performed using the log-rank test. Variables with a P value of <0.1 on univariate analysis were entered into multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards regression model. All statistical analyses were based on a 2-tailed hypothesis test with a significance level of $P < 0.05$.

RESULTS

Clinical Characteristics

Between January 2015 and January 2016, 289 patients with unresectable HCC and PVTT underwent treatment with TACE + apatinib or TACE alone, of whom 188 were included in the final analyses
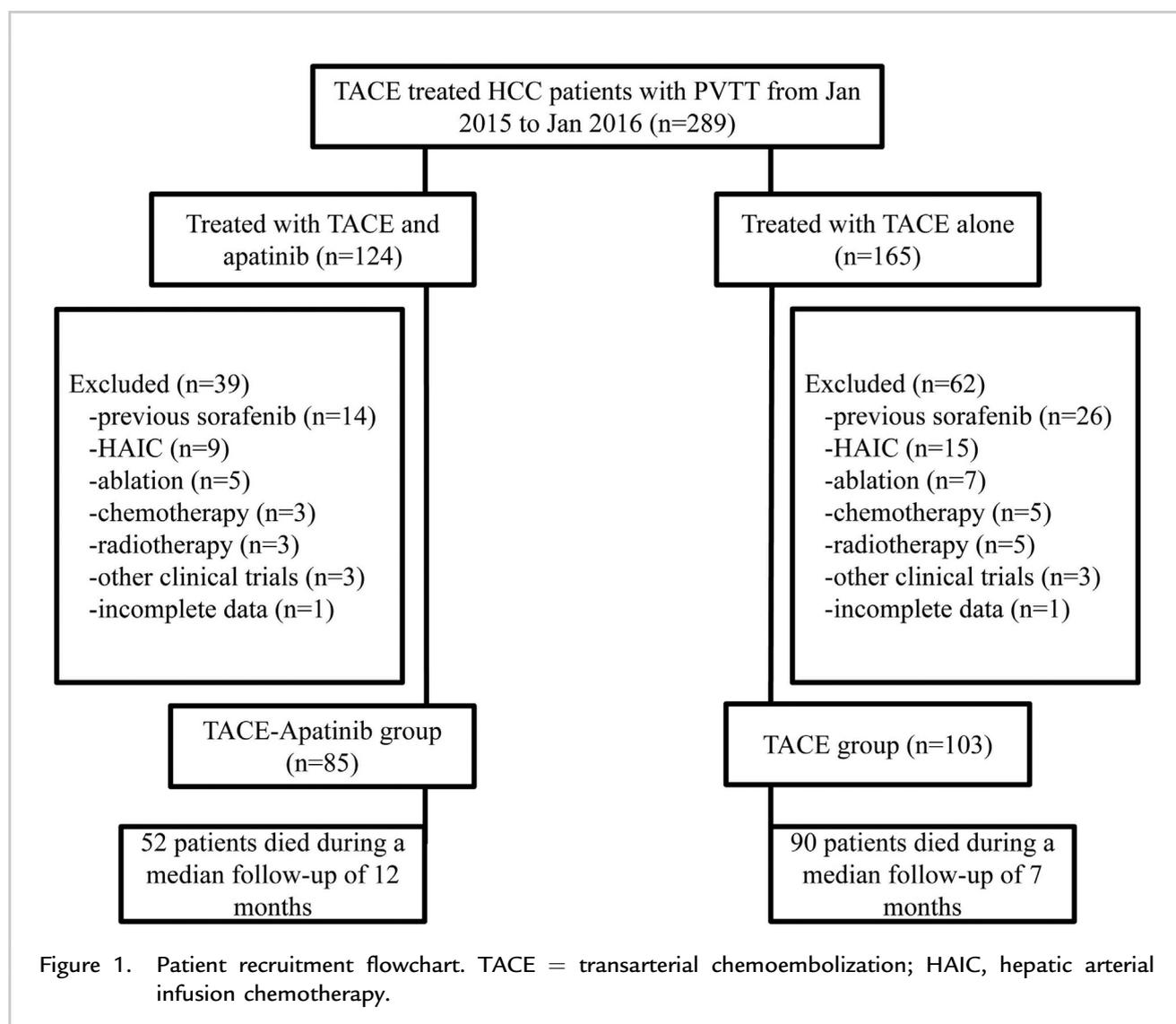

Figure 1. Patient recruitment flowchart. TACE = transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

Table 1.   Baseline Characteristics of TACE treated HCC patients with PVTT.

Characteristic	TACE-Apatinib Group (n=85)	TACE Group (n=103)	P Value
Gender			0.085
Male, n (%)	68 (80)	71 (68.9)	
Female, n (%)	17 (20)	32 (31.1)	
Age (y)	49 (17-71)	50 (19-80)	0.104
ECOG performance			0.116
0, n (%)	67 (78.8)	90 (87.4)	
1-2, n (%)	18 (21.2)	13 (12.6)	
Child-Pugh class			0.786
A, n (%)	73 (85.9)	87 (84.5)	
B, n (%)	12 (14.1)	16 (15.5)	
ALT (U/L)	45.0 (11-281)	39.0 (4-218)	0.976
AST (U/L)	47.7 (15-324)	40.1 (9-157)	0.232
PLT (10^9/L)	179.3 (40.0-636.0)	180.7 (67.0-346.0)	0.124
PT (s)	12.8 (10.4-16.5)	12.9 (10.3-17.3)	0.236
Total bilirubin level (mmol/L)	17.5 (4.7-64.7)	16.8 (4.0-44.5)	0.101
Albumin level (g/L)	38.7 (21.1-48.0)	37.5 (28.0-45.0)	0.132
a-Fetoprotein level (ng/mL)			0.277
≥400, n (%)	47 (55.3)	65 (63.1)	
<400, n (%)	38 (44.7)	38 (36.9)	
Location of PVTT			0.263
First-order portal vein branch, n (%)	51 (60)	54 (52.4)	
Second- or lower-order portal vein branches, n (%)	18 (21.2)	19 (18.4)	
Main portal vein, n (%)	16 (18.8)	30 (29.1)	
HBV infection			0.306
Yes,n (%)	68 (81.9)	78 (75.7)	
No,n (%)	15 (18.1)	25 (24.3)	
Tumor number			0.394
Multiple, n (%)	68 (80)	77 (74.8)	
Single, n (%)	17 (20)	26 (25.2)	
Tumor Size (cm)			0.145
≥7cm, n (%)	58 (68.2)	80 (77.7)	
<7cm, n (%)	27 (31.8)	23 (22.3)	

Note.—TACE = transarterial chemoembolization; HR = hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PLT = platelet count; PT = prothrombin time; TBIL = total bilirubin; ALB = albumin; AFP = α-fetoprotein; PVTT = portal vein tumor thrombus.

(Figure 1). Accordingly, they were divided into 2 groups: the TACE + apatinib group (n = 85 patients; age range, 17−71 years; 68 men) and the TACE group (n = 103; age range, 19−80 years; 71 men). There were no significant differences between the 2 study groups regarding demographic and laboratory characteristics at baseline (Table I). In the subgroups of patients with PVTT types A, B, and C, baseline characteristics between the TACE + apatinib group and the TACE group were not significantly different (data not shown).

Table II. Adverse events related to transarterial chemoembolization (TACE). Data are given as number (%) of patients.

Adverse Event	TACE + Apatinib (n = 85)	TACE (n = 103)	P
Liver dysfunction	11 (12.9)	9 (8.7)	0.352
Inguinal hematoma	3 (3.5)	4 (3.9)	0.898
Gastrointestinal hemorrhage	3 (3.5)	3 (2.9)	0.811
Pleural effusion	3 (3.5)	2 (1.9)	0.501
Liver abscess	2 (2.4)	4 (3.9)	0.552
Spontaneous bacterial peritonitis	2 (2.4)	2 (1.9)	0.846
Ischemic cholecystitis	1 (1.2)	3 (2.9)	0.412
Hepatic arterial dissection	1 (1.2)	2 (1.9)	0.677
Hepatorenal syndrome	1 (1.2)	1 (1.0)	0.891
Pulmonary/cerebral oil embolization	0	0	—

Tolerability of TACE + Apatinib Versus TACE

AEs considered related to TACE treatment are shown in Table II; no significant differences were observed between the 2 groups. Twenty-seven AEs occurred in 21 of the 85 patients (24.7%) in the TACE + apatinib group, while 30 AEs occurred in 26 of the 103 patients (25.2%) in the TACE group.

Seventy-eight patients (91.8%) in the TACE + apatinib group experienced drug-related AEs during apatinib treatment (Table III). The most frequent drug-related AEs were hand-foot-skin reaction (45 [52.9%]), hypertension (43 [50.6%]), and proteinuria (26 [30.6%]). Grade 3 AEs occurred in 27 patients (31.8%): hand-foot skin reaction (20 [23.5%]), hypertension (12 [14.1%]), proteinuria (6 [7.1%]), and gastrointestinal hemorrhage (1 [1.2%]). AEs led to treatment interruption in all patients with grade 3 AEs (n = 39). The mean duration of apatinib treatment was 11.4 months (95% CI, 9.8–13.5).

Tumor Response

The tumor responses in patients with different types of PVTT are shown in Table IV. The disease-control rate (DR + PR + SD) in the TACE + apatinib group was 59%, which was significantly higher than the 14% observed in the TACE group (P < 0.001). Subgroup analysis revealed that disease-control rates in patients with type B or C PVTT in the TACE + apatinib group were 59% and 83%, respectively, which were significantly higher than the rates observed in the TACE group (13% and 3%,

respectively; P < 0.001 and P = 0.002). However, in patients with type A PVTT, the difference in disease-control rate between the 2 treatment groups was not significant (13% vs 3%; P = 0.274).

TTP in Patients With Different Types of PVTT

Median TTP values were 6.1 months (95% CI, 4.9–7.3) in the TACE + apatinib group and 3.7 months (95% CI, 3.1–4.4 months) in the TACE group (P < 0.001). Subgroup analyses results on TTP in the TACE + apatinib group and the TACE group were as follows: in patients with type A PVTT, median TTP was 1.2 versus 2.3 months, respectively (P = 0.054); in patients with type B PVTT, median TTP was 6.9 versus 4.2 months, respectively (P = 0.013); in patients with type C PVTT, median TTP was 8.3 versus 4.6 months, respectively (P = 0.014).

OS in Patients With Different Types of PVTT

Median OS values were 12.0 months (95% CI, 10.3–13.7) in the TACE + apatinib group and 7.0 months (95% CI, 6.4–7.6) in the TACE group (P < 0.001) (Figure 2A). Univariate analysis identified the following factors as affecting OS: treatment strategy, AFP level <400 ng/mL, and PVTT type B/C (all, P < 0.001). These significant factors were entered in multivariate analysis by using the Cox proportional hazards model, and the absence of main PVTT was found to be an independent predictive factor for OS, alongside treatment strategy and AFP level (Table V).

Table III. Adverse events after apatinib application. Data are given as number (%) of patients.

| Adverse Event	TACE + Apatinib (n = 85)						TACE (n = 103)						P
	All Events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Hand-foot skin reaction	45 (52.9)	12 (14.1)	13 (15.3)	20 (23.5)	0	0	0	0	0	0	0	0	<0.001
Hypertension	43 (50.6)	21 (24.7)	10 (11.8)	12 (14.1)	0	0	0	0	0	0	0	0	<0.001
Proteinuria	26 (30.6)	14 (16.5)	6 (7.1)	6 (7.1)	0	0	0	0	0	0	0	0	<0.001
Abdominal pain	21 (24.7)	15 (17.6)	6 (7.1)	0	0	0	36 (35.0)	21 (20.4)	13 (12.6)	2 (1.9)	0	0	0.152
Diarrhea	19 (22.1)	12 (14.1)	7 (8.2)	0	0	0	0	0	0	0	0	0	<0.001
Headache	18 (21.2)	13 (15.3)	5 (5.9)	0	0	0	4 (3.9)	3 (2.9)	1 (1.0)	0	0	0	<0.001
Cough	16 (18.8)	9 (10.6)	7 (8.2)	0	0	0	8 (7.8)	4 (3.9)	4 (3.9)	0	0	0	0.029
Dental ulcer	14 (16.5)	8 (9.4)	6 (7.1)	0	0	0	1 (1.0)	0	1 (1.0)	0	0	0	<0.001
Hoarseness	10 (11.8)	8 (9.4)	2 (2.4)	0	0	0	0	0	0	0	0	0	<0.001
Gingival bleeding	9 (10.6)	6 (7.1)	3 (3.5)	0	0	0	4 (3.9)	4 (3.9)	0	0	0	0	0.087
Fatigue	8 (9.4)	5 (5.9)	3 (3.5)	0	0	0	3 (2.9)	3 (2.9)	0	0	0	0	0.069
Thrombocytopenia	8 (9.4)	4 (4.7)	4 (4.7)	0	0	0	15 (14.6)	13 (12.6)	2 (1.9)	0	0	0	0.372
Gastrointestinal hemorrhage	1 (1.2)	0	0	1 (1.2)	0	0	3 (2.9)	1 (1.0)	2 (1.9)	0	0	0	0.628

TACE = transarterial chemoembolization.

Table IV.   Tumor responses in patients with different types of portal vein tumor thrombus. Data are given as numbers of patients unless otherwise stated.

Tumor Response	All Patients		Type A		Type B		Type C	
	TACE + Apatinib (n = 85)	TACE (n = 103)	TACE + Apatinib (n = 16)	TACE (n = 30)	TACE + Apatinib (n = 51)	TACE (n = 54)	TACE + Apatinib (n = 18)	TACE (n = 19)
Disease control rate,* %	59	14	13	3	59	15	83	26
Complete response	0	0	0	0	0	0	0	0
Partial response	24	4	0	0	13	3	8	2
Stable disease	26	10	2	1	17	5	7	3
Progressive disease	35	89	14	29	21	46	3	14

PVTT = portal vein tumor thrombus; TACE = transarterial chemoembolization.
$P < 0.001$ for all patients (Pearson χ^2), $P = 0.274$ for type A PVTT (Fisher exact test); $P < 0.001$ for type B PVTT (continuity correction), and $P = 0.002$ for type C PVTT (continuity correction).
* Calculated as (Complete response + Partial response + Stable disease)/n.
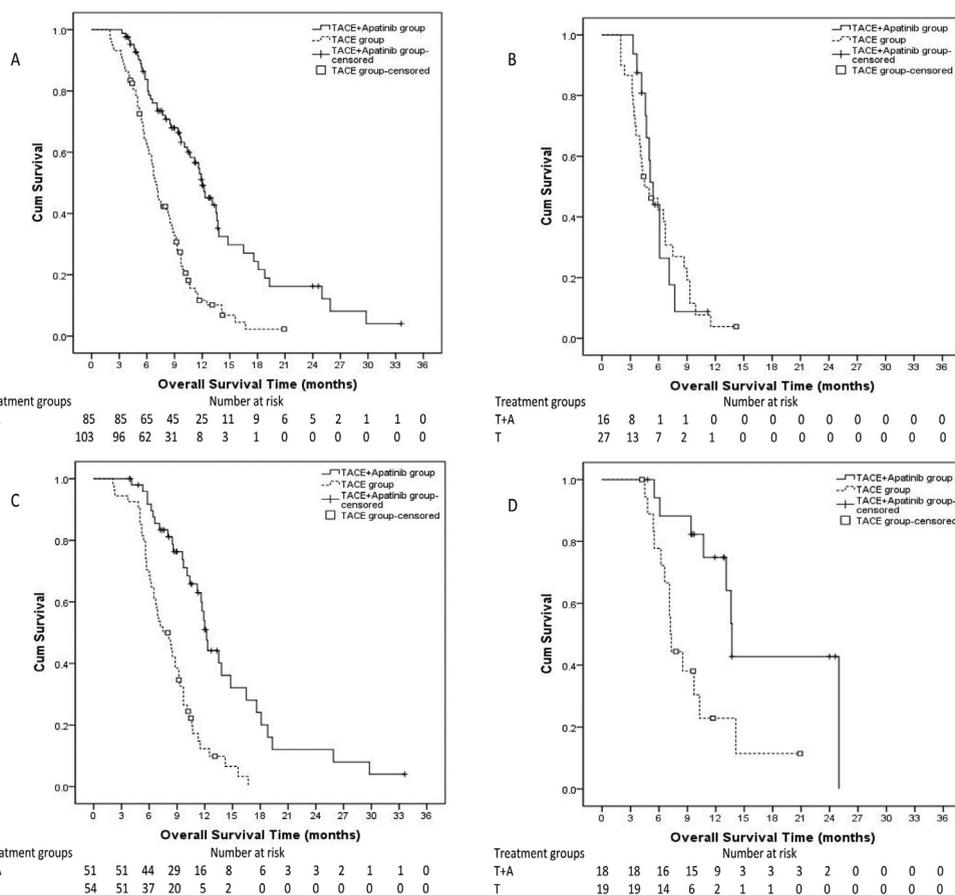
Figure 2. Kaplan−Meier curves of overall survival (OS) in patients with hepatocellular carcinoma and portal vein tumor thrombus (PVTT) who underwent transarterial chemoembolization (TACE) with or without apatinib (T+A and T, respectively). A, Whole study population (median OS [months], 12.0 vs 7.0; $P < 0.001$). B, Patients with type A PVTT (OS, 5.4 vs 4.5; $P = 0.829$). C, Patients with type B PVTT (OS, 12.2 vs 7.5; $P < 0.001$). D, Patients with type C PVTT (OS, 13.7 vs 7.2; $P = 0.006$).

Subgroup analyses of OS in patients with different types of PVTT showed that the median OS values in patients with type A, B, or C PVTT were 5.4 months (95% CI, 4.69−6.11), 12.2 months (95% CI, 11.4−13.0), and 13.7 months (95% CI, 12.8−14.5), respectively, in the TACE + apatinib group, and 4.5 months (95% CI, 2.4−6.6), 7.5 months (95% CI, 5.7−9.3), and 7.2 months (95% CI, 6.8−7.6), respectively, in the TACE group (Figure 2B−D). The median OS values in patients with type B or C PVTT were found to be significantly improved in the TACE + apatinib group compared with those in the TACE group ($P < 0.001$ and $P = 0.006$, respectively).

DISCUSSION

PVTT occurs in a substantial proportion of patients with HCC and is associated with high degrees of malignancy and treatment difficulties.[4,6,10,24,27,31,34] The recommended treatment for advanced HCC according to BCLC is sorafenib. However, the efficacy of sorafenib in the treatment of HCC with PVTT is limited, and sorafenib is too expensive for most patients in China to afford (about 40,000 CNY [5776 USD] per month, while apatinib costs about 10,000 CNY [1444 USD] per month).[35−38] It is therefore necessary to conduct new clinical trials in patients with advanced HCC in China, to identify more efficient and suitable treatments for Chinese

Table V. Univariate and multivariate analysis of baseline variables affecting overall survival in patients receiving transarterial chemoembolization (TACE).

Variable	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Sex: M/F	1.017	0.668–1.548	0.937			
Age	1.002	0.986–1.018	0.820			
Treatment strategies: TACE + apatinib/TACE	0.446	0.295–0.675	<0.0001	0.443	0.306–0.641	<0.0001
ECOG performance: 0/1–2	0.834	0.504–1.379	0.478			
Child-Pugh class: A/B	1.109	0.556–2.213	0.768			
ALT	1.003	0.996–1.009	0.444			
AST	0.998	0.992–1.009	0.572			
PLT	1.001	0.999–1.003	0.253			
PT	1.006	0.856–1.182	0.940			
TBIL	1.008	0.986–1.031	0.475			
ALB	0.984	0.939–1.031	0.494			
α-Fetoprotein <400/≥400 ng/mL	0.433	0.291–0.644	<0.0001	0.455	0.316–0.655	<0.0001
Type of PVTT						
B vs A	0.230	0.124–0.426	<0.0001	0.286	0.165–0.491	<0.0001
C vs A	0.385	0.250–0.595	<0.0001	0.411	0.274–0.617	<0.0001
HBV infection: N/Y	1.232	0.783–1.939	0.366			
Tumor number: single/multiple	1.394	0.892–2.180	0.145			
Tumor size: <7 cm/≥7 cm	0.968	0.624–1.503	0.885			

ALB = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis V virus; HR = hazard ratio; PLT = platelet count; PT = prothrombin time; PVTT = portal vein tumor thrombus; TACE = transarterial chemoembolization; TBIL = total bilirubin.

patients. In the current study, we retrospectively included patients with unresectable HCC and PVTT who underwent treatment with TACE + apatinib or TACE alone. We found that: (1) treatment with TACE + apatinib conferred a significant survival benefit when compared with treatment with TACE alone in patients with HCC and PVTT; (2) along with treatment strategies and AFP, the absence of main PVTT was an independent predictive factor for OS; and (3) apatinib was well tolerated generally and was associated with manageable AEs.

At present, it has been confirmed that there are a variety of angiogenic factors in patients with HCC, with VEGF being the strongest.[39–41] As a highly selective VEGFR-2 blocker, apatinib can block the migration and proliferation of vascular endothelial cells, decrease tumor microvessel density, and inhibit tumor growth.[17,21] An important finding in this study was that in patients with unresectable HCC and PVTT, TACE combined with apatinib could effectively prolong TTP and OS compared with TACE alone. In line with our results, the study by Lu et al[23] also demonstrated that the concurrent administration of apatinib with TACE may increase antitumor efficacy, providing more choices for patients with advanced HCC. The efficacy of TACE combined with apatinib compared with TACE alone in advanced HCC treatment may be attributed to the integrated control effect of locoregional plus systemic therapy. The combination therapy may cause selective hepatic arterial embolization without affecting blood supply to the normal liver, thus avoiding further ischemic liver damage. Furthermore, the expression of VEGF in remnant peripheral tumor

tissues becomes higher, more invasive, and metastatically active after TACE. These factors increase the invasion and metastasis abilities of tumors, and become the basis of disease progression and/or the production of new lesions. Therefore, the inhibition of high expression levels of VEGF in tumor cells induced by TACE could improve the long-term efficacy of TACE.[42−46] The disease-control rates were 59% in the TACE + apatinib group in our current study, 57.3% with sorafenib alone in a randomized controlled trial[15], and 57% with TACE + sorafenib in a study by Zhu et al.[48] These data suggest that apatinib combined with TACE is an effective treatment modality in terms of disease control.

Another important finding in this study was that PVTT involving the main portal vein was an independent predictive factor for OS. Regardless of treatment strategy, TACE + apatinib or TACE alone, patients with PVTT in the first-order portal vein branch or in the second- or lower-order portal vein branch had a better outcome. In addition, TACE + apatinib markedly prolonged TTP and OS when the subgroup of patients with main PVTT was excluded. A likely mechanism is that, as a highly selective VEGFR-2 blocker, apatinib can inhibit VEGF-stimulated endothelial cell migration and proliferation, which is required for native collateral formation and arteriogenesis.[17,19,21,22] Consistent with the treatment outcome with TACE + sorafenib in patients with HCC and PVTT,[48−52] our data suggest that patients with main PVTT should not be considered candidates for TACE + apatinib.

Apatinib was generally well tolerated and was associated with manageable AEs, with the most common drug-related AEs being hand-foot-skin reaction, hypertension, and proteinuria, which were similar to those reported in previous studies of apatinib as the only therapy and of apatinib administered in combination with TACE[21−24]. Most AEs in the present study were grade 1 or 2 and were well tolerated by patients without the need for dose reduction or suspension of treatment. These symptoms gradually alleviated and disappeared within 1 or 2 weeks. Grade 3 AEs were reduced to grade 1 after dose reduction to 250 mg or temporary interruption.

There were some limitations in our study. First, this study was of retrospective design, although objective end points (serologic, biochemical, and imaging data) were elaborately recorded. Second, bias may have been introduced in the course of explaining the treatment options and outcomes assessment, although statistical analysis was repeated 3 times by 3 different authors in the present study. Third, 101 patients with HCC and PVTT were excluded from the final analysis, which might have reduced the power of the statistical analysis. Last, sex differences can affect the prognosis of HCC, and the male/female ratios in our current study could have led to selection bias, although it did not reach the level of significance.

CONCLUSIONS

Our findings suggest that: (1) TACE + apatinib yield a promising outcome in patients with advanced HCC who develop a tumor thrombus in the first- or lower-order portal vein branches; and (2) AEs with apatinib need to be monitored during application, although this drug was generally well tolerated and was associated with manageable AEs, which deserves popularization and clinical application. However, because of the retrospective design and the unavoidable selection bias of this study, our findings and conclusions need to be verified in long-term prospective, randomized studies.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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