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Survival in patients with unresectable hepatocellular carcinoma: TCC cocktail plus TACE vs TACE alone prospective randomized clinical trial

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Abstract

Background Transarterial chemoembolization (TACE) is commonly used to treat patients with unresectable hepatocellular carcinoma (HCC); however, TACE alone has demonstrated unsatisfactory survival benefits. Our previous studies suggested that TACE plus oral medication of thalidomide, carmofur and compound mylabris capsule (TCC cocktail) may be a better therapeutic option.

Methods In this randomized, open-label, multicenter clinical trial, 72 treatment-naive HCC patients were randomly assigned to receive cTACE alone or cTACE plus oral TCC cocktail between July 2018 and October 2019. The primary endpoint of this trial was the 1-, 2- and 3-year overall survival (OS) rates. The second endpoints of this trial included 1-, 2- and 3-year progression-free survival (PFS) rates, objective response rates (ORR) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), and safety with adverse events (AEs).

Results The 1-, 2- and 3-year OS rates were significantly higher in the cTACE plus TCC group than in the cTACE group (83.2% vs 54.3%, 63.1% vs 30.1%, 37.7% vs 18.1%; $p=0.008$), with a significantly longer median OS (29.0 vs 15.0 months; $p<0.001$). Regarding the 1-, 2- and 3-year PFS rates, HCC patients in the cTACE plus TCC group also demonstrated significantly higher rates (66.3% vs 34.4%, 35.8% vs 18.8%, 31.8% vs 15.6%; $p=0.014$) and had a longer median PFS (16.0 vs 8.0 months; $p<0.001$) compared with cTACE group. All treatment-related AEs were tolerated.

Conclusions For patients with unresectable HCC, TACE combined with TCC cocktail was well tolerated and significantly improved clinical outcomes.

Trial registration The trial was registered at https://www.chictr.org.cn/showproj.html?proj=27493 as ChiCTR1800016335 on 25th May 2018 named an open-label, multicenter, randomized, prospective clinical trial of thalidomide based triple oral regimen for low-dose maintenance therapy after TACE in advanced hepatocellular carcinoma.

Keywords Transarterial chemoembolization, Hepatocellular carcinoma, Combination therapy, Thalidomide

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Introduction

Primary liver cancer (PLC) is currently the fourth most common malignant tumor and the third leading cause of death. Hepatocellular carcinoma (HCC) is the predominant histological subtype, accounting for approximately 90% of cases [1]. Owing to the lack of specific early clinical manifestations, the majority of HCC patients are already in the intermediate to advanced stage at the time of initial diagnosis, with only about 20% having the opportunity for surgical treatment [2]. Transarterial chemoembolization (TACE) is considered the primary treatment option for HCC patients in the intermediate stage globally [3], while it is also widely applied in advanced HCC in practice [4], such as HCC with segmental portal vein tumor thrombosis (PVTT) [5].

However, TACE has drawbacks like collateral circulation formation and incomplete tumor embolization, potentially leading to disease progression and requiring repeated procedures [6]. Moreover, there is growing concern that repeated TACE procedures may lead to potential liver function deterioration and TACE failure [7, 8]. To address these challenges, strategies combining TACE with other therapies are being explored [9–11], and combining it with systemic therapies is currently considered one of the promising approaches [12]. Numerous studies have explored the efficacy of TACE combined with tyrosine kinase inhibitors (TKIs) such as sorafenib, lenvatinib, and bevacizumab [13–15], which could theoretically suppress post-TACE angiogenesis and reduce cancer recurrence. However, while some studies have shown improvements in progression-free survival (PFS) and objective response rate (ORR), there has been no significant benefit in overall survival (OS) [16–18]. In the age of molecular targeted therapy (MTT) and immunotherapy, the treatment pattern of TACE combined with immune-targeted therapies has been reported to exhibit favorable efficacy and manageable safety profiles [19–21]. Clinical trials focusing on TACE in combination with immune checkpoint inhibitors (ICIs) or MTT and ICIs have been conducted in HCC patients, such as NCT03572582, NCT03778957 and NCT04246177. It is also important to note that immunotherapy is still facing challenges including modest efficacy, a lack of specific predictive markers, drug resistance, and immune-related adverse effects [22]. Up to now, no guideline has recommended the preferred combination therapy of TACE, which is still under exploration.

Experiences gained from acquired immune deficiency syndrome (AIDS) treatment have demonstrated that the use of multiple drugs having non-overlapping resistance mechanisms can make a deadly disease with a high mutation rate chronic, known as "cocktail therapy" [23, 24]. The concept of "cocktail therapy" has expanded from targeting different stages of viral replication to addressing tumor heterogeneity, specifically that different cells within the tumor may rely on distinct survival mechanisms. Therefore, focusing on finding highly effective combinations of existing drugs may deliver more clinical benefit to HCC patients. In a decade-long clinical practice, our team has made a pioneering discovery of a novel oral and low-dose therapeutic strategy, which comprises thalidomide, carmofur, and compound mylabris capsules (CMC), named TCC cocktail.

The three elements of the TCC cocktail have different known anti-tumor mechanisms. Thalidomide has anti-angiogenic and immunomodulatory effects in patients with HCC, making it a promising candidate for enhancing the benefits of TACE [25, 26]. Carmofur, which exerts an anti-tumor effect through the antimetabolic effect of fluorouracil, has been utilized in the treatment of various solid tumors [27]. A previous study reported that metronomic chemotherapy with carmofur prolonged the survival of advanced HCC patients with minimal side effects [28]. As a traditional Chinese medicinal (TCM) preparation, cantharidin, the main ingredient of CMC, has demonstrated anticancer activity against multiple cancer types, particularly HCC [29]. Several studies have revealed the potential mechanisms of cantharidin and its analogues in HCC, including the regulation of apoptosis, epithelial-mesenchymal transition, and the immune response [30–32].

In a recent study, we validated the combined anti-tumor effect and safety of the TCC cocktail in the in vivo tumor models, and have discovered that the TCC cocktail may exert an efficient anti-HCC effect inducing SAMD4B-APOA2-PD-L1 axis to inhibit tumor immune evasion [33]. The results of our previous retrospective study (unpublished data), which included 545 patients, preliminarily suggested that HCC patients who received TACE combined with TCC cocktail exhibited improved survival benefits and no significant adverse effects compared to those who received TACE alone. In this randomized trial, we aimed to validate the effectiveness and safety of cTACE combined with TCC cocktail in patients with unresectable HCC.

Methods

Study design and participants

This study was a randomized, open-label, multi-center clinical trial conducted at Zhongshan Hospital (leading unit), Ruijin Hospital (participating unit), Kecheng Hospital (participating unit) and Minhang Hospital (participating unit). Patients with unresectable HCC and had received no prior TACE or other locoregional treatment were eligible and other main inclusion criteria comprised the following: Aged 18–75 years; Child–Pugh score of

A or B; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; for advanced patients, prior sorafenib treatment must have been discontinued due to intolerable adverse events at least four weeks before study initiation; at least 1 measurable lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Patients were excluded if they had active bleeding or coagulopathy, complete PVTT with minimal collateral circulation, extensive distant metastases with a life expectancy < 3 months or other uncontrolled comorbidities. More details of the inclusion and exclusion criteria are provided in Document S1.

cTACE procedures

To ensure standardized TACE procedures across different hospitals, a team of skilled interventionalists with uniform training was assembled in each hospital to perform the TACE operations for enrolled patients. During the cTACE procedure, all patients underwent selective catheterization of tumor-feeding vessels. Subsequently, a mixture of Epirubicin (Pfizer, Vienna, Austria) (20–50 mg), Oxaliplatin (Eloxatin, Braine-L'Alleud, Belgium) (50–100 mg), and Lipiodol (Laboratoire Andre´ Guerbet, Aulnay-sous-Bois, France) (5–25 ml) was slowly injected, followed by embolization using gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Michigan, USA). Embolization endpoints were standardized according to established guidelines [34], achieved by monitoring the extent and degree of Lipiodol deposition and the degree of tumor devascularization via real-time angiography. Following completion of the initial cTACE procedure, repeat TACE will be considered for patients with residual active liver lesions on follow-up imaging, provided their liver function and performance status remain adequate (Figure S1).

TCC cocktail

Patients randomly assigned to the cTACE plus TCC group of the trial received TCC cocktail after the first cTACE procedure (within 3 days) and should be continuously administered without interruption during possible subsequent cTACE treatments. For details, all eligible patients were orally given: (1) thalidomide 50 mg qn (Changzhou Pharmaceutical Factory Co., Ltd.); (2) carmofur 100 mg tid (Qilu Pharmaceutical Co., Ltd.) and (3) compound mylabris capsule 750 mg bid (Guizhou Yibai Co., Ltd.). During the course of medication, if the tumor response was complete response (CR) according to mRECIST, the carmofur would be stopped, but thalidomide and CMC were administered at least half a year until the end of follow-up for the trial, or until one of the following events occurred: unacceptable toxicity, death, withdrawal of consent, or other conditions requiring termination of treatment, based on the first occurrence.

Assessment of tumor response and treatment safety

The enrolled patients required comprehensive reassessment 4–6 weeks after the initial TACE treatment to evaluate the necessity and feasibility of subsequent TACE therapy, including physical and vital sign examinations, laboratory tests (such as routine blood, biochemistry, coagulation function and tumor marker tests), and clinical imaging (liver CT or MRI and chest CT). All patients undergo a comprehensive assessment every 2 months for the first 6 months after initial treatment, followed by every 3 months thereafter. Tumor measurement and response assessment were conducted based on the mRECIST via contrast-enhanced dynamic CT or MRI [35]. The evaluation procedure was performed by at least two independent radiologists from a blinded independent radiology committee (BIRC) who were not involved in the study. AEs and complications were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 based on patient complaints and laboratory results. The survival follow-up was performed every 3 months after the initial TACE treatment until death or the last follow-up date, which was September 1, 2023 (data deadline) (Figure S1).

Endpoints

The primary endpoint of this trial was the 1-, 2- and 3-year OS rates. The second endpoints of this trial included 1-, 2- and 3-year progression-free survival (PFS) rates, objective response rates (ORR) and safety. PFS was defined as the time between randomization and the first recorded occurrence of disease progression or death from any cause, whichever occurred first. OS was defined as the time from randomization to death from any cause or the last follow-up. The ORR was defined as the percentage of participants who achieved a complete or partial response according to mRECIST. AEs were graded using NCI CTCAE, version 5.0.

Sample size and randomization

The sample size was determined based on the 3-year OS rate, the primary endpoint for this trial. From the previous data of our early cohort, the 3-year OS rate of patients treated with cTACE plus TCC was about 50% and for patients treated with cTACE alone was about 20%. Based on this expectation, with 80% power, two-sided type I error of 5% (two-sided testing) and 10% loss to follow-up, a 1:1 randomization of 64 subjects was needed, which was estimated using Power Analysis and

Sample Size software (Hintze, J. PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

The study arm assignment was based on a computer-generated table of random numbers. Blinding was achieved using opaque sealed envelopes with patient numbers, containing the group allocation. Once informed consent was obtained from the participants and they passed the pre-trial assessment, the patients were numbered sequentially. The corresponding numbered envelopes were then sent to each site and opened by the researchers. The independent randomization administrator uninvolved in the trial was responsible for preparing and managing the randomization process.

Statistical analysis

The primary dataset was defined as all randomized patients (intent-to-treat [ITT] analysis). The Student's t-test or Mann–Whitney U-test was used to compare continuous variables between different sets, and the chi-square test or Fisher's exact test was used to compare binary categorical variables. The survival curves of PFS and OS were estimated by Kaplan–Meier analysis using the log-rank test. A Cox proportional hazards model was used to assess the effect of underlying prognostic factors and treatment on PFS and OS. To assess potential heterogeneity of treatment effects across subgroups, we introduced interaction terms (e.g., treatment × subgroup variable) into stratified Cox proportional hazards models. The significance of interaction effects was tested via likelihood ratio tests. All subgroup analyses were explicitly framed as exploratory given the limited sample size and the post hoc nature of subgroup investigations. Two-sided tests were performed, and a *p-value* < 0.05 was considered statistically significant. All analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing).

Results

Patients

Between July 2018 and October 2019, a total of 72 eligible patients were enrolled and randomly assigned to either the cTACE group (n = 36) or the cTACE plus TCC group (n = 36). Among the intention-to-treat population, 2 patients discontinued to receive the assigned treatment and 3 patients were lost to follow-up in the cTACE plus TCC group, while 2 patients were lost to follow-up in the cTACE group, resulting in a final total of 65 patients (90.3%) who completed the trial (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. Briefly, the majority of patients were male (87.5%), with a median age of 60.5 (interquartile range, 52.8–68.0) years. As all patients were Chinese, chronic hepatitis B virus (HBV) infection was the predominant underlying cause of liver disease (82.0%). These clinical characteristics were well-balanced between the two groups ($p > 0.05$). Additionally, we compared the number of cTACE sessions that patients received and subsequent treatments after disease progression between the two groups, and no significant differences were observed ($p > 0.05$; Tables S1-S2).

Efficacy

As of September 1, 2023, the median follow-up time was 21 (interquartile range, 9.0–32.0) months. In the cTACE group, 28 patients (77.8%) had died, while in the cTACE plus TCC group, 21 patients (58.3%) had died (Fig. 1). Based on radiologic response within 12 months of the initial treatment, the cTACE plus TCC group demonstrated a superior ORR compared to the cTACE group (88.9% vs 69.4%; $p = 0.042$). Specifically, 7 patients (19.4%) achieved CR in the cTACE plus TCC group, whereas only 2 patients (5.6%) achieved CR in the cTACE group (Table 2). The waterfall plot illustrates the distribution of the best tumor response within 12 months after the initial cTACE treatment among the enrolled patients, specifically the proportion of target lesion tumor regression compared to baseline (Fig. 2). According to the mRECIST, the majority of patients achieved tumor regression to varying degrees (30%−100%). Two representative cases of CR in the cTACE plus TCC group are shown in Figures S2-S3. Only 15 patients were assessed as having stable disease or disease progression, with 11 cases found in the cTACE group.

The 1-, 2- and 3-year OS rates were significantly higher in the cTACE plus TCC group than in the cTACE group (83.2% vs 54.3%; 63.1% vs 30.1%; 37.7% vs 18.1%; $p = 0.008$). The median OS was 29.0 months (95% CI, 23.5–34.5 months) in the cTACE plus TCC group and 15.0 months (95% CI, 9.5–20.6 months) in the cTACE group ($p = 0.001$; Table 2; Fig. 3a). The corresponding HR for OS was 0.48 (95% CI, 0.27–0.84; $p = 0.011$), and the adjusted HR was 0.47 (95% CI, 0.25 to 0.89; $p = 0.019$). (Fig. 3a; Table S3). Regarding the 1-, 2-, and 3-year PFS rates, HCC patients in the cTACE plus TCC group also exhibited significantly higher rates (66.3% vs 34.4%, 35.8% vs 18.8%, 31.8% vs 15.6%; $p = 0.014$). The median PFS in the cTACE plus TCC group was 16.0 months (95% CI 12.3–19.7 months), which was significantly longer than the median PFS in cTACE patients (8.0 months [95% CI 6.6–9.4 months]; $p < 0.001$; Table 2; Fig. 3b). The corresponding HR for PFS was 0.52 (95% CI 0.30–0.90; $p = 0.019$), and the adjusted HR was 0.55 (95% CI 0.31–0.99; $p = 0.046$) (Fig. 3b; Table S4).

The subgroup analyses of OS and PFS demonstrated a consistent benefit trend for cTACE plus TCC compared to cTACE treatment across most stratification factors.

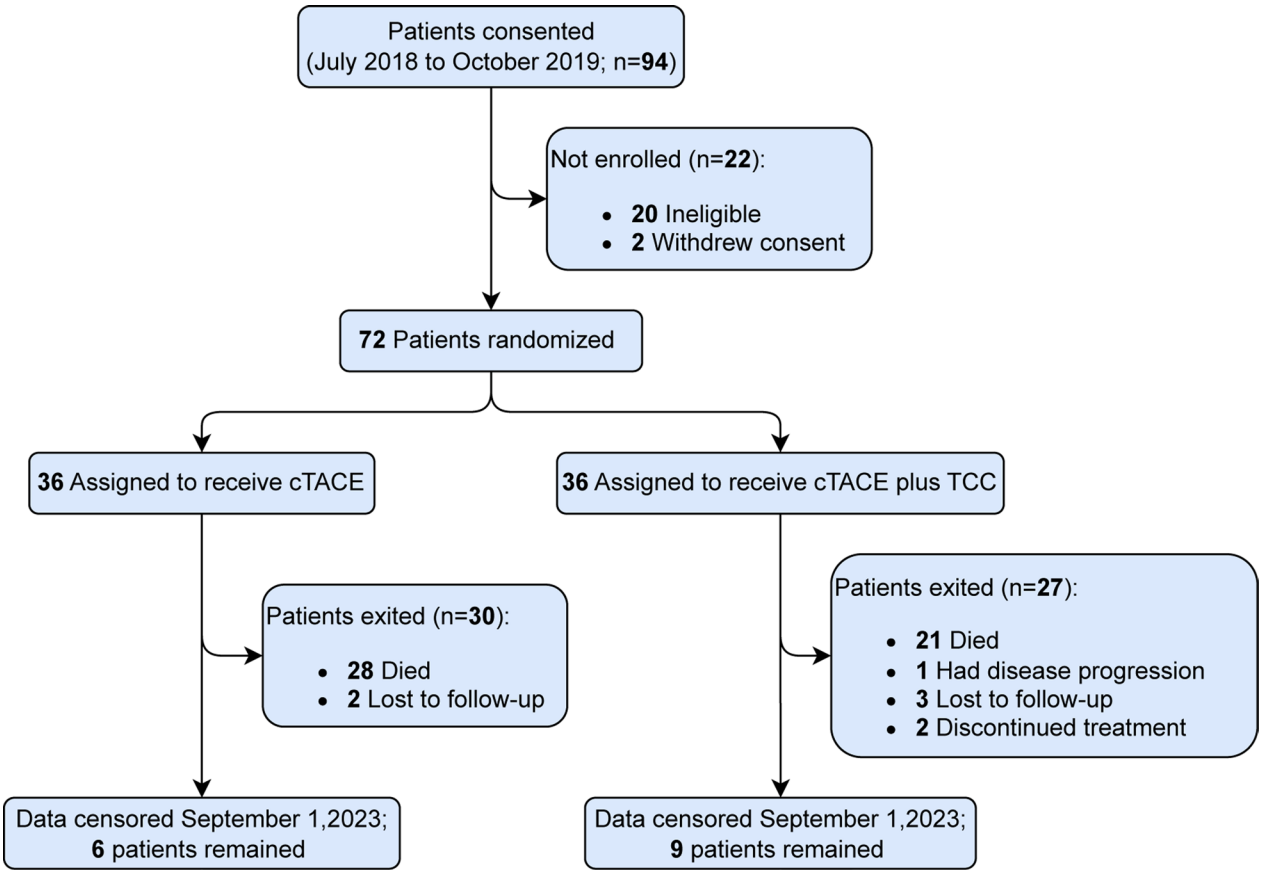

Fig. 1 Patient Flow Diagram. cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules

No significant interaction effects were observed (all $p > 0.05$), indicating no statistically detectable heterogeneity in treatment effect magnitude across subgroups (Figs. 4, 5). Notably, the cTACE plus TCC has also demonstrated relatively better therapeutic outcomes for some HCC patients who are typically classified as having a potentially poor prognosis, such as elderly patients (≥ 60 years) and those with large tumor burden (maximum diameter ≥7 cm) or advanced stages (BCLC-C stage) (Fig. 6). However, due to the exploratory nature of these analyses and the limited sample size, the results should be cautiously interpreted. In addition, we analyzed the potential risk factors of prognosis in all patients in Tables S3-S4. In univariable analysis, portal vein invasion, metastasis, BCLC stage and tumor response were significantly associated with PFS and OS ($p < 0.05$). In multivariable analysis, BCLC stage and tumor response were identified as significant independent prognostic factors for PFS and OS ($p < 0.05$).

Safety

All 72 patients were included in the safety analysis as each of them received at least one cTACE treatment, and all patients in the cTACE plus TCC group received at least one complete course (4 weeks) of TCC cocktail treatment. The majority of patients experienced treatment-related AEs of varying degrees in both treatment groups (94.5% vs 91.6%, $p < 0.05$), but most of these events were mild to moderate according to NCI CTCAE, version 5.0. AEs with an incidence exceeding 5% were listed in Table 3, with abdominal pain (47.2%), fatigue (38.9%) and dyspepsia (38.9%) being the most common AEs in the cTACE group and abdominal pain (38.9%), constipation (36.1%) and dyspepsia (33.3%) being the most common AEs in the cTACE plus TCC group.

Grade 3 or 4 AEs occurred in 4 patients (11.1%) in the cTACE plus TCC group and 3 (8.3%) in the cTACE group. No grade 5 AEs were observed in either treatment group. The incidence of AEs across all grades did not differ significantly between the two groups, except for a higher occurrence of fatigue (38.9% vs 16.7%, $p = 0.035$) observed in the cTACE group. Throughout the trial, no patients required dose reduction or treatment discontinuation, and no treatment-related deaths occurred.

Table 1 Baseline clinical characteristics of patients in the two groups

Characteristic	Mean ± SD/N (%)		*p* value
	cTACE	cTACE + TCC	
N	36	36	
Age (y)	60.1 ± 11.0	59.6 ± 11.4	0.867
Hb (g/L)	128.6 ± 27.1	127.5 ± 22.5	0.862
WBC (10^9/L)	5.9 ± 2.5	5.6 ± 2.4	0.576
PLT (10^9/L)	165.1 ± 109.1	174.2 ± 123.2	0.743
BUN (mmol/L)	6.3 ± 2.6	5.6 ± 2.4	0.261
Cr (μmol/L)	81.2 ± 23.7	80.1 ± 55.8	0.913
AFP (ng/ml)	8763.5 ± 18,134.4	19,312.3 ± 89,430.4	0.490
Tumor diameter (cm)	7.5 ± 4.2	7.4 ± 3.6	0.869
Sex			1.000
Male	31 (86.1)	32 (88.9)	
Female	5 (13.9)	4 (11.1)	
ECOG score			0.238
0	15 (41.7)	20 (55.6)	
1	21 (58.3)	16 (44.4)	
Etiology			0.358
HBV	28 (77.8)	31 (86.1)	
Others	8 (22.2)	5 (13.9)	
Child–Pugh grade			0.101
A	28 (77.8)	33 (91.7)	
B	8 (22.2)	3 (8.3)	
ALBI grade			0.873
I (≤ −2.60)	13 (36.1)	12 (33.3)	
II (−2.60 ~ −1.39)	20 (55.6)	22 (61.1)	
III (> −1.39)	3 (8.3)	2 (5.6)	
Tumor number			0.578
1	3 (8.3)	6 (16.7)	
2	19 (52.8)	16 (44.4)	
≥ 3	14 (38.9)	14 (38.9)	
Metastasis			0.405
Yes	10 (27.8)	7 (19.4)	
No	26 (72.2)	29 (80.6)	
Portal vein invasion			0.458
Yes	15 (41.7)	12 (33.3)	
No	21 (58.3)	24 (66.7)	
CNLC stage			0.475
I	0 (0.0)	2 (5.6)	
II	15 (41.7)	16 (44.4)	
III	21 (58.3)	18 (50.0)	
BCLC stage			0.346
B	16 (44.4)	20 (55.6)	
C	20 (55.6)	16 (44.4)	

cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules; Hb, hemoglobin; WBC, white blood cell; PLT, platelet count; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; HBV, hepatitis B virus; ALBI, albumin–bilirubin; CNLC, China liver cancer; BCLC, Barcelona clinical liver cancer

Discussion

In this randomized trial, compared with cTACE monotherapy, the combined cTACE plus TCC treatment demonstrated significant improvements in the rates of 1-, 2- and 3-year OS (83.2% vs 54.3%; 63.1% vs 30.1%; 37.7% vs 18.1%; $p = 0.008$) and 1-, 2- and 3-year PFS (66.3% vs 34.4%, 35.8% vs 18.8%, 31.8% vs 15.6%; $p = 0.014$), a significantly longer median OS (29.0 vs 15.0 months) with an adjusted HR of 0.47 (95% CI 0.25 to 0.89; $p = 0.019$), and a markedly longer median PFS (16.0 vs 8.0 months) with an adjusted HR of 0.55 (95% CI 0.31–0.99; $p = 0.046$), corresponding to a reduction in the risk of death or progression by about half. Furthermore, the TCC cocktail offered an excellent safety and tolerability profile with a relatively low incidence of AEs. Considering the emerging roles of local combined systemic therapy [36, 37], this study adds a multi-target and low-toxicity strategy for the treatment of unresectable HCC patients.

Due to the upregulation of angiogenic factors following TACE, such as vascular endothelial growth factor (VEGF), inhibiting angiogenesis by blocking VEGF receptor (VEGFR) or reducing VEGF expression can effectively suppress tumor local recurrence and metastasis [6]. In recent years, it has been found that thalidomide not only has anti-angiogenic effects but also plays an immunomodulatory role by regulating the secretion and activity of cytokines, such as tumor necrosis factor (TNF), interferon (IFN) and IL-12 [38]. Findings from a randomized controlled study (RCT) evaluating the combination of thalidomide (100–200 mg PO qd) with TACE for HCC indicated that patients in the combination therapy group achieved a significantly prolonged median disease-free survival (DFS) of 181 days (95% CI: 91–271) compared to 97 days (95% CI: 33–161) in the TACE alone group ($p < 0.05$), suggesting that oral thalidomide could enhance the effects of TACE treatment and delay disease relapse [39]. A meta-analysis of 12 RCTs (n = 894) indicates TACE-thalidomide combination constitutes a second-line treatment option for patients with intermediate or advanced HCC, despite the poor quality of included studies [25]. To enhance treatment compliance and minimize the incidence of adverse effects, considering the dose-dependent toxicity of thalidomide, we innovatively implemented a maintenance low-dose oral thalidomide regimen in the TCC cocktail.

Metronomic chemotherapy entails the administration of cytotoxic drugs at relatively low doses, high frequencies, and continuous intervals. This treatment approach maintains a sustained and effective concentration of the drugs in the bloodstream over an extended period, thereby prolonging disease control while minimizing toxic side effects [40–42]. Carmofur (HCFU) is a fluorouracil derivative that gradually decomposes and

Table 2 Disease Responses in the Intention-to-Treat Population

Outcome	cTACE (N = 36)	cTACE + TCC (N = 36)	*p* value
Best radiologic response in 12 months, n (%)			
ORR	25 (69.4)	32 (88.9)	0.042
CR	2 (5.6)	7 (19.4)	
PR	23 (63.9)	25 (69.4)	
SD	7 (19.4)	3 (8.3)	
PD	4 (11.1)	1 (2.8)	
1-, 2-, 3-year OS rates, % (95% CI)			0.008
1-year	54.3 (37.6–70.9)	83.2 (70.9–95.5)	
2-year	30.1 (14.6–45.6)	63.1 (47.1–79.0)	
3-year	18.1 (5.0–31.1)	37.7 (21.0–54.5)	
Median OS, months (95% CI)	15.0 (9.5–20.6)	29.0 (23.5–34.5)	< 0.001
1-, 2-, 3-year PFS rates, % (95% CI)			0.014
1-year	34.4 (18.4–50.3)	66.3 (50.8–81.9)	
2-year	18.8 (5.4–32.1)	35.8 (19.4–52.2)	
3-year	15.6 (3.2–28.1)	31.8 (15.5–48.1)	
Median PFS, months (95% CI)	8.0 (6.6–9.4)	16.0 (12.3–19.7)	< 0.001

cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

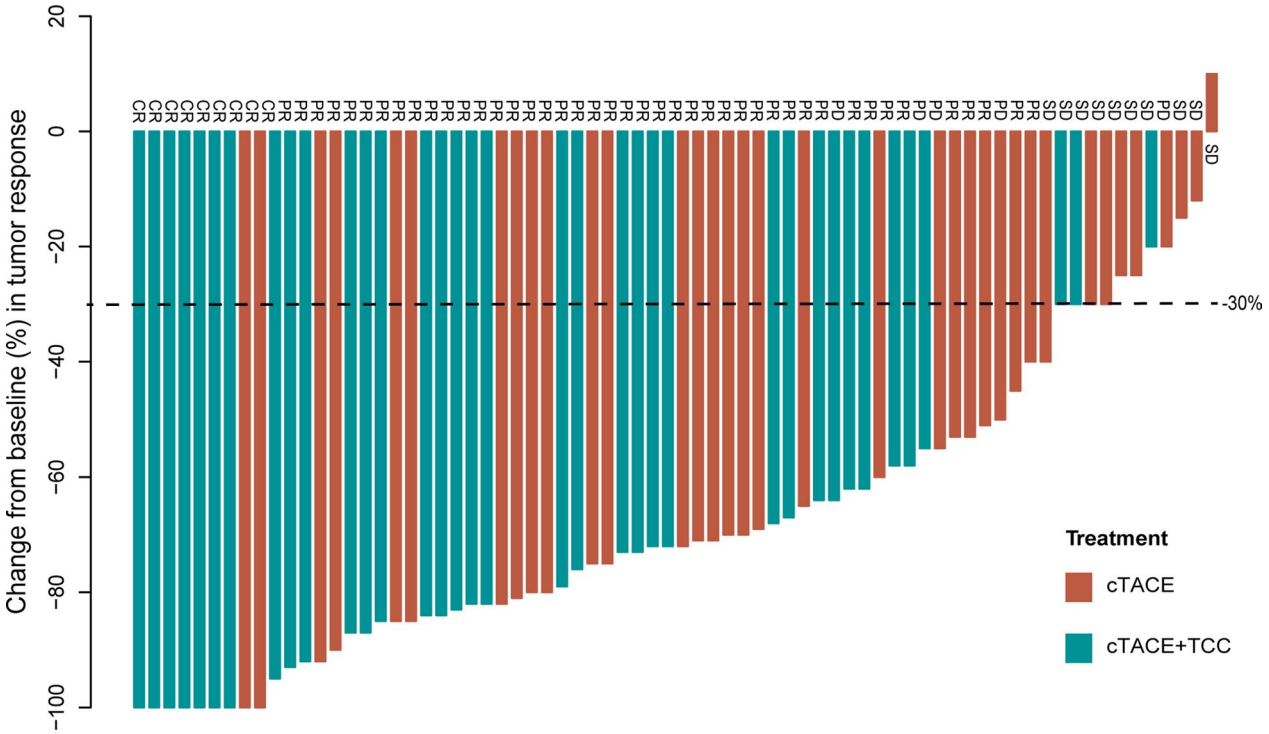

Fig. 2 The best change from baseline in the sum of the target lesion diameter per patient. cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

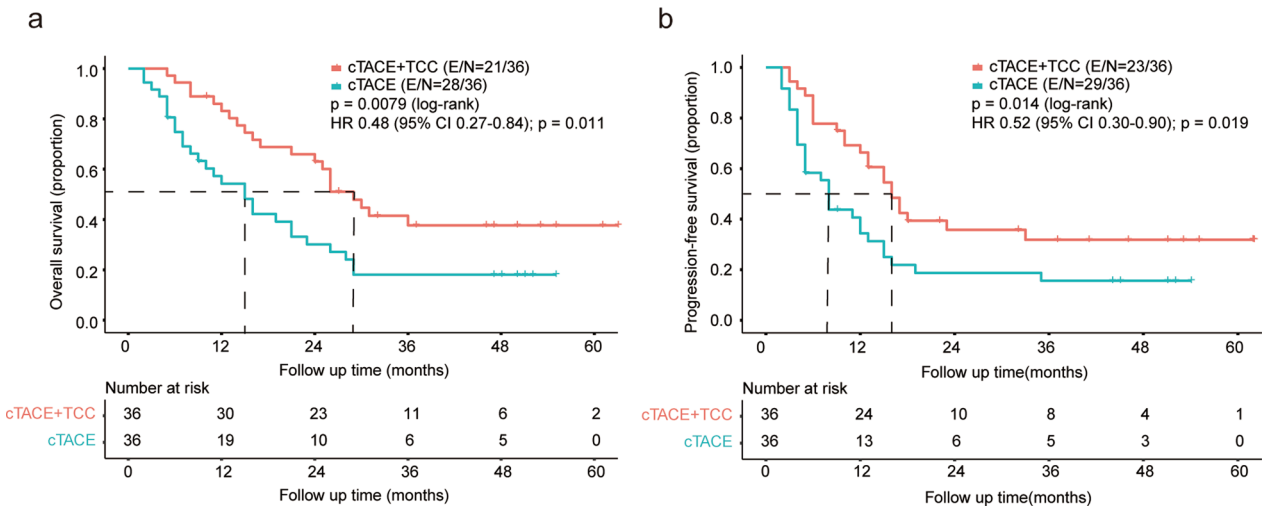

Fig. 3 Kaplan–Meier curves showing overall survival (**a**) and progression-free survival (**b**) in the intention-to-treat population for patients receiving cTACE plus TCC cocktail (study group) and cTACE only (control group). cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules

releases 5-Fu in the human body. It primarily targets tumor cells in the S-phase to inhibit their proliferation. Given the toxic effects of MTTs, carmofur metronomic chemotherapy represents a promising alternative for patients with intermediate and advanced HCC. It has demonstrated efficacy in delaying disease progression, even in TACE-received patients with impaired liver function [28].

Adverse effects following TACE may include fever, abdominal pain, vomiting and acute and chronic liver failure, etc. [43]. To mitigate these adverse effects and enhance therapeutic efficacy, the Chinese guidelines for liver cancer recommend TCM as an adjuvant therapy [44, 45]. Cantharidin, derived from the bodies of cantharides, exhibits antitumor activity and immunomodulatory effects, making it a valuable treatment option for HCC [29]. As the toxicity of cantharidin has limited its wide application, some detoxified derivatives and compound preparations have been developed, and CMC is one of them [46, 47]. In China, CMC has been approved by NMPA (National Medical Products Administration) for the treatment of primary liver cancer. An RCT involving 100 patients with intermediate and advanced PLC demonstrated that the combination of TACE with CMC significantly increased the number of patients with PR and SD compared to the TACE alone group ($p < 0.05$), indicating that the combination therapy improved the clinical benefit of TACE while reducing adverse effects [48]. Another clinical study confirmed that TACE combined with CMC effectively improved liver function, reduced alpha-fetoprotein (AFP) levels following TACE, and prolonged OS in PLC patients compared to TACE alone [49].

In patients receiving cTACE plus TCC cocktail, we observed a reduction of approximately 50% in the risk of death (HR 0.47) and disease progression (HR 0.55) with significantly longer median OS (29.0 months) and PFS (16.0 months). While direct comparisons among trials can only generate hypotheses at best, it is noteworthy that the recently reported HR benefit for PFS by the combination of TACE with durvalumab and bevacizumab was only 0.77 in the EMERALD-1 trial [20]. In a large retrospective study (CHANCE001), the HR benefit for TACE combined with PD-(L)1 inhibitors and MTT compared with TACE monotherapy was 0.63 for OS and 0.70 for PFS, with a median OS of 19.2 months and a median PFS of 9.5 months [19]. In addition to the individual mechanisms for each drug when combined with TACE as previously mentioned, one potential hypothesis for the substantial benefit observed for TCC cocktail might be the immunomodulating activity resulting from the three medications, counteracting TACE-induced hypoxia-driven immunosuppression while amplifying antitumor immunity. Indeed, our previous study has found that the TCC cocktail exerts an efficient anti-HCC effect by inducing the SAMD4B-APOA2-PD-L1 axis to inhibit tumor immune evasion [33]. Specifically, TCC therapy enhanced SAMD4B expression, which then facilitated the instability of APOA2 mRNA. The decreased APOA2 further reduced programmed death ligand 1 (PD-L1) level with a direct interaction pattern, attenuating tumour immunosuppression. Importantly, retrospective analyses of serological immune profiles revealed that, compared to the cTACE group, the cTACE plus TCC group exhibited significantly lower levels of inflammatory

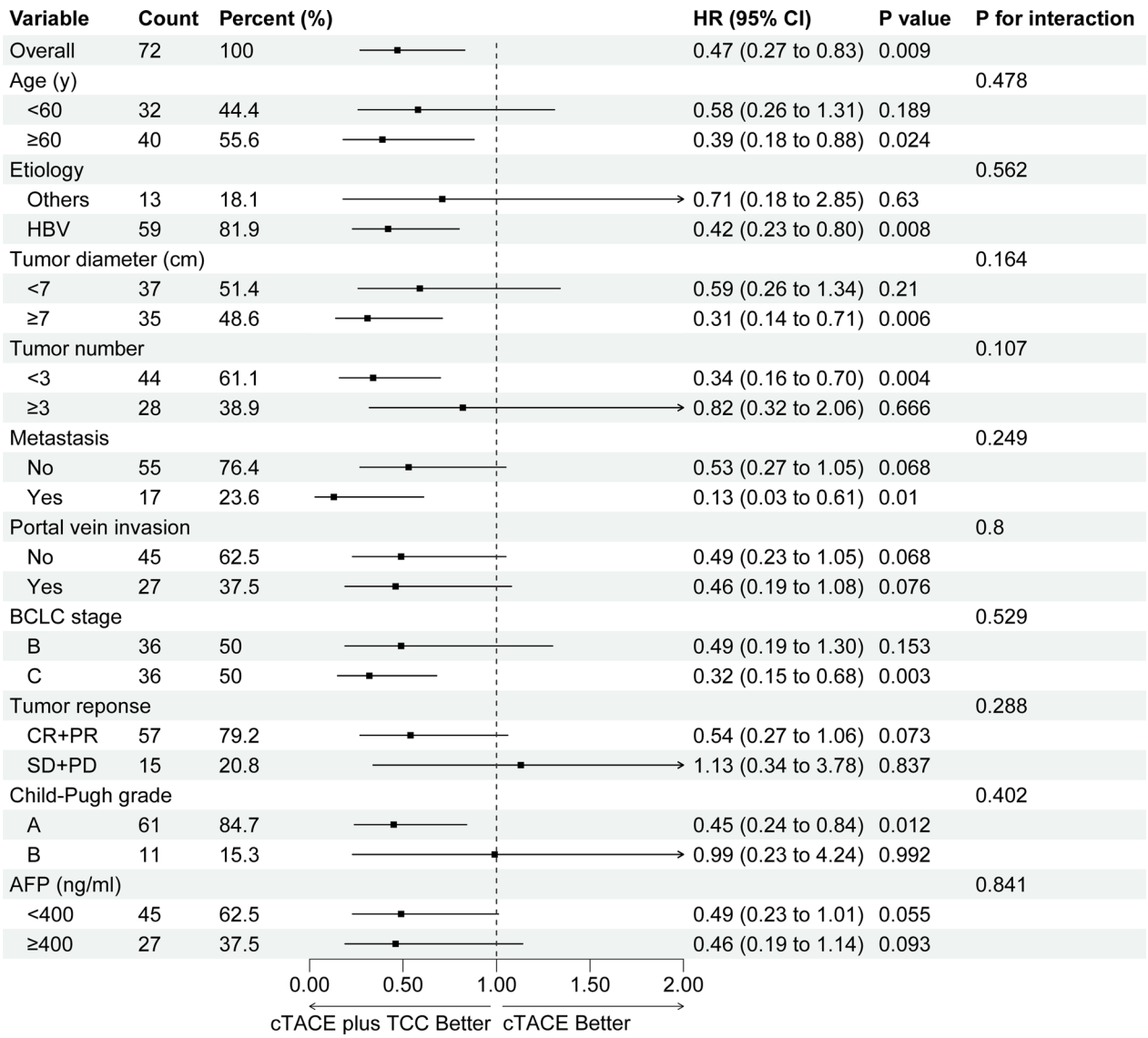

Fig. 4 Forest plots of overall survival (OS) in different patient subgroups. cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules; HBV, hepatitis B virus; BCLC, Barcelona clinical liver cancer stage; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

cytokines (including TNF, IL-2R, IL-6, and IL-8) and a significantly higher CD4/CD8 ratio, indicating a profile favoring immune activation (Tables S5-S6). Furthermore, reductions in serum AFP and IL-6 levels, alongside the restored CD4 +/CD8 +ratio post-treatment, were significantly correlated with improved OS and PFS (Tables S7-S8; Figure S4). Although indirect, these clinical immune markers provide preliminary translational support for the bridging of preclinical mechanisms to therapeutic outcomes, which still needs further prospective studies to fully confirm. In addition, as cancer is a complex disease driven by multiple and interrelated biological mechanisms, combinatorial multi-targeting with distinctive classes of cancer drugs could disrupt tumor-driving mechanisms as well as systemic manifestations [50].

Safety is one of the important indicators to ensure patient treatment compliance. Studies of TACE in combination with systemic therapies have reported varying degrees of increased incidence of grade 3–4 AEs (15.8% vs. 7.5% [19], 32.5% vs. 13.5% [20], 45% vs. 30% [51]), as well as dose reductions and treatment discontinuations due to AEs. However, our trial results demonstrated that long-term administration of the TCC cocktail did not observe increased drug toxicities (11.1% vs. 8.3%),

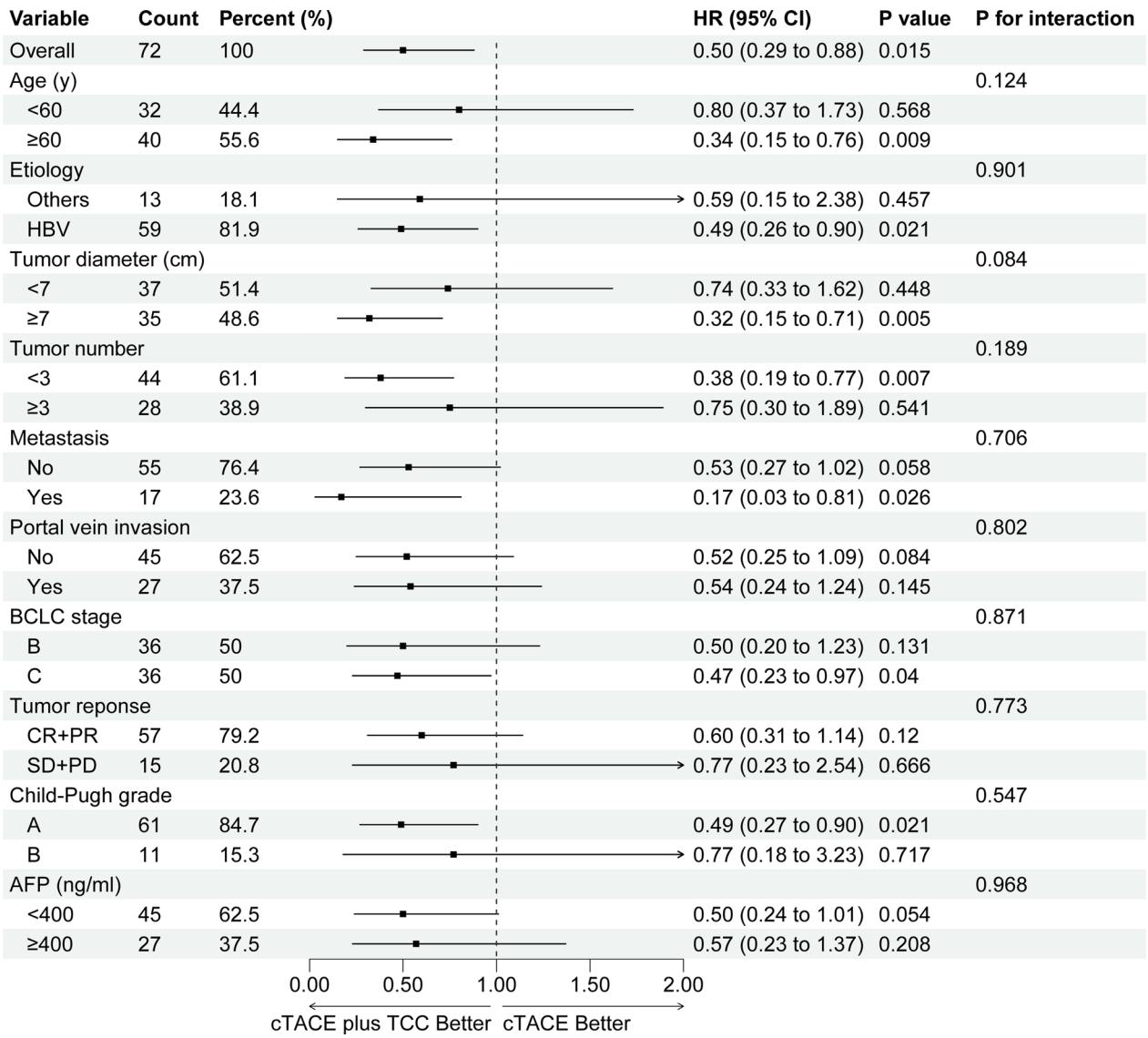

Fig. 5 Forest plots of progression-free survival (PFS) in different patient subgroups. cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules; HBV, hepatitis B virus; BCLC, Barcelona clinical liver cancer stage; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

but rather, it could potentially reduce the incidence of common AEs reported during each drug therapy. For instance, previous studies have indicated that thalidomide may be associated with an increased risk of developing peripheral neuropathy and venous thromboembolism in cancer patients [52, 53]. However, these adverse effects were not observed in this trial. One possible explanation is that we have employed a low-dose maintenance strategy of thalidomide and carmofur, which has been demonstrated to effectively prevent the occurrence of severe AEs. Our study provides a multi-target and low-toxicity oral therapeutic strategy to assist TACE-treated patients in improving clinical benefit.

The study has several limitations. First, as an open-label trial, this study may be prone to bias, but objective clinical results can be assured by having BIRC assess tumor imaging progress. Second, the development of this study protocol predates the formalization of ICI combinations in HCC guidelines. In light of our previous findings, future trials will consider the potential of combining TCC cocktail with immunotherapy. Last, as a local pilot trial, the limited sample size was another limitation of this study. To address these limitations, a large-scale

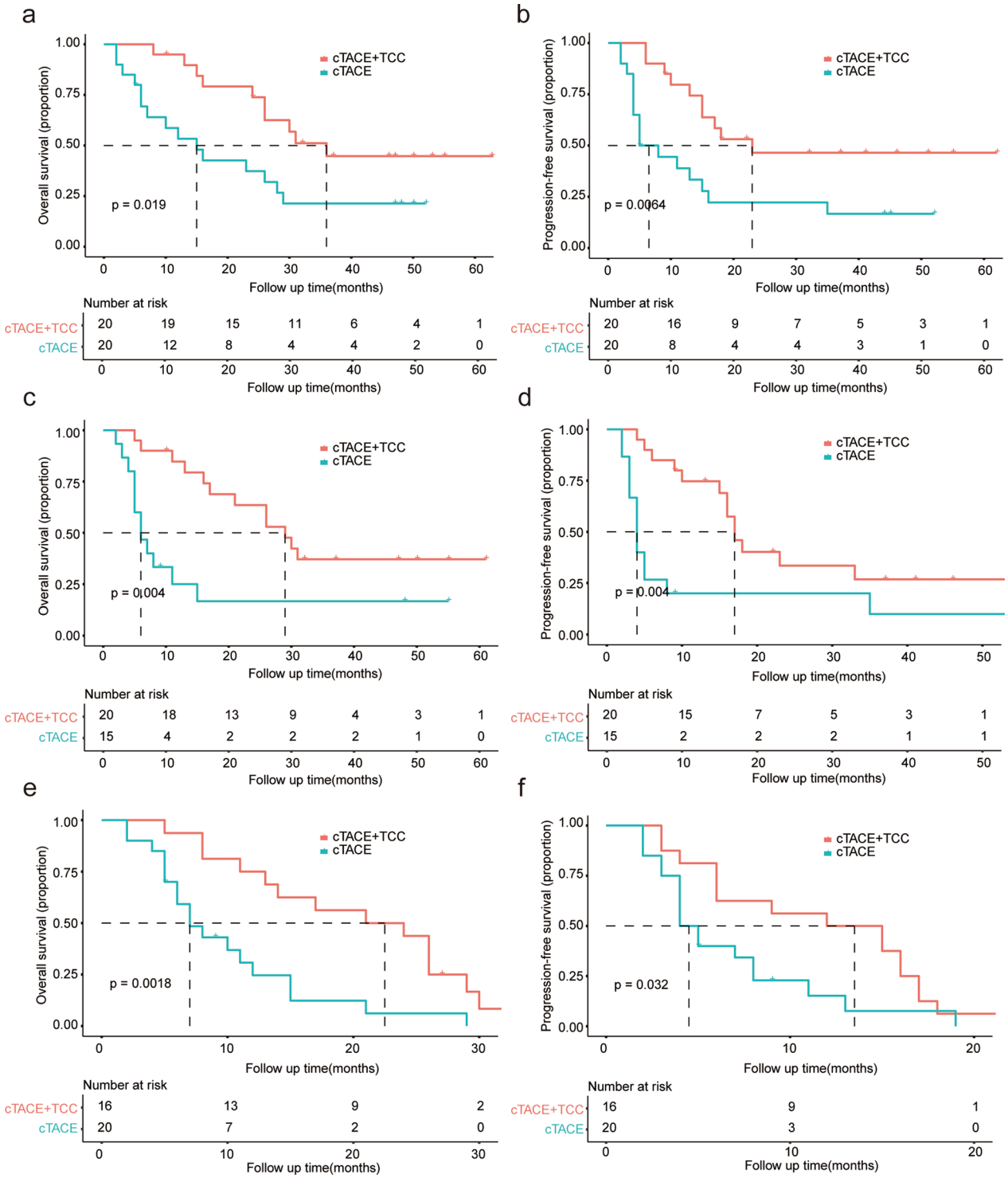

Fig. 6 Kaplan–Meier curves showing overall survival (OS) and progression-free survival (PFS) in the subgroups of patients with age ≥ 60 years (**a**, **b**), tumor diameter ≥ 7 cm (**c**, **d**) and BCLC stage C (**e**, **f**) who receiving cTACE plus TCC cocktail or cTACE only. cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules

Table 3 Adverse Events

AEs	Any Grade			Grade 3–4		
	Group, N (%)			Group, N (%)		
	cTACE (N = 36)	cTACE + TCC (N = 36)	*p*	cTACE (N = 36)	cTACE + TCC (N = 36)	*p*
Abdominal pain	17 (47.2)	14 (38.9)	0.475	3 (8.3)	2 (5.6)	1.000
Nausea	13 (36.1)	9 (25.0)	0.306	3 (8.3)	3 (8.3)	1.000
Fever	9 (25.0)	5 (13.9)	0.234	2 (5.6)	1 (2.8)	1.000
Fatigue	14 (38.9)	6 (16.7)	0.035	2 (5.6)	0 (0.0)	0.493
Dyspnea	3 (8.3)	1 (2.8)	0.614	0	0	-
Vomiting	10 (27.8)	7 (19.4)	0.405	1 (2.8)	1 (2.8)	1.000
Diarrhea	12 (33.3)	8 (22.2)	0.293	2 (5.6)	0 (0.0)	0.493
Dyspepsia	14 (38.9)	12 (33.3)	0.624	3 (8.3)	2 (5.6)	1.000
Peripheral neuropathy	0 (0.0)	2 (5.6)	0.493	0	0	-
Weight decrease	9 (25.0)	7 (19.4)	0.571	2 (5.6)	1 (2.8)	1.000
Edema	5 (13.9)	2 (5.6)	0.429	0	0	-
Constipation	10 (27.8)	13 (36.1)	0.448	1 (2.8)	3 (8.3)	0.614
Skin rash	5 (13.9)	11 (30.6)	0.089	0 (0.0)	1 (2.8)	1.000
ALT increase	12 (33.3)	8 (22.2)	0.293	4 (11.1)	2 (5.6)	0.674
AST increase	11 (30.6)	9 (25.0)	0.599	3 (8.3)	2 (5.6)	1.000
Hyperbilirubinemia	8 (22.2)	5 (13.9)	0.358	2 (5.6)	1 (2.8)	1.000

cTACE, conventional transarterial chemoembolization; TCC, Thalidomide, Carmofur and Compound mylabris capsules; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase

multicenter randomized clinical trial incorporating advanced methodology [54–56], longitudinal biomarker profiling and translational substudies is warranted to definitively confirm the clinical efficacy and generalizability of this novel strategy while dissecting its mechanistic underpinnings in human systems.

Conclusions

In conclusion, the randomized clinical trial demonstrated that cTACE combined with TCC cocktail was well tolerated and significantly improved clinical outcomes compared with TACE alone treatment. This novel strategy may be a promising option for patients with unresectable HCC.

Abbreviations

TACE	Transarterial chemoembolization
cTACE	Conventional transarterial chemoembolization
HCC	Hepatocellular carcinoma
CMC	Compound mylabris capsules (CMC)
TCC	Thalidomide, carmofur and compound mylabris capsule
OS	Overall survival
PFS	Progression-free survival
ORR	Objective response rates
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
AEs	Adverse events
PLC	Primary liver cancer
PVTT	Portal vein tumor thrombosis
TKIs	Tyrosine kinase inhibitors
MTT	Molecular targeted therapy
ICIs	Immune checkpoint inhibitors
AIDS	Acquired immune deficiency syndrome
TCM	Traditional Chinese medicinal
ECOG	Eastern Cooperative Oncology Group
BIRC	Blinded independent radiology committee
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ITT	Intent-to-treat
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
TNF	Tumor necrosis factor
IFN	Interferon
RCT	Randomized controlled study
DFS	Disease-free survival
NMPA	National Medical Products Administration
Hb	Hemoglobin
WBC	White blood cell
PLT	Platelet count
BUN	Blood urea nitrogen
Cr	Creatinine
AFP	Alpha-fetoprotein
HBV	Hepatitis B virus
ALBI	Albumin–bilirubin
CNLC	China liver cancer
BCLC	Barcelona clinic liver cancer
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
ALT	Alanine aminotransferase
AST	Aspartate transaminase
PD-L1	Programmed death ligand 1

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06624-x.

Supplementary material 1: Document S1. Tables S1–S8 and Figures S1–S4. Table S1 Number of cTACE sessions that patients received in two groups. Table S2 Number of patients that received subsequent treatments after progression in two groups. Table S3 Univariable and multivariable analyses of factors associated with overall survival. Table S4 Univariable and multivariable analyses of factors associated with progression-free survival. Table S5 Comparison of TNF, IL-1β, IL-2R, IL-6 and IL-8 levels between the two groups before and after treatment. Table S6 Comparison of CD19+, CD3+, CD4+, CD8+, CD4+/CD8+ and CD56+ levels between the two groups before and after treatment. Table S7 Univariate COX regression analyses of factors associated with overall survival. Table S8 Univariate COX regression analyses of factors associated with progression-free survival. Figure S1. Study schema. Figure S2. A complete response representative case with portal vein tumor thrombus who was assigned to the transarterial chemoembolization plus TCC cocktail group. Figure S3. A complete response representative case who was assigned to the transarterial chemoembolization plus TCC cocktail group. Figure S4. Kaplan-Meier curves showing overall survival and progression-free survival in the patients with varying AFP, IL-6, and CD4/CD8 changes following treatment.

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Author contributions
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Concept and design: J. Xia. Acquisition, analysis, or interpretation of data: J. Li, B. Lv, L. Song, M. Guo, T. Fang. Drafting of the manuscript: J. Li, B. Lv, L. Song. Statistical analysis: J. Li, X. Zhang, J. Zhang. Reviewing and Editing: J. Xia, T. Ye, Y. Liu, X. Ding. Funding acquisition: J. Xia. Administrative, technical, or data support: B. Yang, Z. Zhao, P. Huang, Y. Chen, N. Ge, T. Ye, Y. Liu, X. Ding. Supervision, guarantor: J. Xia.

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Data availability
Re-identified participant data will be made available to qualified researchers upon request, starting 24 months after the completion of the study, including follow-up. Researchers interested in accessing the data should submit a methodologically sound research proposal to the corresponding author. To obtain access, a data access agreement must be signed. The dataset supporting the conclusions of this article is included within the article (and its additional file).

Declarations

Ethics approval and consent to participate
The trial protocol and consent form were approved by the ethics committee of Zhongshan Hospital (No. B2018-061R), and complied with the Declaration of Helsinki and Good Clinical Practice guidelines. The other participating units were subject to ethical examination and approval by the leading unit. The trial was registered at www.chictr.org.cn as ChiCTR1800016335. All patients provided written informed consent before participation.

Competing interests
We have read and understood the journal policy on declaration of interests and declare that we have no competing interests.

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