Transarterial Chemoembolization Improves Survival in Advanced Hepatocellular Carcinoma Patients Treated with Tyrosine Kinase Inhibitors Plus Immune Checkpoint Inhibitors

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Research Article

Keywords: Hepatocellular carcinoma (HCC), TACE, Sorafenib, Lenvatinib, Nivolumab, Pembrolizumab, Camrelizumab, Combination therapy, Overall survival, Tumor response, Adverse events

Posted Date: July 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-679376/v1

Abstract

Background

The survival benefit and safety of transarterial chemoembolization (TACE) for advanced Hepatocellular Carcinoma (HCC) patients treated with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) is unclear. We aimed to investigate the efficacy and safety of TACE combined with TKIs and ICIs the treatment of advanced HCC.

Methods

In this study, the conditions of 147 patients with advanced HCC who underwent TKIs plus ICIs treatment between July 2017 and April 2020 were evaluated. We divided these patients into the TACE group and non-TACE group based on whether they were treated with TACE during TKIs plus ICIs treatment, and compared their survival outcomes, especially overall survival (OS), and whether they were exposed to unexpected toxicities.

Results

In this study, a total of 98 patients who underwent TACE during TKIs plus ICIs treatment were included in the TACE group, while the other 49 patients were included in the non-TACE group. According to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST), the objective response rate (ORR) of the TACE group was higher than that of the non-TACE group (ORR 74.5% vs. 40.8%, p 0.001). The OS of the TACE group was significantly longer than the non-TACE group (OS 19.3 months vs. 10.8 months, p = 0.010). The incidence of grade 3-4 toxicities in the TACE group was similar to that in the non-TACE group (33.7% vs. 28.6%, p = 0.532).

Conclusions

The TACE treatment combined with TKIs plus ICIs resulted in longer OS compared to the treatment of systemic TKIs plus ICIs without TACE during the process of advanced HCC.

Introduction

Hepatocellular Carcinoma (HCC) is the fifth most common cancer worldwide and the second most common cause of cancer-related death [1]. The radical treatment of early HCC includes local resection, liver transplantation and ablation. However, most HCC patients are complicated with more serious cirrhosis or are diagnosed during the advanced stage (unresectable/extrahepatic metastasis) [2]. These patients are no longer suitable for radical treatment. Thus, more effective treatments need to be explored for them.

The systematic treatment of HCC has undergone profound changes in the past decade. Since 2007, the tyrosine kinase inhibitors (TKIs) represented by sorafenib have significantly prolonged survival in patients

with advanced HCC [3], thus having profoundly improved treatment strategies of HCC. In 2018, clinical trial results demonstrated that the overall survival of Lenvatinib treatment is not inferior to sorafenib and is recommended by several guidelines as the standard of first-line systemic treatment [4–6]. In addition, three other drugs, regorafenib, cabozantinib, and ramucirumab, have been used as second-line therapy since then [1,7]. However, the survival improvement of TKIs monotherapy for HCC was not satisfactory. In recent years, a variety of immune checkpoint inhibitors (ICIs), such as nivolumab, pembrolizumab, and camrelizumab, successfully demonstrated their effectiveness as a treatment of HCC [8–10]. However, head-to-head clinical trials of ICIs and sorafenib failed to improve outcomes [11,12].

TKIs can reprogram the immunosuppressive microenvironment around tumors into an immune-stimulating environment, in which conditions the use of ICIs enhances the antitumor activity of T cells [13]. Currently, several studies have demonstrated the great potential of TKIs combined with ICIs in the treatment of HCC. A Phase 1b, single-arm study [14]showed that the median overall survival (OS) of lenvatinib plus pembrolizumab were obviously improved (OS: 22 months, 95% confidence intervals [CI]: 20.4 months, not estimable [NE]), which are encouraging signs of antitumor activity observed in HCC patients. The IMbrave150 trial [15] showed that atezolizumab plus bevacizumab delivered a higher survival rate than sorafenib in patients with untreated unresectable HCC (6 months OS 84.8% vs. 72.2%, p 0.001), which is the first further improvement of OS in unresectable HCC patients. The treatment mode of TKIs combined with ICIs greatly extended the survival time compared to the TKIs monotherapy. Nevertheless, the tumor response rate remains at a low level even after combination treatment, which is an outcome that may further benefit patients.

Transarterial chemoembolization (TACE), an effective locoregional therapy, has been recommended as one of the common treatments for HCC by most guidelines[5,16,17] In 2020, TACTICS trial[18] comparing TACE plus sorafenib with TACE alone reported a major improvement in PFS based on a new definition of untreatable progression, TACE plus TKIs proved to be feasible. Otherwise, TACE can promote immunogenic cell death and induce tumor-associated antigen specific response, thus enhance tumor response to ICIs [19]. The combination of TACE with TKIs and ICIs is expected to further improve the survival outcome for HCC patients.

So far, there have been few formal reports on TACE combined with TKIs plus ICIs for the treatment of advanced HCC, and the efficacy and safety are still uncertain. In this study, we divided the treated patients into two groups according to whether they underwent TACE during the treatment of TKIs plus ICIs. Survival outcomes of TACE combined with TKIs plus ICIs in advanced HCC patients were compared and observed, as well as any unexpected toxicities.

Materials And Methods

Study Design

The Ethics Review Committee has approved this study of The Third Affiliated Hospital of Sun Yat-sen University. Data of patients with advanced HCC who received TKIs plus ICIs treatment between July 2017 and April 2020 were respectively collected, and the follow-up period was up to January 2021. As it is a retrospective study, informed consent of patients was waived.

The diagnosis of HCC meets the requirements of the AASLD guidelines [6]. Inclusion criteria for patients were as follows: (a) 18–75 years old, (b) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, (c) had Child-Pugh class A or B liver disease, and (d) adequate organ function. Patients were excluded from our study if they (a) missed follow-up data, (b) had any prior systemic therapy, (c) had other previous malignant tumors, (d) had no assessable intrahepatic tumor, (e) had hepatic encephalopathy, uncontrolled ascites or pleural effusion.

From July 2017 to April 2020, a total of 147 eligible patients with advanced HCC received TKIs plus ICIs, including 98 patients who received TACE during combination therapy (hereafter, TACE group) and 49 who received combination therapy without TACE (hereafter, non-TACE group), as shown in retrospective data compilation (Fig. 1). The TACE treatment was performed according to the evaluation of the attending physician and the patient's willingness. Before treatment, the attending physician fully informed the patients of the possible treatment costs, possible treatment outcomes and treatment-related side effects. All of the included patients expressed understanding regarding the potential effects of the TACE, and therefore made clear treatment choices.

TACE Procedure

TACE is performed under the guidance of digital subtraction angiography (DSA) by experienced interventional radiologists during endovascular interventional therapy. TACE received 1 week prior to baseline was allowed as intra-follow-up treatment. The chemotherapeutic agents, embolization materials used in TACE, and detailed TACE procedures have been described in previously published articles [20]. Repeat TACE is allowed if the follow-up imaging taken after one month of operation suggests tumor survival and the TACE-induced damaged is tolerated by liver function.

TKIs Management

Alternative TKIs during TKIs plus ICIs treatment include sorafenib and lenvatinib. The initial oral dose of sorafenib is 400mg twice daily, and lenvatinib is 12 mg (if bodyweight $\geq$ 60 kg) or 8 mg (if bodyweight<60 kg) once per day. The initial dose should be maintained and continued if there is no intolerant toxicity or radiographic disease progression. Patients in the TACE group resumed their prescribed dose of TKIs 3–5 days after TACE. If the adverse events of TKIs are not tolerated at the standard dose, the dose is allowed to be halved to reduce the adverse effects. If the toxic effects are still intolerable with the halved dose, treatment should be suspended until the adverse events are relieved or disappeared.

ICIs Management

During the TKIs plus ICIs treatment, the options for ICIs include nivolumab, pembrolizumab, and camrelizumab, and the administration of ICIs and TKIs start on the same day. These ICIs were given intravenously every 3–4 weeks at a standard dose, with each infusion lasting for at least half an hour until disease progression changes or intolerable toxicity associated with ICIs appears.

Assessment of Tumor Response and Treatment Safety

Patients in both groups received abdominal contrast-enhanced CT or MR examination to setup baseline, followed by initial and follow-up exams within 1–3 months and every 1–2 months thereafter until data cutoff, death or loss of follow-up occurs. Response to treatment was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST1.1) [21]and modified RECIST (mRECIST) [22]. Two radiologists with more than 15 years of experience in abdominal imaging independently evaluate the target lesions, and any inconsistencies in the evaluation results were resolved by consensus. Tumor evaluation indexes include complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD). The ORR includes CR and PR, while the disease control rate (DCR) is defined as the sum of CR, PR and SD.

Adverse events (AEs) that occurred during the follow-up were evaluated in terms of classification, incidence and severity, according to National Cancer Institute Common Terminology Criteria Version 4.0 [23] at each follow-up.

Overall survival (OS) in both groups was defined as the time period from the start of TKIs plus ICIs treatment to the patient's death or survival to the cut-off date (January 31, 2021). PFS was defined as either radiologic evidence of tumor progression at the time of TKIs plus ICIs therapy initiation or patient death/ survival until the cutoff date, whichever occurred first.

Statistical Analyses

The population baseline characteristics were determined using descriptive statistical methods, with categorical variables represented by median and quaternary intervals while continuous variables represented by median and 95% CI. Categorical variables were tested by χ^2 test or Fisher's exact test, and continuous variables were tested by t test or u test. Kaplan-Meier survival analysis was used for PFS and OS, while log-rank was used to test for differences between groups. Cox proportional hazard regression models were utilized for univariate and multivariate analyses of OS in the total population of patients. The dichotomous variables $p \leq 0.1$ from univariate analyses were included in the multivariate analysis to describe the prognostic correlation of the potential survival predictors. SPSS Statistics (version 26.0; IBM, Armonk, NY) was employed for all statistical analyses, and bilateral tests were used for all statistical tests. A two-sided p value less than 0.05 indicated statistical significance.

Results

Patient Characteristics

147 advanced HCC patients who received TKIs plus ICIs with or without TACE between July 2017 and April 2020 were evaluated in this study. Among them, 98 patients who underwent TACE during TKIs plus ICIs treatment were included in the TACE group (median age, 52 years; interquartile range [IQR] 42–62 years; 87 men), while the other 49 patients were included in the non-TACE group (median age, 53 years; IQR 47–63 years; 47 men). Baseline characteristics of the two groups are shown in Table 1, including age, gender, hepatitis B surface antigen, tumor size, tumor number, tumor involvement, main portal vein tumor thrombus, macrovascular invasion, extrahepatic metastasis, ascites, albumin (ALB), total bilirubin (TBIL), platelet count (PLT), prothrombin time (PT), α-fetoprotein (AFP) level, Child–Pugh Score, BCLC stage and history of locoregional therapy. There was no significant difference between the two groups of independent variables (all comparisons, p 0.05; Table 1).

Table 1
Baseline patient characteristics

Variable	TACE group (n = 98)	Non-TACE group (n = 49)	p value
Mean age (y)	52 (42–62)	53 (47–63)	0.108
Sex			0.150
Male	87 (88.8)	47 (95.9)	
Female	11 (11.2)	2 (4.1)	
hepatitis B surface antigen			0.862
Positive	85 (86.7)	43 (87.8)	
Negative	13 (13.3)	6 (12.2)	
Maximum diameter of intrahepatic tumors (cm)	8.8 (6.4–12.4)	7.8 (3.8–12.6)	0.209
No. of intrahepatic tumors			0.692
≤ 3	27 (27.6)	12 (24.5)	
> 3	71 (72.4)	37 (75.5)	
Tumor involvement			0.806
Unilobar	34 (34.7)	16 (32.7)	
Bilobar	64 (65.3)	33 (67.3)	
Main portal vein tumor thrombus			0.744
Yes	14 (14.3)	8 (16.3)	
No	84 (85.7)	41 (83.7)	
Macrovascular invasion ¶			0.098
Yes	73 (74.5)	30 (61.2)	
No	25 (25.5)	19 (38.8)	
Extrahepatic metastasis			0.726
Yes	49 (50.0)	26 (53.1)	
No	49 (50.0)	23 (46.9)	
Ascites			0.468
Yes	34 (34.7)	20 (40.8)	
No	64 (65.3)	29 (59.2)	

Variable	TACE group (n = 98)	Non-TACE group (n = 49)	p value
Median ALB (g/L)	35.8 (33.4–38.8)	35.5 (31.3–40.2)	0.887
Median total bilirubin (mmol/L)	16.7 (11.6–27.0)	11.5 (9.2–19.9)	0.148
Median platelet count (×10^9/L)	158 (107–232)	114 (91–224)	0.767
Median PT (second)	14.2 (13.4–15.1)	14.0 (13.3–14.7)	0.617

Table 1
(continued) Baseline Patient Characteristics

Variable	TACE Group (n = 98)	Non-TACE Group (n = 49)	P value
AFP (ng/mL)			0.554
≥200	59 (60.2)	27 (55.1)	
≤200	39 (39.8)	22 (44.9)	
Child-Pugh liver function class			0.234
A5-A6	75 (76.5)	33 (67.3)	
B7-B9	23 (23.5)	16 (32.7)	
BCLC stage			0.728
B	12 (12.2)	7 (14.3)	
C	86 (87.8)	42 (85.7)	
History of locoregional therapy	69 (70.4)	40 (81.6)	0.143
Except where indicated, data are numbers of patients, with percentages in parentheses. Abbreviations: AFP, a-fetoprotein; ALB, albumin; BCLC, Barcelona Clinic Liver Cancer; PT, Prothrombin time; TACE, transarterial chemoembolization. Non-TACE group refers to patients who who received systemic combination therapy without transarterial chemoembolization.			
* Numbers in parentheses are the interquartile range.			
¶ Some patients had hepatic venous invasion and no portal vein invasion (five in the TACE group and one in the non-TACE group).			

By the cut-off date (January 31, 2021), 45 (45.5%) of the 98 patients in the TACE group and 31 (63.3%) of the 49 patients in the non-TACE group died. 7 (7.1%) patients in the TACE group and 4 (8.2%) patients in the non-TACE group continued TKIs plus ICIs therapy until the cut-off date, respectively. Sequential treatment of patients in the two groups after TKIs plus ICIs treatment was presented in Table 2.

Table 2
Sequential treatment after TKIs plus ICIs therapy

Variable	TACE group (*n* = 46)	Non-TACE group (*n* = 14)
Downstaging hepatectomy	1 (2.2)	1 (7.1)
Downstaging ablation	2 (4.3)	1 (7.1)
TACE	19 (41.3)	4 (28.6)
HAIC	4 (8.7)	3 (21.4)
Radiotherapy	4 (8.7)	1 (7.1)
Replace TKIs	23 (50.0)	9 (64.3)
Best supportive care	5 (10.9)	1 (7.1)

Except where indicated, data are numbers of patients, with percentages in parentheses. Abbreviations: ICIs, Immune checkpoint inhibitors; HAIC, hepatic artery infusion chemotherapy; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors.

Treatment Outcomes and Survival Analysis in the Overall Cohort

The median OS of the TACE group and the non-TACE group were 19.3months (95%CI 14.6–24.1) and 10.8months (95%CI 6.7–14.9), respectively, meaning that the TACE group had significantly longer (p = 0.010) OS time (Fig. 2a). Median PFS for the TACE group was 9.3 months (95%CI 7.5–11.1), and for the non-TACE group, it was 7.6 months (95%CI 5.8–9.4) (p = 0.308) (Fig. 2b).

As shown in Table 3, 17 clinical factors were included in the Cox proportional hazard regression models. The multivariate analysis indicated that the TACE group still had a significant advantage regarding patients' survival over non-TACE group (p = 0.004, hazard ratio [HR] = 2.00, 95% CI 1.25–3.19). In addition, the main portal vein tumor thrombus (p = 0.001, HR = 0.37, 95% CI 0.20–0.66), and the AFP > 200 ng/mL (p = 0.001, HR = 0.41, 95% CI 0.27–0.71) were also independent predictors associated with OS (Fig. 3).

Table 3
Risk factors analysis for death

	Univariable Analysis			Multivariable Analysis		
Variable	Hazard Ratio	95% CI	*p* Value	Hazard Ratio	95% CI	*p* Value
TACE group	0.55	0.35–0.87	0.011	0.50	0.31–0.80	0.004
Age > 60 y	0.73	0.43–1.23	0.233			
Men	0.74	0.35–1.54	0.428			
Positive for HBsAg	1.21	0.60–2.44	0.586			
Size of main tumor > 10 cm	1.53	0.97–2.41	0.070	0.99	0.60–1.62	0.952
Number of intrahepatic tumors > 3	2.08	1.16–3.72	0.014	1.67	0.89–3.14	0.113
Involvement of bilobar	1.85	1.10–3.12	0.021	1.58	0.92–2.72	0.103
Main portal vein tumor thrombus	2.00	1.14–3.48	0.015	2.73	1.52–4.90	0.001
Macrovascular invasion	1.18	0.71–1.95	0.525			
Extrahepatic metastasis	1.30	0.82–2.05	0.267			
Ascites	1.22	0.77–1.94	0.400			
ALB ≤ 36 g/L	1.08	0.69–1.71	0.730			
total bilirubin > 34 mmol/L	1.10	0.55–2.22	0.781			
Platelet count ≤ 100×10^9/L	0.76	0.43–1.34	0.340			
AFP > 200ng/mL	2.02	1.23–3.32	0.006	2.42	1.41–4.13	0.001
Child-Pugh class B	1.21	0.72–2.02	0.474			
BCLC stage C	1.99	0.86–4.58	0.107			

	Univariable Analysis	Multivariable Analysis
All 147 patients were analyzed. $p \leq 0.05$ was considered to indicate statistical significance. Abbreviations: AFP, a-fetoprotein; ALB, albumin; BCLC, Barcelona Clinic Liver Cancer; PT, Prothrombin time.		

Details of the different combinations of TKIs and ICIs are shown in Table 4. The radiological evaluation outcomes of two groups of patients with advanced HCC are revealed in Table 5. According to the RECIST 1.1, the ORR of the TACE group was 37.8% (37/98), and this value of the non-TACE group was 26.5% (13/49) ($p = 0.176$), while the DCR was 90.1% (89/98) for the TACE group and 63.3% (31/49) for the non-TACE group ($p = 0.002$), respectively. According to mRECIST, the ORR and DCR of the TACE group were significantly higher than that of the non-TACE group (ORR 74.5% vs. 40.8%, P 0.001; DCR 83.7% vs. 67.3%, $p = 0.012$). A representative case receiving systemic combination therapy with TACE is shown in Fig. 4.

Table 4
Collocation selection of systemic combination therapy at baseline

TACE group, non-TACE group	Sorafenib	Lenvatinib
Nivolumab	14 (14.3), 5 (10.2)	7 (7.1), 1 (2.0)
Pembrolizumab	4 (4.1), 2 (4.1)	14 (14.3), 4 (8.2)
Camrelizumab	40 (40.8), 30 (61.2)	19 (19.4), 7 (14.3)
Except where indicated, data are numbers of patients, with percentages in parentheses.		

Table 5
Outcomes in patients with advanced HCC treated with TACE group and non-TACE group

	RECIST 1.1			mRECIST		
Variable	TACE group (n = 98)	Non-TACE group (n = 49)	*p* Value	TACE group (n = 98)	Non-TACE group (n = 49)	*p* Value
Best response						
CR	0 (0)	0 (0)		20 (20.4)	4 (8.2)	
PR	37 (37.8)	13 (26.5)		53 (54.1)	16 (32.7)	
SD	52 (53.1)	22 (44.9)		16 (16.3)	17 (34.7)	
PD	9 (9.2)	14 (28.6)		9 (9.2)	12 (24.5)	
ORR (CR + PR)	37 (37.8)	13 (26.5)	0.176	73 (74.5)	20 (40.8)	0.001
DCR (CR + PR + SD)	89 (90.1)	31 (63.3)	0.002	82 (83.7)	33 (67.3)	0.012

Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages. Outcomes were determined according the Response Evaluation Criteria in Solid Tumors, version 1.1 and modified Response Evaluation Criteria in Solid Tumors. Non-TACE group refers to patients who who received systemic combination therapy without transarterial chemoembolization. Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progression disease; PR, partial response; SD, stable disease.

Complications

Table 6 reveals an incidence that greater than 10% regarding the TACE-related and drug-related AEs for all grades, and grades 3–4 in the TACE group and the non-TACE group. The median treatment duration of TKIs plus ICIs for the TACE group was 5.6 months (95%CI 3.0-11.2), and it was 3.4 months (95%CI 0.9–5.8) for the non-TACE group. Patients in the TACE group received a total of 224 TACE procedures, with a median of 3.0 (IQR 1.0–3.0) times per patient.

Table 6
Adverse events with an incidence of more than 10% in either group

	TACE group (n = 98)		Non-TACE group (n = 49)	
Parameter	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Abdominal pain	73 (74.5)	10 (10.2)	21 (42.9)	0 (0)
AST/ALT increased	55 (56.1)	4 (4.1)	12 (24.5)	1 (2.0)
Constipation	35 (35.7)	0 (0)	13 (26.5)	0 (0)
Pyrexia	34 (34.7)	7 (7.1)	14 (28.6)	2 (4.1)
Hypertension	31 (31.6)	9 (9.2)	13 (26.6)	4 (8.2)
PLT decreased	26 (26.5)	3 (3.1)	20 (40.9)	2 (4.1)
Fatigue	24 (24.5)	4 (4.1)	15 (26.5)	1 (2.0)
Weight decreased	24 (24.5)	0 (0)	13 (26.5)	0 (0)
Diarrhea	22 (22.4)	0 (0)	7 (14.4)	0 (0)
Rash	21 (21.4)	1 (1.0)	10 (20.4)	1 (2.0)
Pneumonitis	13 (13.3)	2 (2.0)	5 (10.2)	2 (4.1)
Nausea	11 (11.2)	2 (2.0)	6 (12.2)	0 (0)
Proteinuria	11 (11.2)	0 (0)	6 (12.2)	1 (2.0)
TBIL increased	10 (10.2)	2 (2.0)	8 (16.3)	2 (4.1)

Data in parentheses are percentages. Non-TACE group refers to patients who who received systemic combination therapy without transarterial chemoembolization. Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; PLT, platelet; TBIL, Total bilirubin.

The incidence of grade 3–4 toxicities in the overall population was 32.0% (47/147). 98.0% (96/98) and 33.7% (33/98) of patients in the TACE group and 98.0% (48/49) and 28.6% (14/49) of patients in the non-TACE group experienced any grade of AEs and grade 3–4 AEs, respectively. No patients discontinued TKIs plus ICIs treatment due to TACE-related toxic side effects. There were no previously unreported AEs or death because of TACE or TKIs plus ICIs therapy. 35 (35.7%) patients from the TACE group and 16 (32.7%) patients from the non-TACE group were prescribed dose change or interruption due to treatment-related toxicity of systemic combination therapy, respectively. Grade 3–4 abdominal pain was observed more frequently in the TACE group compared to the non-TACE group (10.1% vs. 0%), but symptoms were effectively controlled with analgesic medication. The overall incidence of grade 3–4 AEs in TACE group was similar to that in non-TACE group (33.7% vs. 28.6%, $p = 0.532$) (Table 7).

Table 7
Comparison of adverse events between TACE group and non-TACE group

Parameter	TACE group (n = 98)	Non-TACE group (n = 49)	All patients (n = 147)	*p* value
Any Grade	96 (98.0)	48 (98.0)	144 (98.0)	1.0
Grade 3–4	33 (33.7)	14 (28.6)	47 (32.0)	0.532

Data in parentheses are percentages. Non-TACE group refers to patients who who received systemic combination therapy without transarterial chemoembolization.

Discussion

In previous studies regarding the treatment of advanced HCC, the clinical effectiveness of TACE in the therapeutic combination of TKIs and ICIs has not been explored. In this study, we firstly validated the positive effect of TACE in HCC patients treated with TKIs and ICIs. We described that the OS of TKIs plus ICIs with TACE was significantly longer than systemic combination therapy without TACE (19.3 months vs. 10.8 months, $p = 0.010$), which is consistent with the analysis using the cox proportional hazard regression models. The PFS of TACE combined with TKIs and ICIs was also improved compared with that of treatment without TACE (9.3 months vs. 7.6 months, $p = 0.308$), although the statistical difference was not significant. According to the mRECIST, the objective response rate (ORR) of the TACE group was higher than the non-TACE group as well (ORR 74.5% vs. 40.8%, p□0.001). These results provide hypothesis-generating data for the design of prospective, randomized, phase 2 efficacy trials.

Several reasons may explain the improvement of the survival time for the advanced HCC patients brought by the addition of TACE into the treatment of TKIs plus ICIs. On the one hand, despite the fact that TACE has long been recognized to promise prolonged survival in HCC patients, the TACE-induced tumor hypoxia and up-regulation of vascular endothelial growth factor (VEGF) and platelet- derived growth factor (PDGF) can also be a cause of tumor recurrence [24,25]. What's more, enhanced VEGF expression promotes immune evasion, because of which some HCC patients fail to benefit from immunotherapy. TKIs can inhibit TACE-related tumor recurrence by blocking VEGF receptors and preventing the surge of pro-angiogenic factors, and they can reprogram the immunosuppressive microenvironment around tumors into an immune-stimulating environment, in which conditions the efficacy of immunotherapy is enhanced [26,27]. On the other hand, TACE induces cell death to release tumor antigens, thus improving the immunotherapy efficacy [28]. TACE, especially those induced by locally infused chemotherapeutic agents (e.g., doxorubicin, a classic chemotherapeutic agent that induces immunogenic cell death), causes changes in tumor-specific and innate immune responses, thus inducing anti-tumor immunity, and thereby enhances the ICIs response [29]. Potentially positive interactions among these treatment modalities have further improved survival outcomes in patients with advanced HCC. However, the exact molecular mechanism still needs to be discovered.

Compared to the OS revealed by phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable HCC [30], the survival outcome in TKIs plus ICIs with TACE in our study did not appear to be further improved. The underlying reason could be the worse baseline status in this study, the inclusion of more than 70% of patients with macrovascular invasion and nearly one-third of patients with Child-Pugh class B liver disease. Exceptionally, the median maximum intrahepatic tumor diameter in these patients was approximately 8cm, and this higher tumor burden also affected the survival improvement. All of the above-described reasons are vital factors that limit improvement. As a real-world cohort study, the baseline status of the enrolled population was worse than those in previous clinical studies, making this study more representative of the actual clinical treatment effect of TKIs plus ICIs with TACE.

In this study, the treatment of TACE combined TKIs and ICIs was validated to be clinically effective and safe. The classification, incidence and severity of AEs in the whole population were also divided into two groups according to whether TACE was done or not during systemic combination therapy for comparative analysis. We found that the difference in AEs between the TACE group and non-TACE group was mainly reflected in post-embolism syndromes after TACE. Especially, the incidence of abdominal pain in the TACE group is higher than that of TKIs plus ICIs without TACE, regardless of disease level or grade. All patients with grade 3–4 abdominal pain occurred within 3 days after TACE, which can be effectively controlled by analgesic medication. In addition, all types of AEs were similar in both groups and were generally consistent with safety conclusions from other known trials, and TACE did not lead to more severe AEs associated with systemic combination therapy.

There are several limitations in this study. First, as a retrospective study with a real-world cohort, there is an inevitable selection bias affecting the results. Second, numerous combinations of TKIs and ICIs were involved in this study, while it is impossible to determine the best combination due to the small sample size. Thirdly, the diagnosis of HCC in most patients was determined by combining contrast-enhanced CT or MR imaging findings and α-fetoprotein level with no pathological confirmation. Research and analysis at the cellular and molecular levels also cannot be carried out due to the lack of tumor tissue specimens before and after treatment in these patients. Finally, although the baseline status after grouping was balanced, the limited number of enrolled patients in the study affected the validity of the analysis.

In summary, TACE combined with TKIs and ICIs had a better OS than TKIs plus ICIs without TACE for the treatment of advanced HCC. What's more, TACE did not lead to more severe AEs associated with TKIs plus ICIs therapy. However, more extensive prospective clinical trials are needed to further confirm these findings.

Declarations

Conflicts of Interest Yue Hu, Tao Pan, Xi Cai, Quansheng He, Bing Hu, Yubao Zheng, Ting Jiang, Mingsheng Huang, Zaibo Jiang, JunWei Chen and Chun Wu declare that they have no conflict of interest.

Ethics approval The study protocol was approved by the ethical committee of the Third Affiliated Hospital of Sun Yat-Sen University. All procedures followed were in accordance with the ethical standards of the

responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent Patient consent was waived due to this was a retrospective study.

Code availability: Not applicable.

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Figures

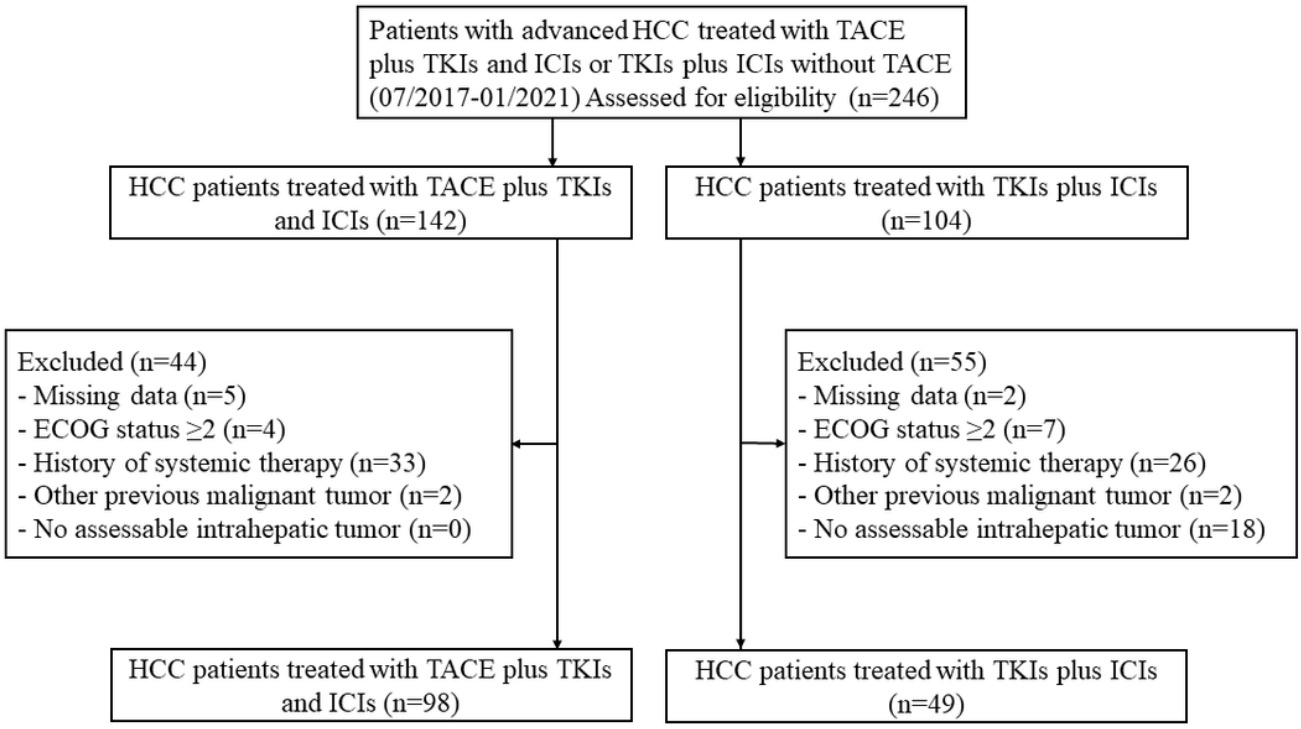

Figure 1

Flowchart of patient inclusion and outcomes. Abbreviations: ICIs, immune checkpoint inhibitors; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors

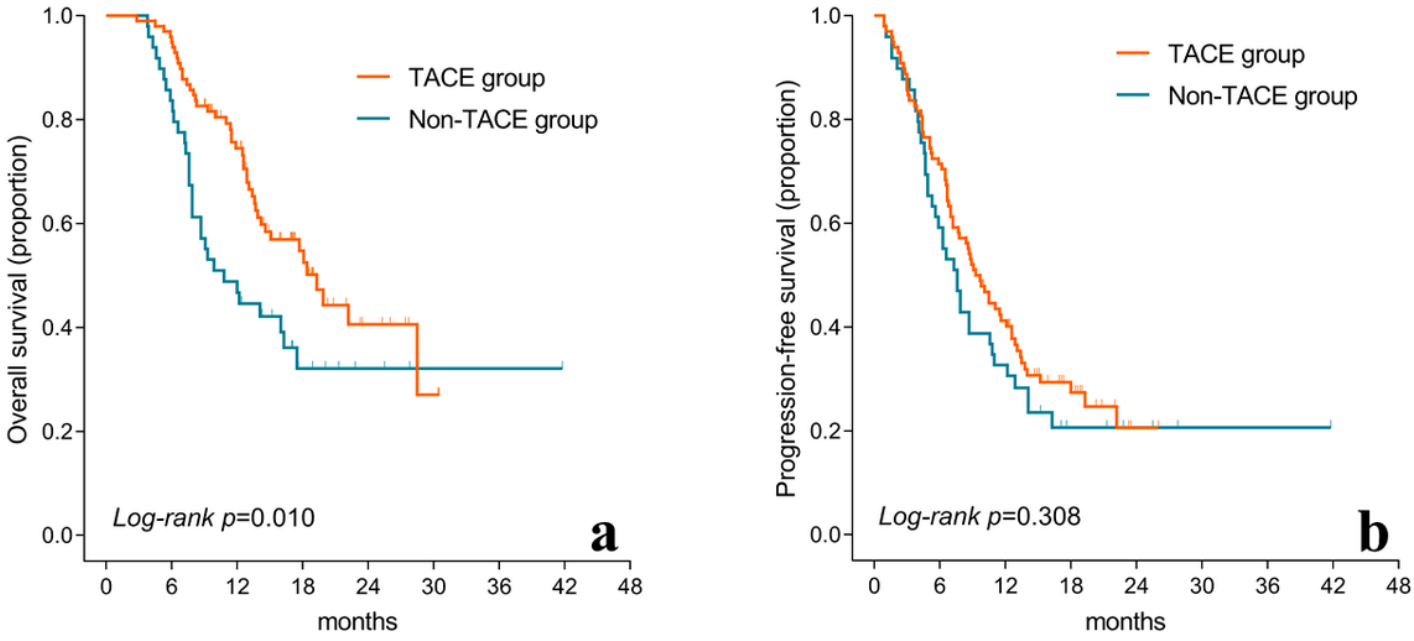

Figure 2

Kaplan-Meier curves of survival outcomes in patients with advanced hepatocellular carcinoma who received tyrosine kinase inhibitors plus immune checkpoint inhibitors with or without transarterial chemoembolization (TACE). (a) cumulative overall survival (OS) curves. (b) cumulative progression-free survival (PFS) curves

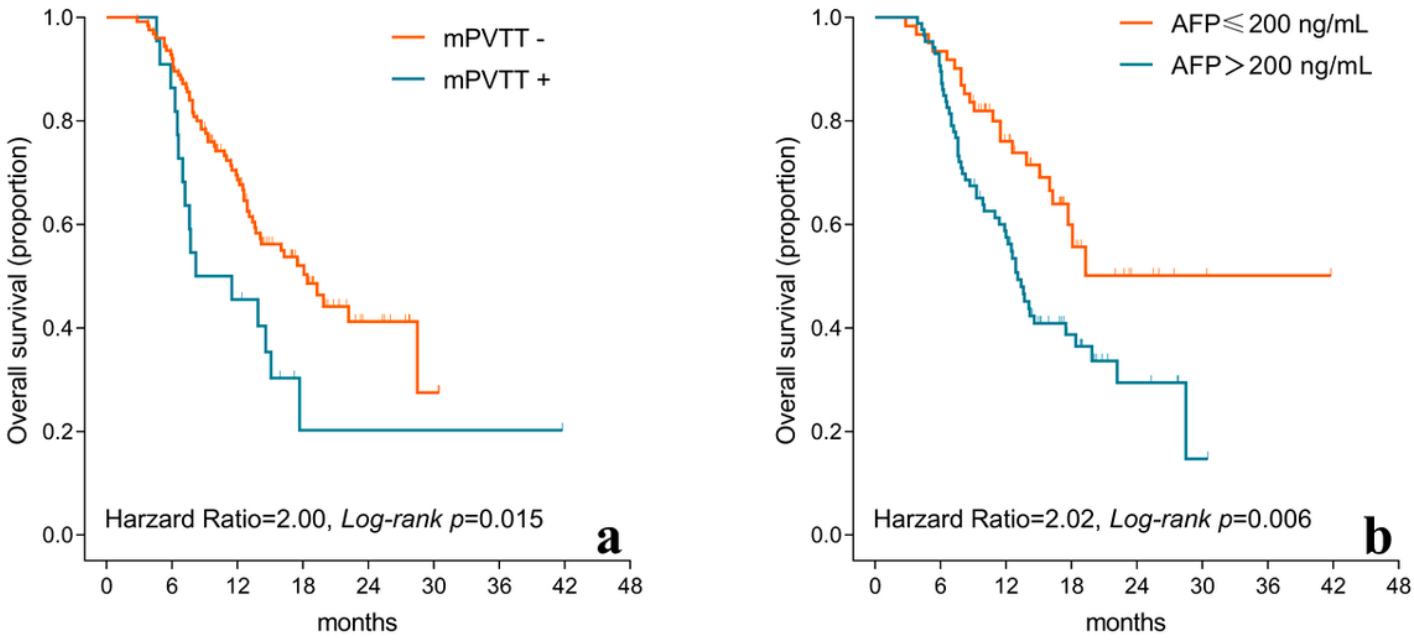

Figure 3

Curves nerated with univariate analysis (the log-rank test) to determine prognostic factors for overall survival (OS) in all patients. (a) Cumulative OS curve according to the presence or absence of main portal vein tumor thrombus (mPVTT). (b) Cumulative OS curve according to α-fetoprotein (AFP) levels (≤200 ng/mL vs 200 ng/mL)

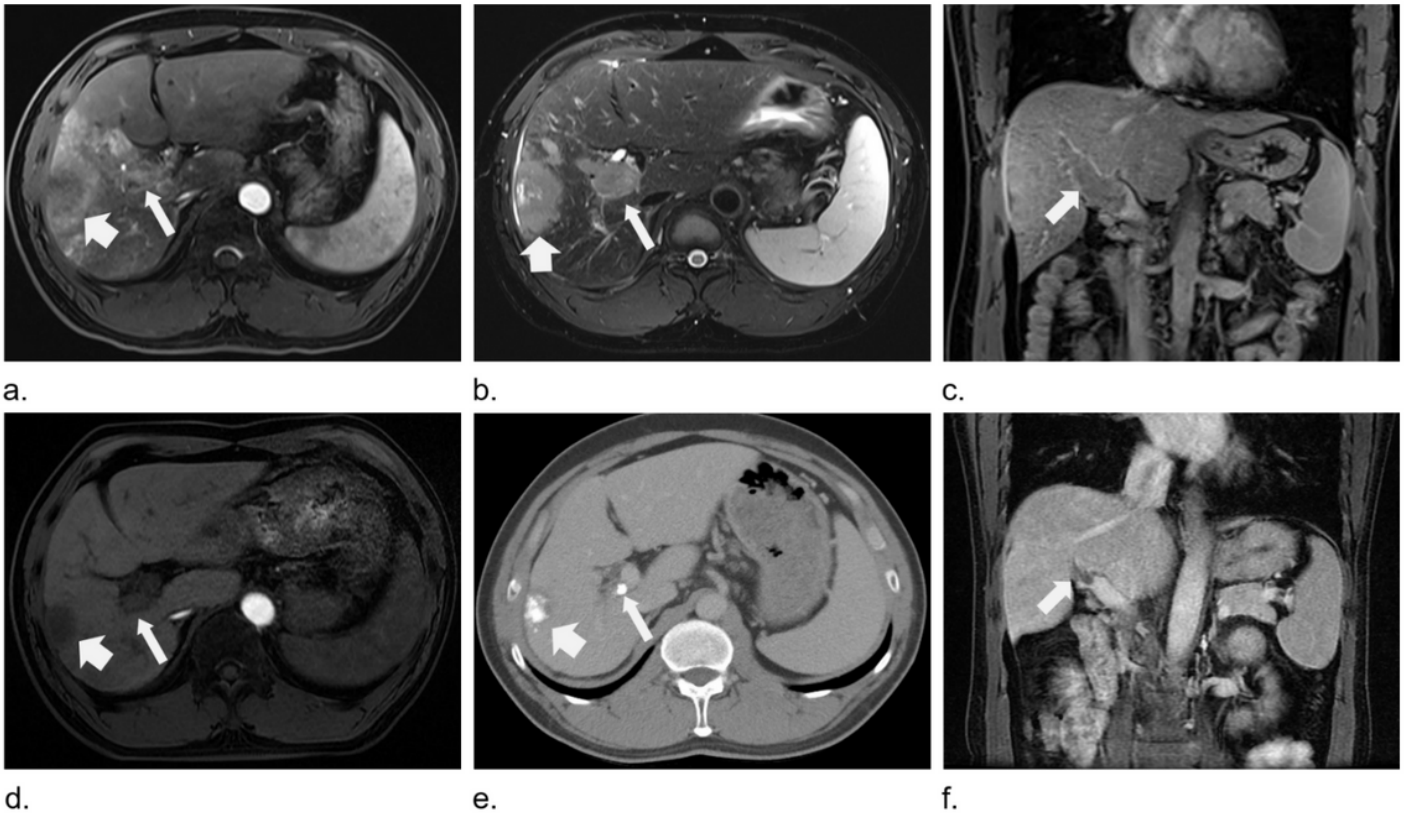

Figure 4

Images in a 40-year-old man with hepatocellular carcinoma (HCC) with right portal vein tumor thrombus who underwent systemic combination therapy (lenvatinib plus nivolumab) with transarterial chemoembolization (TACE). (a, c) Axial acquired contrast-enhanced T1-weighted MRI and (b) T2-weighted MRI at baseline shows and segment with irregular masses and right portal vein tumor thrombus (arrow) before treatment. (d, f) Enhanced MRI obtained 3 months after systemic combination therapy with TACE of 3 times shows tumor and the right portal vein thrombus was necrotic and significantly reduced (arrow). (e) Hepatobiliary-phase CT shows lipiodol deposition in the tumor (coarse arrow) and right portal vein thrombus (thin arrow) at 3 months after combination therapy. The patient showed partial response to the combination therapy with TACE