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Transarterial chemoembolization plus apatinib for unresectable hepatocellular carcinoma: a multicenter, randomized, open-label, phase III trial

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Abstract

Background This study aimed to assess the efficacy and safety of transarterial chemoembolization (TACE) in combination with apatinib (TACE-apatinib) for patients with unresectable hepatocellular carcinoma (HCC).

Methods This study was a multicenter, randomized, open-label, prospective, phase III trial. Patients with unresectable HCC were randomly assigned in a 1:1 ratio to receive either TACE-apatinib or TACE-alone treatment. Patients in the TACE-apatinib group began with a dosage of 500 mg/day of oral apatinib administered 4 days after the first TACE. The primary endpoint of this study was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), time to untreatable (unTACEable) progression (TTUP), and safety assessment.

Results From November 1, 2018 to November 18, 2021, a total of 196 patients were randomly assigned to either the TACE-apatinib ($n=86$) or TACE-alone ($n=92$) group. The median PFS in the TACE-apatinib group was significantly longer than that of in the TACE-alone group (6.1 months vs. 3.4 months, $p<0.0001$). The median OS was significantly prolonged in the TACE-apatinib group compared to the TACE-alone group (28.9 months vs. 24.0 months, $p=0.0005$). The median TTUP in the TACE-apatinib group was 26.8 months, which was significantly longer than that of 20.1 months in the TACE-alone group ($p=0.0003$). A significantly higher ORR and DCR were observed in the TACE-apatinib group compared to the TACE-alone group (ORR: 58.1% vs. 31.5%, $p<0.001$; DCR: 87.2% vs. 69.6%, $p=0.004$). Most of the treatment-related adverse events were grades 1–2, and no treatment-related deaths were observed.

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Conclusions Apatinib significantly improved the treatment effects of TACE for patients with unresectable HCC. TACE-apatinib could serve as a promising treatment option for this patient population, offering notable survival benefits while maintaining an acceptable safety profile.

Trial registration Chinese Clinical Trial Register, No. ChiCTR1800018621.

Keywords Transarterial chemoembolization, Apatinib, Hepatocellular carcinoma, Progression free survival

Background

Hepatocellular carcinoma (HCC) accounted for approximately 90% of all cases of primary liver cancer and ranked seventh in terms of morbidity among human cancers [1, 2]. It represented the third leading cause of cancer-related deaths [2]. Since transarterial chemoembolization (TACE) had been shown to effectively prolong survival, organizations such as the Barcelona Clinic Liver Cancer (BCLC) [3], the American Association for the Study of Liver Diseases (AASLD) [4], the European Association for the Study of the Liver [5], and the Asian Pacific Association for the Study of Liver [6] recommended TACE as the standard treatment for intermediate-stage (BCLC-B) HCC. Additionally, TACE was used as a first-line therapy for BCLC stage C HCC without extrahepatic metastasis (China liver cancer staging IIIa stage) in China [7]. Due to the high incidence of postoperative recurrence, multiple sessions of TACE were typically administered. However, repetitive TACE procedures could contribute to the decline in liver function, consequently leading to a poorer prognosis [8]. In addition, TACE-induced tumor hypoxia elevated the expression of angiogenic factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), leading to an increased tumor angiogenesis after TACE [9-11]. These findings suggested that blocking VEGF receptor could suppress the post-TACE surge of relevant proangiogenic factors. In 2020, a randomized, multicenter trial (TACTICS) reported that TACE plus sorafenib (a multikinase inhibitor) significantly improved progression-free survival (PFS) (progression here in referred to untreatable tumor progression) in patients with unresectable HCC compared with TACE alone [12]. Therefore, TACE in combination with antiangiogenic therapy may promise to be a strategy of improving the outcomes in patients with unresectable HCC.

Apatinib (Jiangsu Hengrui Pharmaceuticals Co., Ltd., China), a new small-molecule tyrosine kinase inhibitor, inhibits tumor angiogenesis by targeting vascular endothelial growth factor receptor-2 (VEGFR-2). Compared to sorafenib, apatinib has a significantly higher affinity for VEGFR-2 [13]. Preliminary studies have reported that apatinib achieves a higher objective response rate (ORR) in patients with advanced HCC compared to sorafenib [13].

The AHELP trial [14] showed that apatinib significantly improved the overall survival (OS) of HCC patients as a second-line therapy as compared with placebo (8.7 months vs. 6.8 months, $p=0.048$). Furthermore, a small-sized randomized controlled trial [15] and several retrospective control studies [16–19] report that the combined therapy of TACE with apatinib (TACE-apatinib) yielded a more favorable survival and a significantly higher tumor response with unresectable HCC when compared to TACE alone, and it was also safe for these patients. These results suggested that TACE-apatinib might be an effective and safe therapeutic choice for patients with unresectable HCC. Therefore, it is necessary to conduct a large-scale clinical trial to further verify these findings.

Current guidelines lack a clear recommendation on the use of TACE in combination with antiangiogenic therapy for unresectable HCC. In this study, we conducted a multicenter, randomized, open-label, prospective, phase III trial to assess the efficacy and safety of TACE-apatinib and compared it with TACE alone in patients with unresectable HCC. The findings from this trial may help fill the existing evidence gap regarding the role of TACE in combination with antiangiogenic therapy for unresectable HCC.

Methods

Study design and participants

This multicenter, randomized, open-label, prospective, phase III trial spanned from November 1, 2018 to November 18, 2021, was conducted at 15 hospitals in China (Chinese Clinical Trial Register, No. ChiCTR1800018621). The trial protocol was approved by the ethics committee of all participating centers. All patients provided a written informed consent before inclusion.

Patients with unresectable HCC were eligible for inclusion if they satisfied the following criteria: (1) patients were diagnosed with HCC by pathological examination or according to AASLD criteria; (2) aged 18–80 years; (3) having a life expectancy of at least 12 weeks; (4) BCLC stage B or stage C disease; (5) Eastern Cooperative Oncology Group (ECOG) performance status being 0 or 1; (6) Child–Pugh scores ≤ 7 points; (7) having a history of ≤ 2 TACE procedures; and (8) having the satisfactory blood, renal, and hepatic function parameters (hemoglobin ≥ 90

g/L, white blood cell count $\geq 1.5 \times 10^9$/L, platelet count $\geq 60 \times 10^9$/L, serum creatinine < 1.5 upper limit of normal [ULN], serum albumin ≥ 29 g/L, bilirubin ≤ 50 μmol/L, ALT and AST < 5 ULN). Patients were excluded if they had (1) main portal vein obstruction; (2) extrahepatic metastasis; (3) been preparing for liver transplantation; (4) an abnormal coagulation function (INR > 1.5 ULN or prothrombin time > ULN + 4 s); (5) a tumor burden > 70%; (6) a history of allergy to any component of apatinib; and (7) received radiotherapy, chemotherapy, or other molecularly targeted therapies. Full lists of inclusion and exclusion criteria can be found in the protocol.

Randomization and masking

Patients were randomly assigned to receive either TACE-apatinib or TACE alone at a 1:1 ratio using a computerized minimization technique. The assigned patients were stratified by BCLC stage (B versus C). Subsequently, patients were assigned to each group using stratified block randomization with a block size of four. Random measure stratification factors were unchanged. Patients and investigators were not masked to treatment allocation.

Treatment protocol

In the TACE-apatinib group, patients initiated treatment with oral apatinib at a dose of 500 mg/day, starting 4 days after the first TACE procedure. Apatinib was discontinued 2 days before and 3 days after each TACE procedure. TACE procedures in both groups involved intra-arterial injection of lipiodol (≤ 20 mL) plus epirubicin (≤ 60 mg) via the hepatic artery, followed by injection of gelatin sponge particles to interrupt the flow of blood. For patients who were HBsAg-positive with a HBV DNA level > 10^4 IU/mL, antiviral treatment was administered for 1 to 2 weeks, and TACE was performed until the HBV DNA level was lowered. After tumor progression, patients could receive secondary treatments. For patients in the TACE-alone group, if their tumors were suitable for TACE treatment, they received repeated-TACE treatment as needed, and oral sorafenib or lenvatinib treatment was added. For patients in the TACE-apatinib group, oral apatinib treatment was changed to oral sorafenib or lenvatinib treatment, and TACE treatment were repeated if patients were suitable for TACE treatment.

Tumor status was assessed locally by investigators in accordance with the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The first local radiological assessment was conducted at baseline, and subsequent images were obtained 4–6 weeks after TACE. If a complete response (CR) was achieved, the radiographic follow-up would be done every 2–3 months. However, if the initial response to the treatment was not CR, the radiographic examinations were performed every 4–6 weeks and timely treatment of TACE would be given. The treatment would be terminated, if the following took place: withdrawal of consent, toxicity intolerance, disease progression, or some other specified reasons. To manage adverse events associated with apatinib, dose interruptions and reductions were permitted. The dose of apatinib could be reduced stepwise from 500 to 250 mg/day and then to 0 mg/day. Once adverse events subsided or disappeared, the dose was incrementally adjusted to 500 mg/day.

Study endpoints

The primary endpoint was progression-free survival (PFS), which was defined as the time from the randomization to disease progression or death of any cause. The secondary endpoints included overall survival (OS), defined as the time from randomization to death of any cause; ORR, defined as the percentage of patients achieving complete response (CR) and partial response (PR); disease control rate (DCR), defined as the percentage of patients achieving CR, PR, and stable disease (SD); safety assessment; and time to untreatable (unTACE-able) progression (TTUP), defined as the duration from randomization to the point at which patients were considered unsuitable for further TACE treatment, including liver function of patients deterioration to Child–Pugh grade C, tumor size of patients exceeding 70% of the liver volume, patients with complete thrombosis of the main portal vein, patients with tumor extrahepatic metastasis, patients with an ECOG score ≥ 2 points, and the tumor progression of patients to the TACE refractoriness [20]. Adverse events were assessed by investigators and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE, version 4.0).

Statistical analysis

Efficacy and safety analyses were conducted in all patients who had received at least one session of TACE-apatinib treatment in the TACE-apatinib group or one session of TACE treatment in the TACE-alone group. The sample size was calculated based on the assumption of a median PFS of 4.5 months in the TACE-alone group and 7.0 months in the TACE-apatinib group, the data of which were calculated and estimated from unresectable HCC patients treated with TACE-apatinib or TACE in our center before October 2018 [17]. On the basis of a two-sided stratified log-rank test at a significance level of $\alpha = 0.05$, 161 PFS events were required for the analysis to detect the difference in PFS between the two groups with a power of 80% ($\beta = 0.2$). Assuming a 20% dropout rate,

280 patients should be recruited. The primary outcome of PFS and the secondary outcome of OS were estimated by examining differences between the TACE-apatinib group and TACE-alone group with a stratified log-rank test. A p value less than 0.05 was considered statistically significant. PFS and OS were evaluated by employing Kaplan–Meier method. The hazard ratio (HR) was estimated by utilizing a stratified Cox regression model. The baseline characteristics of patients, ORR, DCR, and safety were compared between the two groups using the χ^2 test, Fisher exact test, or a Student's t-test as appropriate. The statistical analyses were performed using the SAS 9.4 software package (SAS Institute, Cary, NC) or SPSS (version 26, Chicago, IL, USA).

Results

Patient characteristics

Between November 1, 2018 and November 18, 2021, 196 patients were randomly assigned to receive either TACE-apatinib ($n=86$) or TACE-alone treatment ($n=92$) (Fig. 1), and the two groups were compared in terms of efficacy and safety. The baseline characteristics of patients between the two groups were well balanced (Table 1). However, due to slow enrollment resulting from the COVID-19 pandemic and the update of BCLC guidelines in the treatment of unresectable HCC [3], the recruitment was closed before reaching the intended sample size of 280 patients. The data analysis was performed in advance.

Efficacy outcomes

As the time of data cutoff on November 30, 2023, 65 patients (75.6%) in the TACE-apatinib group and 87 patients (94.6%) in the TACE-alone group had died. The median follow-up duration of this study was 25.7 months. The total number of PFS events was 169, surpassing the preset requirement of 161 events, thereby meeting the statistical target for analysis. The median PFS was significantly improved with therapy of TACE-apatinib as compared to TACE alone (6.1 months [95% CI 4.5–7.3] vs. 3.4 months [95% CI 2.8–4.0]; HR 0.45 [95% CI 0.33–0.63]; two-sided $p<0.0001$) (Fig. 2). The median OS was significantly prolonged with TACE-apatinib treatment in comparison with TACE alone (28.9 months [95% CI 18.6–37.1] vs. 24.0 months [95% CI 17.1–27.1]; HR 0.55 [95% CI 0.40–0.77]; two-sided $p=0.0005$) (Fig. 3). After deleting the crossover-treated patients, the median OS in the TACE-apatinib group was also significantly longer than that of in the TACE-alone group (31.4 months [95% CI, 21.9–40.9] vs. 24.0 months [95% CI, 18.1–27.9]; HR 0.53 [95% CI, 0.38–0.74]; two-sided $p=0.001$). The median TTUP in the TACE-apatinib group was also

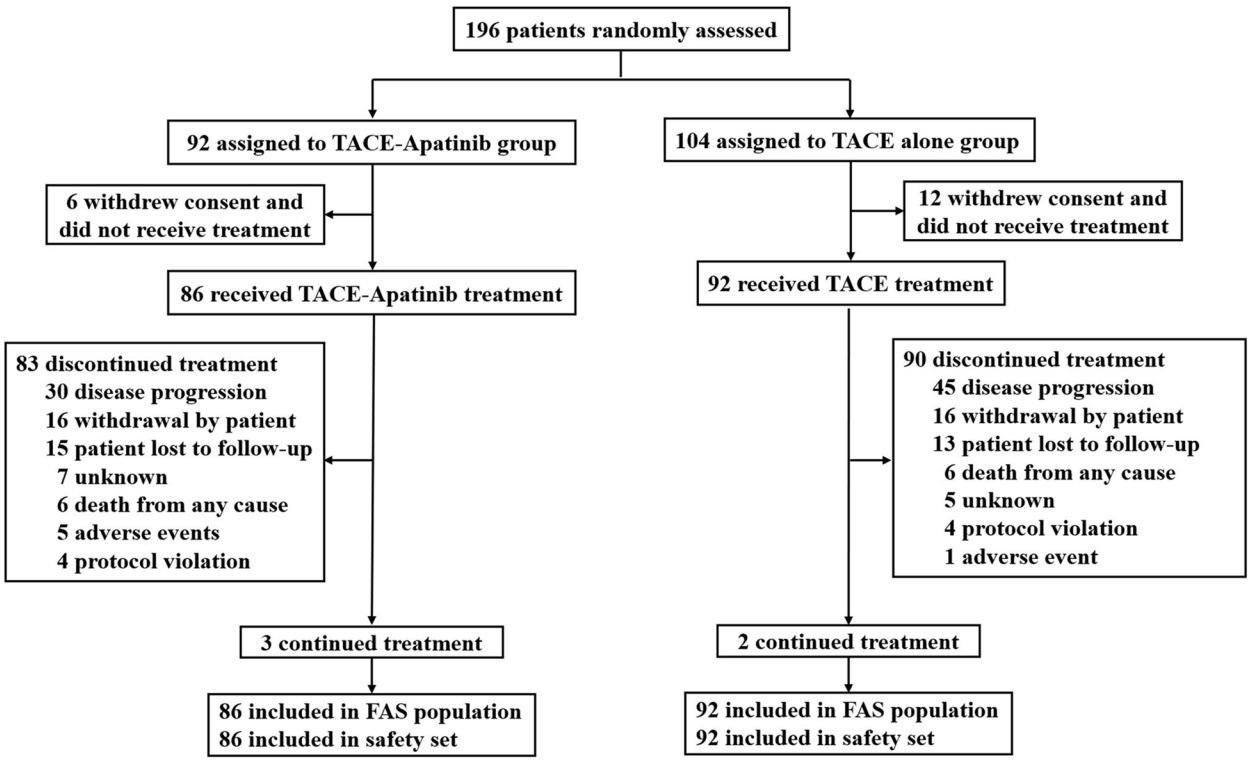

Fig. 1 Patient flow chart (consort diagram). TACE, transarterial chemoembolization; FAS, full analysis set

Table 1 The baseline characteristics of patients in the two groups

	TACE-apatinib group ($n=86$)	TACE alone ($n=92$)	p
Sex, *n* (%)			0.130
Male	77 (89.5)	75 (81.5)	
Female	9 (10.5)	17 (18.5)	
Age (years), mean ± SD	52.7 ± 11.5	52.9 ± 10.1	0.105
Eastern Cooperative Oncology Group performance status, *n* (%)			0.494
0	48 (55.8)	56 (60.9)	
1	38 (44.2)	36 (39.1)	
Barcelona Clinic Liver Cancer stage, *n* (%)			0.992
B	42 (48.8)	45 (48.9)	
C	44 (51.2)	47 (51.1)	
Child–Pugh class, *n* (%)			0.298
A (5–6)	75 (87.2)	75 (81.5)	
B (7)	11 (12.8)	17 (18.5)	
Etiology, *n* (%)			0.297
Hepatitis B	44 (51.2)	49 (53.3)	
Hepatitis C	0	3 (3.3)	
Others[a]	42 (48.8)	40 (43.5)	
α-Fetoprotein concentration, *n* (%)			0.201
< 400 ng/mL	36 (41.9)	48 (52.2)	
≥ 400 ng/mL	49 (57.0)	44 (47.8)	
Missing	1 (1.2)	0	
Prior TACE, *n* (%)			0.707
0	49 (57.0)	58 (63.0)	
1	29 (33.7)	27 (29.3)	
2	8 (9.3)	7 (7.6)	
Cirrhosis, *n* (%)			0.594
No	35 (40.7)	31 (33.7)	
Yes	45 (52.3)	55 (59.8)	
Unknown	6 (7.0)	6 (6.5)	
Albumin, *n* (%)			0.729
≥ 29 and ≤ 35 g/L	8 (9.3)	10 (10.9)	
> 35 g/L	78 (9.1)	82 (89.1)	
Mild ascites, *n* (%)			0.481
No	67 (77.9)	68 (73.9)	
Yes	18 (20.9)	24 (26.1)	
Unknown	1 (1.2)	0	

SD Standard deviation, *TACE* Transarterial chemoembolization

[a] Includes alcoholic liver disease, autoimmune liver disease, and various additional etiologies

significantly longer than that of in the TACE-alone group (26.8 months [95% CI 17.2–36.2] vs. 20.1 months [95% CI 13.2–22.2]; HR 0.53 [95% CI 0.37–0.75]; two-sided $p=0.0003$) (Additional file 1: Fig. S1). As shown in Additional file 2: Table S1, a significantly higher ORR and DCR were observed in the TACE-apatinib group compared with the TACE-alone group (ORR: 58.1% vs. 31.5%, $p<0.001$; DCR: 87.2% vs. 69.6%, $p=0.004$).

For patients in the TACE-alone group, 86 patients received repeated-TACE treatments, 30 patients received sorafenib treatments, 56 patients received lenvatinib treatments, and 6 patients refused further treatments after tumor progression. For patients in the TACE-apatinib group, 82 patients received repeated-TACE treatments, 29 patients received sorafenib treatments, 53 patients received lenvatinib treatments after tumor progression, and 4 patients refused further treatments after tumor progression. The PFS rate at 1 year in the TACE-apatinib group was significantly higher than that of in the TACE-alone group (26.7% vs. 5.4%, $p<0.001$). The OS

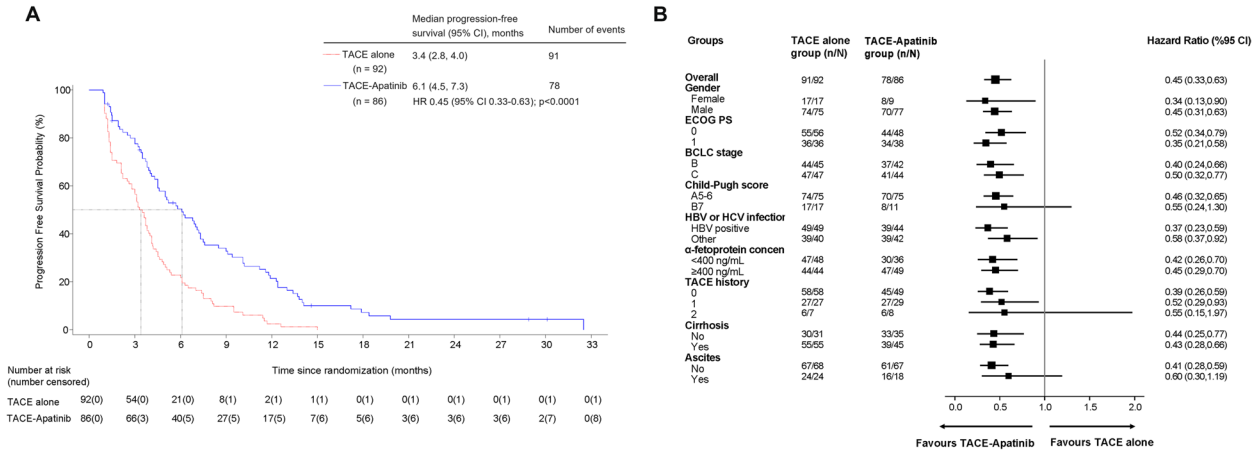

Fig. 2 Kaplan–Meier curve (**A**) and forest plot (**B**) of progression-free survival for patients in the TACE-apatinib group and TACE-alone group. TACE, transarterial chemoembolization; TACE-apatinib, TACE combined with apatinib

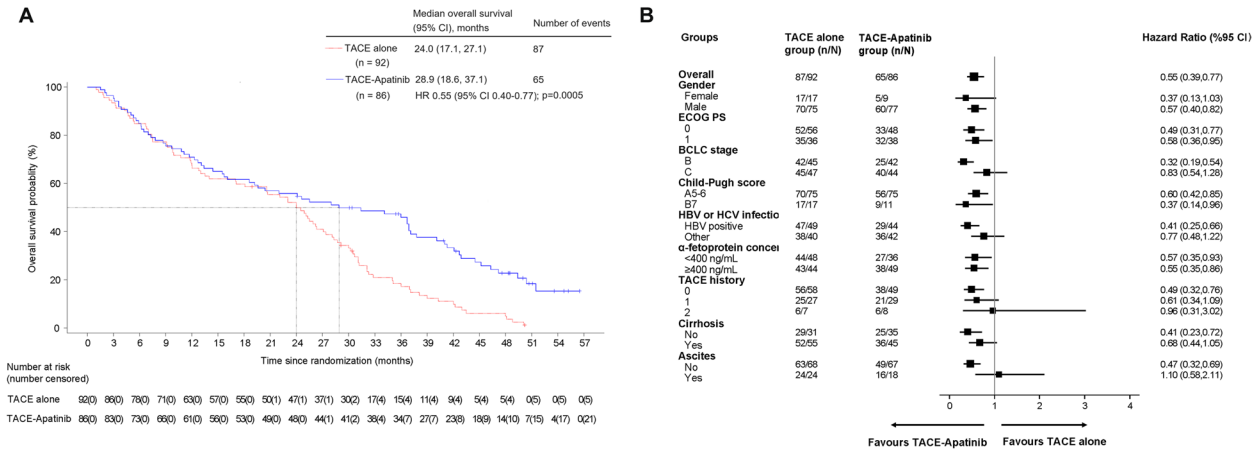

Fig. 3 Kaplan–Meier curve (**A**) and forest plot (**B**) of overall survival for patients in the TACE-apatinib group and TACE-alone group. TACE, transarterial chemoembolization; TACE-apatinib, TACE combined with apatinib

rate at 2 years was similar between the two groups (58.1% vs. 50.0%, $p=0.276$), and the OS rates at 3 and 4 years in the TACE-apatinib group were significantly higher than those of in the TACE-alone group (3 years: 43.0% vs. 18.5%, $p<0.001$; 4 years: 22.1% vs. 7.3%, $p=0.006$).

Safety outcomes

At least one treatment-emergent adverse event (TEAE) occurred in 67 (77.9%) of 86 patients in the TACE-apatinib group and in 59 (64.1%) of 92 patients in the TACE-alone group. Among patients in the TACE-apatinib group, dosage interruption due to TEAEs occurred in 19 (22.1%) of 86 patients, while 15 (17.4%) of 86 patients experienced a dosage reduction because of a TEAE (Additional file 3: Table S2).

As shown in Table 2, the treatment-related adverse events (TRAEs) of all grades were observed in 65 (75.5%) of 86 patients in the TACE-apatinib group, with grades 1–2 occurring in 50 patients (58.1%) and grade ≥ 3 in 15 patients (17.4%). In the TACE-alone group, TRAEs were observed in 54 (58.7%) of 92 patients, with grades 1–2 observed in 43 patients (46.7%) and grade ≥ 3 in 11 patients (12.0%). Three patients of grade 4 adverse events were observed in each group. No treatment-related deaths occurred in either group. Apatinib-related TRAEs included hand-foot skin reaction, hypertension, fatigue, proteinuria, diarrhea, oral ulcer, and decreased appetite. The post-treatment liver function profiles revealed no statistically significant differences between the two groups. Additionally, five patients in the TACE-apatinib group and one patient in the TACE-alone group discontinued or withdrew treatment due to adverse events.

Table 2 Treatment-related adverse events

	TACE-apatinib ($n=86$) *n* (%)		TACE alone ($n=92$) *n* (%)		*p*
	Grades 1–2	Grade ≥ 3	Grades 1–2	Grade ≥ 3	
Any events	50 (58.1)	15 (17.4)	43 (46.7)	11 (12.0)	0.017
Pain	37 (43.0)	3 (3.5)	39 (42.4)	1 (1.1)	0.684
Vomit	24 (27.9)	2 (2.3)	25 (27.2)	3 (3.3)	0.977
Hand-foot skin reaction	24 (27.9)	2 (2.3)	0	0	< 0.001
Nausea	24 (27.9)	1 (1.2)	26 (28.3)	3 (3.3)	0.722
Fever	20 (23.3)	2 (2.3)	32 (34.8)	2 (2.2)	0.102
Hypertension	20 (23.3)	2 (2.3)	1 (1.1)	1 (1.1)	< 0.001
Fatigue	20 (23.3)	1 (1.2)	2 (2.2)	0	< 0.001
Decreased platelet count	12 (14.0)	1 (1.2)	5 (5.4)	3 (3.3)	0.185
Increased aspartate aminotransferase	11 (12.8)	2 (2.3)	5 (5.4)	1 (1.1)	0.064
Increased alanine aminotransferase	10 (11.6)	1 (1.2)	5 (5.4)	0	0.086
Proteinuria	8 (9.3)	2 (2.3)	1 (1.1)	1 (1.1)	0.012
Increased blood bilirubin	8 (9.3)	2 (2.3)	5 (5.4)	1 (1.1)	0.234
Increased gamma (γ)-glutamyl transferase	8 (9.3)	1 (1.2)	6 (6.5)	1 (1.1)	0.506
Diarrhea	8 (9.3)	1 (1.2)	0	0	< 0.001
Hypoalbuminemia	8 (9.3)	0	6 (6.5)	0	0.434
Abdominal distension	7 (8.1)	1 (1.2)	2 (2.2)	0	0.032
Decreased appetite	7 (8.1)	1 (1.2)	1 (1.1)	0	0.025
Oral ulcer	5 (5.8)	1 (1.2)	0	0	0.026
Decreased white blood cell	5 (5.8)	0	1 (1.1)	1 (1.1)	0.335

Discussion

The present study represents the first randomized phase III trial to compare TACE-apatinib with TACE alone in terms of the efficacy and safety in patients with unresectable HCC. In this study, we observed that TACE-apatinib treatment was associated with a significantly longer median PFS and median OS as compared to TACE alone. The benefit in PFS was consistent across various patient subgroups. The median TTUP was significantly prolonged in the TACE-apatinib group compared with the TACE-alone group. These results strongly suggested that TACE plus apatinib is more effective than TACE alone in controlling intrahepatic tumors and improving patients' survival. Besides, patients with unresectable HCC may obtain survival benefits from the treatment of TACE with early combination of apatinib, which may be the main reasons for the differences of median OS and median PFS observed between the two groups in our study.

The combination of TACE with antiangiogenic therapy presents a promising treatment approach for patients with unresectable HCC. The TACTICS trial [12], a randomized, multicenter, prospective study conducted in patients with unresectable HCC who were not candidate for resection or ablation, reported that the combined use of TACE with sorafenib resulted in a significantly prolonged median PFS based on unTACEable progression (25.2 months vs. 13.5 months, $p=0.006$) and median TTUP (26.7 months vs. 20.6 months, $p=0.02$) compared with TACE alone. The results of our study further confirmed the efficacy of TACE plus antiangiogenic therapy, exhibiting clinical benefits for patients with unresectable HCC. The prolonged TTUP in the TACE-apatinib group suggests that the combination therapy may help preserve liver function by delaying TACE refractoriness. By extending the period during which TACE remains effective, patients may experience better disease control and prolonged survival without a significant deterioration in liver function.

Vascular endothelial growth factor (VEGF) signaling is important in angiogenesis and has been identified as an effective therapeutic target in diverse cancer types, including HCC [21]. Among the VEGF receptors, VEGFR-2 was considered the main receptor, and VEGFR-2 activation promoted endothelial cell mitogenesis and vascular permeability [21]. A randomized phase III trial [22], brivanib (a VEGFR-2 inhibitor) as adjuvant therapy to TACE in patients with HCC, showed brivanib significantly improved time to extrahepatic spread or vascular invasion and time to radiographic progression. The results of our study confirmed that the VEGFR-2 inhibitors could improve the effect of TACE on unresectable HCC.

The China liver cancer (CNLC) staging system recommended TACE as the first-line therapy for BCLC stage B HCC, and its indications were extended to BCLC stage C HCC without extrahepatic metastasis (CNLC IIIa HCC) [7]. Moreover, TACE has long been used in East Asian countries beyond China for the treatment of tumors confined within the liver with microvascular invasion (MVI) that would benefit from local therapy. The Japan Society of Hepatology (JSH) consensus recommends TACE for select patients with minor vascular invasion and for Child–Pugh class C patients (aged < 65 years) who meet the Milan criteria (a single tumor up to 5 cm in diameter, or with ≤ 3 tumors up to 3 cm in diameter) [23]. Similarly, the 2022 Korean Liver Cancer Association (KLCA)-National Cancer Center (NCC) guidelines recommended TACE treatment for patients with portal vein invasion, intrahepatic localized tumors, and well-preserved liver function [24]. Previous studies [25–27] have also shown significant survival benefits from TACE in patients with BCLC stage C HCC. In view of these, in the present study, BCLC stage C HCC patients without extrahepatic metastasis and tumor thrombus in the main portal vein treated with TACE-apatinib and those in the control group received TACE-alone treatment. Additionally, the modified RECIST criteria were used for treatment assessment over a relatively short duration. If tumor progression occurred in TACE-alone group or TACE-apatinib group, patients had an option to promptly initiate the systemic treatment with oral sorafenib or lenvatinib. Subgroup analysis demonstrated that patients with both BCLC stage B and C benefited from TACE-apatinib, as indicated by the subgroup analyses of PFS and OS. These findings suggest that the combination of TACE with apatinib may serve as an effective treatment strategy for BCLC-B and C stages of unresectable HCC.

In this study, apatinib was tolerated by most patients, and the related adverse events were acceptable for patients with unresectable HCC. These events included hand-foot skin reaction, hypertension, fatigue, proteinuria, diarrhea, oral ulcer, and decreased appetite, predominantly of grade 1 or 2. The symptoms could be mitigated or fully resolved through dose reduction or symptomatic treatments. In the TACE-apatinib group, the adverse events were well-tolerated, and there were no reports of new safety signals. These results demonstrated that apatinib did not increase the incidence of TACE-related adverse events. Moreover, no significant statistical differences were observed in serum elevation of hepatic enzymes or hyperbilirubinemia between the two groups, indicating that apatinib did not significantly impact liver function when it was used in combination with TACE. Overall, our results demonstrate that TACE-apatinib is safe for patients with unresectable HCC.

Our study is subject to some limitations. Firstly, the COVID-19 pandemic and the update of BCLC guidelines in the treatment of unresectable HCC resulted in the enrollment of fewer patients than planned. Secondly, only Chinese patients were included, and additional studies involving more diverse geographic populations are necessary to further validate our findings. Thirdly, despite not achieving the planned sample size, the trial met the required number of PFS events, ensuring statistical reliability. However, the reduced enrollment may still limit the generalizability of the findings.

Conclusions

In conclusion, TACE-apatinib is a safe and effective treatment for patients with unresectable HCC, offering significant improvements in survival outcomes compared with TACE-alone treatment, with an acceptable safety profile. This combination therapy could serve as a promising treatment option for this patient population.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ALT	Alkaline phosphatase
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
CNLC	China liver cancer
CR	Complete response
DCR	Disease control rate
ECOG	Eastern Cooperative Oncology Group
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HR	Hazard ratio
JSH	Japan Society of Hepatology
KLCA	Korean Liver Cancer Association
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MVI	Microvascular invasion
NCC	National Cancer Center
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PDGF	Platelet-derived growth factor
PFS	Progression free survival
PR	Partial response
SD	Stable disease
TACE	Transarterial chemoembolization
TACE-apatinib	The combination of TACE with apatinib
TEAE	Treatment-emergent-related adverse event
TRAE	Treatment-related adverse events
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor receptor-2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04159-y.

Additional file 1: Fig. S1 Kaplan-Meier curve of time to unTACEable progression for patients in the TACE-apatinib group and TACE-alone group. TACE, transarterial chemoembolization; TACE-apatinib, TACE combined with apatinib.

Additional file 2: Table S1 The best tumor response after treatments.

Additional file 3: Table S2 Summary of adverse events.

Additional file 4.

Additional file 5.

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Authors' contributions
CSZ, XFK, BL, XLZ, CZ, and MH conceived and designed the study; XFK, BL, XLZ, LY, YCL, SZ, RBL, GHX, HLL, ZYL, HX, WL, LFX, YLM, XWX, KQ, XJD, FX, SLS, CZ, and MH enrolled patients and collected the data; XFK, BL, and CSZ analyzed the data; All authors participated in data interpretation and manuscript development; All authors approved the final version to be submitted.

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Data availability
The data that support the findings of this study are available by contacting the corresponding authors.

Declarations

Ethics approval and consent to participate
This multicenter, randomized, open-label, prospective, phase III trial was carried out in accordance with the principles of the Declaration of Helsinki. The trial protocol was approved by the ethics committee of all participating centers (No. S249-1). All the patients provided a written informed consent before inclusion. This study was registered with the Chinese Clinical Trial Register (Number: ChiCTR1800018621).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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