The Efficacy and Safety of Transarterial Chemoembolization Combined With Tyrosine Kinase Inhibitors Plus Camrelizumab for Unresectable Hepatocellular Carcinoma: a Two-center Retrospective Study

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Research Article

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Abstract

Object: This study aimed to evaluate the efficacy and safety of transarterial chemoembolization (TACE) combined with tyrosine kinase inhibitors (TKIs: sorafenib, lenvatinib, and apatinib) plus camrelizumab (TACE-TKIs-C) vs. TACE combined with TKIs (TACE-TKIs) for unresectable hepatocellular carcinoma.

Methods: In this two-center retrospective study, patients with unresectable HCC treated with TACE-TKIs-C or TACE-TKIs were enrolled between January 1, 2018 to October 1, 2020. A total of 260 eligible patients received TACE-TKIs-C (N=70) or TACE-TKIs (N=190). The differences in overall survival (OS), progression free survival (PFS) and tumor response were compared between two groups. The risk factors affecting OS or PFS were analyzed.

Results: The OS of TACE-TKIs-C was significantly longer than TACE-TKIs (P<0.0001). The median OS of TACE-TKIs-C was not reached and the OS of TACE-TKIs was 12 months ((95% CI, 11.0 to 13.0 months). The estimated rates of survival at 6 months and 12 months were 88.6±3.8% and 76.1±5.3%, respectively, in the TACE-TKIs-C group and 86.2±2.5% and 52.0±3.7% in the TACE-TKIs group. The median PFS of TACE-TKIs-C was significantly improved compared with TACE-TKIs (10.0 vs 6.0 months, P<0.0001). Multivariate analysis showed that ECOG performance, number of tumors, tumor size and treatment were independent factors of OS and treatment were independent predictive factors of PFS. Grade 3 or 4 hypertension occurred in 14.3% of patients in the TACE-TKIs-C group and other high-grade toxic effects were infrequent.

Conclusion: In patients with unresectable HCC, TACE-TKIs-C may improve overall and progression-free survival outcomes over TACE-TKIs with manageable safety profile.

Introduction

Hepatocellular carcinoma (HCC) is the leading course of cancer-related death worldwide with high morbidity [1]. Although emerging advances in treatments with resection, liver transplantation, ablation, tyrosine kinase inhibitors (TKIs), or immunotherapy, a majority of HCC patients still have a poor prognosis [2].

Recently, transarterial chemoembolization (TACE) is recommended as palliative treatment for unresectable HCC with preserved liver function to control tumor burden [3,4]. Most clinical practice guidelines, such as the Barcelona Clinic Liver Cancer (BCLC), the European Association for the Study of the Liver, the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver and the Japan Society of Hepatology (JSH), have recommended TACE as standard treatment [5,6]. In order to control tumor, repeated TACE is necessary because of the high recurrence rate after TACE procedure. However, with the increase in TACE sessions, the efficacy of TACE declines significantly [7]. Due to upregulation of vascular endothelial growth factor (VEGF) concentration in residual tumor, the combination of TACE with antiangiogenic therapy, like sorafenib, lenvatinib, and apatinib may improve clinical outcomes. A randomised, multicenter prospective trial (RCT)

by Kudo et al reported that this combination improved progression-free survival (PFS) significantly [8]. However, other RCTs focused on combinations of TACE with TKIs such as sorafenib, brivanib and orantinib have failed to improve clinical outcomes when compared with TACE alone [9–13].

In addition to TKIs, TACE has also shown the potential to combined with immunotherapy. As a locoregional therapy, TACE was expected to release neoantigens, which could enhance immunotherapy by activating relevant system [18]. As the big topic of immunotherapy, immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) have shown promising clinical activity as second-line treatment for hepatocellular carcinoma based on phase I/II clinical trial, CheckMate040, KEYNOTE-224 [14,15]. However, in phase 3 studies of single-agent treatment, nivolumab and pembrolizumab failed to improve overall survival significantly [16,17]. Due to the need for combinatorial protocols with other antitumor approaches to reduce tumor burden or stimulate system immune, combination immunotherapy has become an urgent need in HCC therapy research. Combination strategies include two types of immune checkpoint inhibitors (anti-PD-1/PD-L1 and anti-CTLA-4 antibodies), anti-PD-1/ PD-L1 antibody with TKIs, and anti-PD-1/PD-L1 or -CTLA-4 antibody with locoregional therapies [18]. Among these, the combination of ICIs with TKIs reached a remarkable outcome which has been recognized as first line treatment by the National Comprehensive Cancer Network (NCCN) based on IMbrave150 [25].

The hypoxia response induced by TACE could not only upregulate VEGF but also stimulate system immune, which indicates that TACE, ICIs and TKIs may have the potential to combined with each other. However, there was rare study which focus on TACE + ICIs + TKIs. Zheng et al has reported TACE + ICIs + sorafenib has promising outcomes in treating intermediate and advanced TACE-refractory compared with TACE-sorafenib. Thus, it was of much value to explore whether the ICIs + TKIs could benefit the HCC receiving initial TACE when compared with TKIs.

As the most common TKIs in China, sorafenib, lenvatinib, and apatinib have been approved as the first-line or second-line treatment for advanced HCC in China. Recently, camrelizumab, an anti-PD-1 monoclonal antibody with a high affinity for PD-1 and a different binding epitope than nivolumab and pembrolizumab, was approved in China as a second-line treatment for unresectable HCC. In last three years, a subset of HCC patients receiving TACE was treated with sorafenib, lenvatinib, or apatinib monotherapy or combination of sorafenib, lenvatinib, or apatinib with camrelizumab. Thus, we conducted this comparative study to elevate the efficacy and side effects of the real-world use of TACE with TKIs (sorafenib, lenvatinib, or apatinib) plus camrelizumab in patients with unresectable HCC.

Materials And Methods

Study design and participants

From January 1, 2018 to October 1, 2020, consecutive patients treated with TACE for HCC in our centers were reviewed. Among these patients, patients treated with camrelizumab combining with sorafenib, lenvatinib or apatinib were classified into TACE-ICI-TKIs group. The patients who treated with sorafenib, lenvatinib or apatinib were classified into TACE-TKIs group. All patients were pathologically or clinically

diagnosed with HCC based on the standard of AASLD. This retrospective study has been approved by our hospital ethics committee and the written informed consent was waived because of the nature of retrospective study.

Inclusion criteria comprised the following: (A) age of 18 years or older; (B) radiological diagnosed with unresectable HCC; (C) Child-Pugh class A, B; (D) measurable tumor lesions on computed tomography (CT) or magnetic resonance imaging (MRI);(E) Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1.

Exclusion criteria comprised the following:(A) metastatic liver malignant;(B) Child-Pugh class C; (C) portal vein invasion with Vp4;19 (D) any contraindication for therapy with TACE.

TACE procedure

All patients in both groups received TACE once at least. TACE was conducted by specialists with 10 years` experiences. Under the guidance of digital subtraction angiography (DSA), a 5-F catheter (Cook, Bloomington, Indiana, USA) was placed into the hepatic artery and a 2.7-F microcatheter (Progreat, Terumo, Tokyo, Japan) was inserted selectively into tumor feeding arteries. 2–20 mL lipiodol and 20–60 mg epirubicin were prepared to make emulsion. Then, the emulsion was administrated into the tumor feeding arteries though the microcatheter. Gelatin sponge particles (350-710 μm, Alicon, Hangzhou, China) were used to embolize completely the tumor feeding arteries. Finally, hepatic artery angiography was performed to validate the complete embolism of the feeding arteries. If the residual lesions were confirmed by enhanced CT, the repeated TACE would be recommended.

Camrelizumab and TKIs Administration

Camrelizumab and TKIs were administrated within 2 weeks after TACE therapy. Camrelizumab was recommended at a dose of 200mg every 3 weeks and administrated intravenously. If patients developed serve adverse events (AEs), camrelizumab was interrupted or discontinued and symptomatic treatment such as glucocorticoids or immune-suppressant agents were administered, depending on the severity and the affected organs. Sorafenib was orally administrated at a dose of 400mg twice a day. Lenvatinib was recommended at a dose of 12 mg (≥60 kg) or 8 mg (<60 kg) once daily based on body weight. Apatinib was orally administered at a dose of 200 mg once daily for 28 days as a treatment cycle. When the tolerable AEs grade 1-2 occurred, the TKIs administration were continued. Once serve AEs occur, TKIs administration were discontinued.

Follow up and assessment

The first follow up was conducted within 6 weeks after TACE procedure, and the next clinical follow up was recommended every 2 or 3 months. The tumor response was evaluated by contrasted MRI or CT according to the mRECIST. The coprimary end points included overall survival (OS, defined as the time from first TACE procedure to death from any cause) and progression free survival (PFS, defined as the time from first TACE procedure to disease progression according to mRECIST). Secondary endpoints were

disease control rate (DCR, the percentage of patients with a complete or partial response, or stable disease) and objective response rate (ORR, the percentage of patients with a complete or partial response). AEs was recorded and evaluated by vital signs and clinical laboratory test results and assessment of the incidence and severity of adverse events according to the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

The statistical analyses were performed using the SPSS 24.0 software (IBM, Armonk, NY, USA). Continuous variables are presented as the mean ± standard deviation (SD) and calculated using the Student`s t-test. Categorical variables are reported by frequency with percentages and calculated using Chi-squared test. The survival curve of PFS was analyzed using Kaplan–Meier analysis and log rank test. Variables with the value of P < 0.10 at univariate analysis were entered into multi univariate Cox proportional hazards regression model analysis, which was used to identify risk factors affecting OS. *P*-value < 0.05 (two-tailed) was considered statistically significant.

Results

Baseline characteristics of the study population

From January 1, 2018 to October 1, 2020, a total of 260 patients (70 TACE-TKIs-C, 190 TACE-TKIs) were included (Fig. 1). The detailed baseline characteristics were listed in Table 1. The TKIs was adopted as sorafenib, lenvatinib, apatinib in 17(24.3%), 24 (38.6%), and 26 (37.1%) patients, respectively, in the TACE-TKIs-C group, and 52 (27.3%), 52 (27.3%), and 86 (45.3%) patients, respectively, in the TACE-TKIs group. There was no significant difference in the composition of the TKIs in the two groups ($P = 0.214$). Besides, the other baseline characteristics between two groups was not significantly different. The median follow-up duration was 9.7 months (95%CI, 8.3–11.3 months).

Table 1
Baseline characteristics of patients between the two groups

Characteristics	TACE-TKIs-C (N = 70)	TACE-TKIs (N = 190)	*P* value
Age(years)	53.8 ± 10.4	51.9 ± 10.1	0.172
Genders			0.350
Male	58/82.9%	166/87.4%	
Female	12/17.1%	24/12.6%	
ECOG performance			0.085
0	47/67.1%	105/55.3%	
1	23/32.9%	85/44.7%	
BCLC stage			0.268
B	28/40.0%	62/27.4%	
C	42/60.0%	128/72.6%	
HBV infection			0.328
Yes	54/77.1%	135/71.1%	
No	16/22.9%	55/28.9%	
AFP (ng/ml)			0.470
>400	40/57.1%	99/52.1%	
≤ 400	30/42.9%	91/47.9%	
Child-Pugh Class			0.822
A	57/81.4%	157/82.6%	
B	13/18.6%	33/17.4%	
ALT(IU/L)	58.1 ± 23.8	60.5 ± 72.7	0.374
AST(IU/L)	58.0 ± 62.2	56.8 ± 133.3	0.257
TB (μmol/L)	16.4 ± 7.4	19.2 ± 13.4	0.104
PLR	149.4 ± 98	157.3 ± 114	0.606

ECOG, Eastern Cooperative Oncology Group; BCLC Barcelona Clinic Liver Cancer;HBV, hepatitis B virus; AFP, a-fetoprotein; TACE, transarterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; PLR, platelet-to-lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; TKIs, tyrosine kinase inhibitors; TACE-TKIs-C, transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs, transcatheter arterial chemoembolization with tyrosine kinase inhibitors.

Characteristics	TACE-TKIs-C (N = 70)	TACE-TKIs (N = 190)	*P* value
NLR	3.3 ± 2.8	3.7 ± 2.6	0.291
Albumin(g/dl)	36.4 ± 4.3	37.1 ± 5.0	0.304
PT(S)	13.3 ± 1.4	14.0 ± 1.2	0.295
Tumors number			0.762
≤ 3	24/34.3%	69/36.3%	
>3	46/65.7%	121/63.7%	
Tumor size(cm)	8.5 ± 4.8	8.7 ± 4.4	0.798
TKIs type			0.214
Sorafenib	17/24.3%	52/27.3%	
Lenvatinib	27/38.6%	52/27.3%	
Apatinib	26/37.1%	86/45.3%	

ECOG, Eastern Cooperative Oncology Group; BCLC Barcelona Clinic Liver Cancer;HBV, hepatitis B virus; AFP, a-fetoprotein; TACE, transarterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; PLR, platelet-to-lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; TKIs, tyrosine kinase inhibitors; TACE-TKIs-C, transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs, transcatheter arterial chemoembolization with tyrosine kinase inhibitors.

Efficacy

At the date of clinical cutoff, a total of 24 patients (34.3%) in the TACE-TKIs-C group and 147 patients (77.4%) in the TACE-TKIs group died. The median OS of TACE-TKIs-C group was not reached and the median OS of TACE-TKIs was 12.0 months (95%CI, 11.8–14.2 months). However, OS was significantly longer with TACE-TKIs-C (*P*<0.0001)(Fig. 2A). The rates of 6 months OS and 12 months OS were 90% (± 3.6%) and 78.8% (± 5.1%), respectively, in the TACE-TKIs-C group, and 86.2% (± 2.5%) and 44.0% (± 3.7%) in the TACE-TKIs group (Table 3). PFS was significantly longer with TACE-TKIs-C than TACE-TKIs (median, 10.0 months [95% CI, 8.9–11.0 months] vs. 6.0 months [95%CI, 5.4–6.6 months], *P*<0.0001) (Fig. 2B). The rates of 6 months PFS and 12 months PFS were 82.9% (± 4.5%) and 19.8% (± 5.2%), respectively, in the TACE-TKIs-C group, and 47.7% (± 3.8%) and 13.0% (± 3.0%) in the TACE-TKIs group (Table 3).

Table 2
Tumor response in both groups

Tumor response	TACE-TKIs-C(N = 70)	TACE-TKIs-C (N = 190)	*P* value
CR	4/5.7%	0	
PR	15/21.4%	19/10.0%	
SD	35/50.0%	104/54.7%	
PD	16/22.9	67/35.3%	
ORR	19/27.1%	19/10.0%	0.001
DCR	54/77.1%	123/64.7%	0.057

Data are presented as n (%) TACE transcatheter arterial chemoembolization, CR complete response, PR partial response, SD stable disease, PD progressive disease, ORR objective response rate, DCR disease control rate.

Table 3
Rate of overall survival at 6 months and 12 months

rate, %	TACE-TKIs-C (N = 70)	TACE-TKIs(N = 190)
OS 6 months	90 ± 3.6%	86.2 ± 2.5%
OS 12 months	78.8 ± 5.1%	44.0 ± 3.7%
PFS 6 months	82.9%±4.5%	47.7%±3.8%
PFS 12 months	19.8%±5.2%	13%±3.0%

OS, overall survival; PFS, progression-free survival; TACE-TKIs-C, transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs, transcatheter arterial chemoembolization with tyrosine kinase inhibitors.

Prognostic Factors Affecting OS and PFS

Univariate analysis indicated ECOG, Number of tumors, Tumor size, and Treatment were significantly associated with OS. Multivariate Cox analysis showed that tumor size and treatment were significantly predictive factors for OS of the patients in the two groups (HR = 1.057, 95%CI, 1.020–1.096, *P* = 0.005; HR = 3.342, 95%CI: 2.033–5.495, P<0.001, respectively) (Table 4). Moreover, univariate analysis showed that ECOG, Tumor size, PLR, and treatment was associated with PFS. Multivariate Cox analysis indicated treatment was significantly predictive factors (HR = 0.537, 95%CI, 0.393–0.732, *P*<0.001).

Table 4
Univariate and multivariate analysis of prognostic factors for OS

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.009(0.993 ~ 1.024)	0.763		
Gender		0.231		
Male	Reference			
Female	0.726 (0.430 ~ 1.226)			
ECOG performance		0.041		0.057
0	Reference		Reference	
1	1.829(1.304 ~ 2.576)		1.748(1.271 ~ 2.404)	
Number of tumors		0.015		0.173
>3	1.233(1.041 ~ 1.461)		1.268(1.046 ~ 1.452)	
≤ 3	Reference		Reference	
HBV infection		0.270		
No	Reference			
Yes	1.231 (0.851 ~ 1.781)			
Child-Pugh class		0.277		
A	0.777(0.493 ~ 1.225)			
B	Reference			
BCLC stage		0.575		
B	Reference			
C	1.107 (0.775 ~ 1.582)			
AFP (ng/ml)		0.156		
>400	1.391(1.005 ~ 1.926)			
≤ 400	Reference			
Tumor size(cm)	1.060 (1.018 ~ 1.102)	0.004	1.057(1.020 ~ 1.096)	0.005

HR hazard ratio; CI confidence interval; BCLC Barcelona Clinic Liver Cancer; HBV hepatitis B; AFP alpha-fetoprotein; ALT alanine transaminase; AST aspartate aminotransferase; TACE-TKIs-C, transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs, transcatheter arterial chemoembolization with tyrosine kinase inhibitors; HCC hepatocellular carcinoma; OS overall survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
PLR	1.000 (0.999 ~ 1.002)	0.583		
NLR	1.010 (0.937 ~ 1.090)	0.793		
ALT(IU/L)	0.999 (0.994 ~ 1.003)	0.499		
AST (IU/L)	1.000 (0.999 ~ 1.002)	0.794		
Albumin (g/dL)	0.998 (0.964 ~ 1.034)	0.915		
TB (μmol/L)	1.009 (0.994 ~ 1.025)	0.240		
PT(s)	1.035 (0.905 ~ 1.184)	0.611		
Treatment		< 0.001		< 0.001
TACE-TKIs	4.409(2.301 ~ 8.449)		3.342(2.033 ~ 5.495)	
TACE-TKIs-C	Reference		Reference	

HR hazard ratio; CI confidence interval; BCLC Barcelona Clinic Liver Cancer; HBV hepatitis B; AFP alpha-fetoprotein; ALT alanine transaminase; AST aspartate aminotransferase; TACE-TKIs-C, transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs, transcatheter arterial chemoembolization with tyrosine kinase inhibitors; HCC hepatocellular carcinoma; OS overall survival.

OS and PFS subgroup analysis by the TKIs type of TACE-TKIs-C group

In the subgroup analysis, median OS of TACE-Apatinib-C was 15.0 months (95%CI, 12.173–17.827 months) and the median OS of TACE-Sorafenib-C group and TACE-Lenvatinib-C groups were not reached. The median PFS of TACE-Sorafenib-C, TACE-Lenvatinib-C, and TACE-Apatinib-C was 6 months (95%CI, 5.073–6.927 months), 7 months (95%CI, 6.4–7.6 months), and 5 months (95%CI, 3.749–6.251 months), respectively. There were significant differences in OS and PFS between different TKIs types of TACE-TKIs-C group ($P = 0.012$, $P = 0.0027$) (Fig. 3AB).

Tumor response evaluation

To evaluate the tumor response, ORR and DCR were both tested (Table 2). ORR was significantly higher with TACE-TKIs-C group (27.1% vs. 10.0%, $P = 0.001$). 4 patients (5.7%) in the TACE-TKIs-C group, as compared with no patients in the TACE-TKIs group, had a CR. The confirmed DCRs were 77.1% with TACE-TKIs-C and 64.7% with TACE-TKIs ($P = 0.057$), respectively.

Table 5
Univariate and multivariate analysis of prognostic factors for PFS

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.0051(0.988 ~ 1.013)	0.916		
Gender		0.924		
Male	Reference			
Female	0.982 (0.672 ~ 1.4355)			
ECOG performance		**0.006**		0.065
1	Reference		Reference	
0	0.695(0.537 ~ 0.898)		0.781(0.600 ~ 1.016)	
Number of tumors		0.055		0.087
>3	Reference		Reference	
≤ 3	0.770 (0.589 ~ 1.006)		0.731(0.554 ~ 0.965)	
HBV infection		0.352		
No	Reference			
Yes	1.071 (0.927 ~ 1.237)			
Child-Pugh class		0.621		
A	Reference			
B	1.046 (0.741 ~ 1.477)			
BCLC stage		0.100		0.339
B	Reference		Reference	
C	0.888 (0.771 ~ 1.023)		1.153 (0.861 ~ 1.544)	
AFP (ng/ml)		0.112		
> 400	Reference			
≤ 400	0.813 (0.629 ~ 1.050)			
Tumor size (cm)	1.040 (1.011 ~ 1.069)	**0.007**	1.027 (0.995 ~ 1.059)	0.099

HR hazard ratio; CI confidence interval; BCLC Barcelona Clinic Liver Cancer; HBV hepatitis B; AFP alpha-fetoprotein; ALT alanine transaminase; AST aspartate aminotransferase; TACE-TKIs-C transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs transcatheter arterial chemoembolization with tyrosine kinase inhibitors; HCC hepatocellular carcinoma; PFS progression-free survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
PLR	1.002 (1.001 ~ 1.003)	**0.002**	1.001 (1.000 ~ 1.003)	0.058
NLR	1.040 (0.994 ~ 1.088)	0.089	0.990 (0.933 ~ 1.049)	0.729
ALT(IU/L)	1.002 (1.000 ~ 1.004)	0.065	0.998 (0.996 ~ 1.001)	0.235
AST (IU/L)	1.002 (1.001 ~ 1.003)	0.139		
Albumin (g/dL)	0.986 (0.962 ~ 1.012)	0.290		
TB (μmol/L)	0.999 (0.988 ~ 1.010)	0.876		
PT(s)	1.068 (0.966 ~ 1.181)	0.201		
Treatment		**< 0.001**		**< 0.001**
TACE-T	Reference		Reference	
TACE-T-I	0.519 (0.383 ~ 0.702)		0.537 (0.393 ~ 0.732)	

HR hazard ratio; CI confidence interval; BCLC Barcelona Clinic Liver Cancer; HBV hepatitis B; AFP alpha-fetoprotein; ALT alanine transaminase; AST aspartate aminotransferase; TACE-TKIs-C transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs transcatheter arterial chemoembolization with tyrosine kinase inhibitors; HCC hepatocellular carcinoma; PFS progression-free survival.

Safety

Any grade AEs from any cause were reported by 63 patients (90.0%) who received TACE-TKIs-C and by 175 (92.1%) who received TACE-TKIs. The common AEs included hypertension, hand-foot skin reaction, elevated TB, and fatigue in the TACE-TKIs-C group, as consistent with TACE-TKIs group (Table 6). Grade 3–4 AEs occurred in 28 patients (40.0%) with TACE-TKIs-C and in 48 patients (25.3%) with TACE-TKIs and it occurred more common in patients who received TACE-TKIs-C when compared with TACE-TKIs (P = 0.02). Grade 5 AEs did not occur among all patients. However, there was no significant difference between the TACE-TKIs-C group and the TACE + TKIs group in embolization-related syndrome.

Table 6
Adverse events (> 10%) from Any Cause.

Adverse events	TACE-TKIs-C(N = 70)		TACE-TKIs (N = 190)	
	All grades N (%)	Grade 3/4 N (%)	All grades N (%)	Grade 3/4 N (%)
Decreased albumin	16/22.8%	0	39/20.5%	0
Hypertension	25/35.7%	10/14.3%	52/27.4%	21/11.1%
Decreased PLT	16/22.8%	0	32/16.8%	0
Bleeding (gingiva)	15/21.4%	0	28/14.7%	0
Elevated TB	22/31.4%	2/2.3%	69/36.3%	13/6.8%
Diarrhea	14/20.0%	0	29/15.3%	0
Fatigue	20/28.6%	4/4.6%	45/23.7%	8/4.2%
Dysphonia	14/20.0%	1/1.4%	23/12.1%	0
Hand-foot skin reaction	22/31.4%	0	89/46.8%	5/2.5%
Elevated creatinine	7/10.0%	0	24/12.6%	0
Prolonged PT	8/11.4%	0	19/10.0%	1/0.5%
Albuminuria/Proteinuria	12/17.1%	0	23/12.1%	0
Decreased appetite	8/11.4%	0	27/14.2%	0
Joint pain	14/20.0%	1/1.4%	28/14.7%	0
Edema	13/18.6%	0	25/13.2%	1/0.5%
Constipation	10/14.3%	0	28/14.7%	0

TACE transcatheter arterial chemoembolization; PLT platelet; AST aspartate transaminase; GGT γ-glutamyl transpeptidase; ALT alanine aminotransferase;TB total bilirubin;PT prothrombin time;TACE-TKIs-C transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs transcatheter arterial chemoembolization with tyrosine kinase inhibitors.

Discussion

In recent years, application of ICIs against immune checkpoints, especially PD-1, represents a major breakthrough in the treatment of HCC [20,21]. The Check Mate-040 and the KEYNOTE-224 trial showed that advanced HCC could benefited from nivolumab or pembrolizumab, anti-PD-1 humanized antibodies, respectively [22,23]. However, these treatments were characterized with low ORR, 20% for nivolumab and 16.9% for pembrolizumab. Hence, investigators proposed to combine TKIs with ICIs due to the additional immunomodulatory effects of TKIs [24]. Based on the remarkable results of IMbrave150 trial achieving

ORR with 27.3%, the combination of atezolizumab and bevacizumab has been approved by US FDA as the first-line treatment for patients with unresectable HCC [25, 26]. Thus, the combination of ICIs with TKIs may be the optimal treatment strategy. As a kind of locoregional therapies, TACE plays a key role in the treatment of unresectable HCC [27]. Apart from destroying the primary tumor, TACE could not only promote the release of vascular endothelial growth factor (VEGF) but also facilitate antitumor immunity by releasing the neoplasm antigens from killed tumor cells [28 29]. The treatment of TACE combined with TKIs plus ICIs may obtain a better clinical effect for unresectable HCC.

TKIs including sorafenib, lenvatinib, and apatinib could prolong the OS of advanced HCC, which were recommended as first-line or second-line treatment for IIa-IIIb HCC patients by China Diagnosis, management, and treatment of hepatocellular carcinoma(V2019). Previous studies about TACE plus TKIs have not yielded the desired results [30,31,32,33]. TACTICS trial reported TACE plus sorafenib achieved better PFS compared with TACE alone but without survival benefits in the later data [34]. In this two-center retrospective study, results showed significantly better OS and PFS outcomes with TACE-TKIs-C than with TACE-TKIs (median OS:NE vs. 12.0 months, P<0.0001; median PFS 10.0 months vs. 6.0 months, P<0.0001). Multivariate analysis also confirmed that treatment was the significant predictive factor for OS and PFS. Besides, our results also revealed that the TACE-TKIs-C group had better OS 6/12 months and PFS 6/12 months compared with TACE-TKIs group, which illustrated the efficacy of TACE with TKIs plus camrelizumab. As reported by IMbrave150 trial, the median PFS of atezolizumab–bevacizumab group was 6.8 months, which was lower than that of patients with TACE-TKIs-C group in our study. Just like median PFS, the 6 months PFS of atezolizumab–bevacizumab group was also lower than that of patients with TACE-TKIs-C group in our study (54.5% vs 82.9%). The benefits of OS and PFS in our study over IMbrave150 trial may due to the role of TACE. Although the PFS of TACE plus sorafenib reported by TACTICS trial was up to 25.2 months which was much higher over that of TACE-TKIs-C group in our study, the new intrahepatic lesions were not regarded as PD in the TACTICS trial [34].

There were several trials which reported combinations of TKIs and ICIs including apatinib plus camrelizumab, lenvatinib plus camrelizumab and sorafenib plus camrelizumab, but with totally different OS [35,36,37]. Thus, different types of TKIs may have different influence on efficacy when combined with camrelizumab. To determine the impact of TKIs types on efficacy of TACE-TKIs-C group, we evaluated the OS and PFS of TACE-sorafenib-camrelizumab, TACE-lenvatinib-camrelizumab, and TACE-apatinib-camrelizumab by Kaplan–Meier analysis and log rank test. TACE-lenvatinib-camrelizumab group had longer median OS and median PFS, which indicated that different TKIs may affect efficacy and exploring different combinations of TACE-TKIs-camrelizumab is promising

Similar to other studies, the most common AEs were hypertension, hand-foot skin reaction, elevated TB, and fatigue in the TACE-TKIs-C group which were easily to be controlled. Although the incidence of Grade 3–4 AEs of TACE-TKIs-C was much higher than that of TACE-TKIs, these AEs including hypertension, fatigue, and elevated TB were significantly improved after symptomatic treatment. No grade 5 AEs were observed in both groups. Thus, these results indicated that the treatment of TACE with TKIs plus camrelizumab for unresectable HCC was effective and safe.

The two-center retrospective study has several limitations. First, the background of patients may have an impact on choice of treatment because of the nature of retrospective study. Second, the median OS of TACE-TKIs-C group did not reach because of short follow-up. Third, although this study contained two-center` data, the sample size was too small. More convincing studies like prospective, large-scale randomized and controlled trials are needed to confirm the efficacy of TACE with TKIs plus camrelizumab in future.

Conclusion

In patients with unresectable HCC, TACE-TKIs-C may improve overall and progression-free survival outcomes over TACE-TKIs with manageable safety profile and different types of TKIs may influence the efficacy.

Declarations

Author contribution

Chuansheng Zheng, Lijie Zhang, Fengyong Liu conceived and designed the study. Sun tao contributed signifcantly to analysis and manuscript preparation. Yanqiao Ren, Bo Sun performed the data analysis and wrote the manuscript. Lei Chen, Yanyan Cao, Weihua Zhang, and Licheng Zhu helped to perform the analysis with constructive discussions. All authors read and approved the manuscript.

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Conflict of interest

The authors declare that there was no potential conflict of interest.

Research ethics and consent

This study was approved by ethics committee of Union Hospital of Huazhong University of Science and Technology. Written informed consent was waived by this institution.

Data deposition and data sharing

The data used in the study were available from the correspondence author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

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Figures

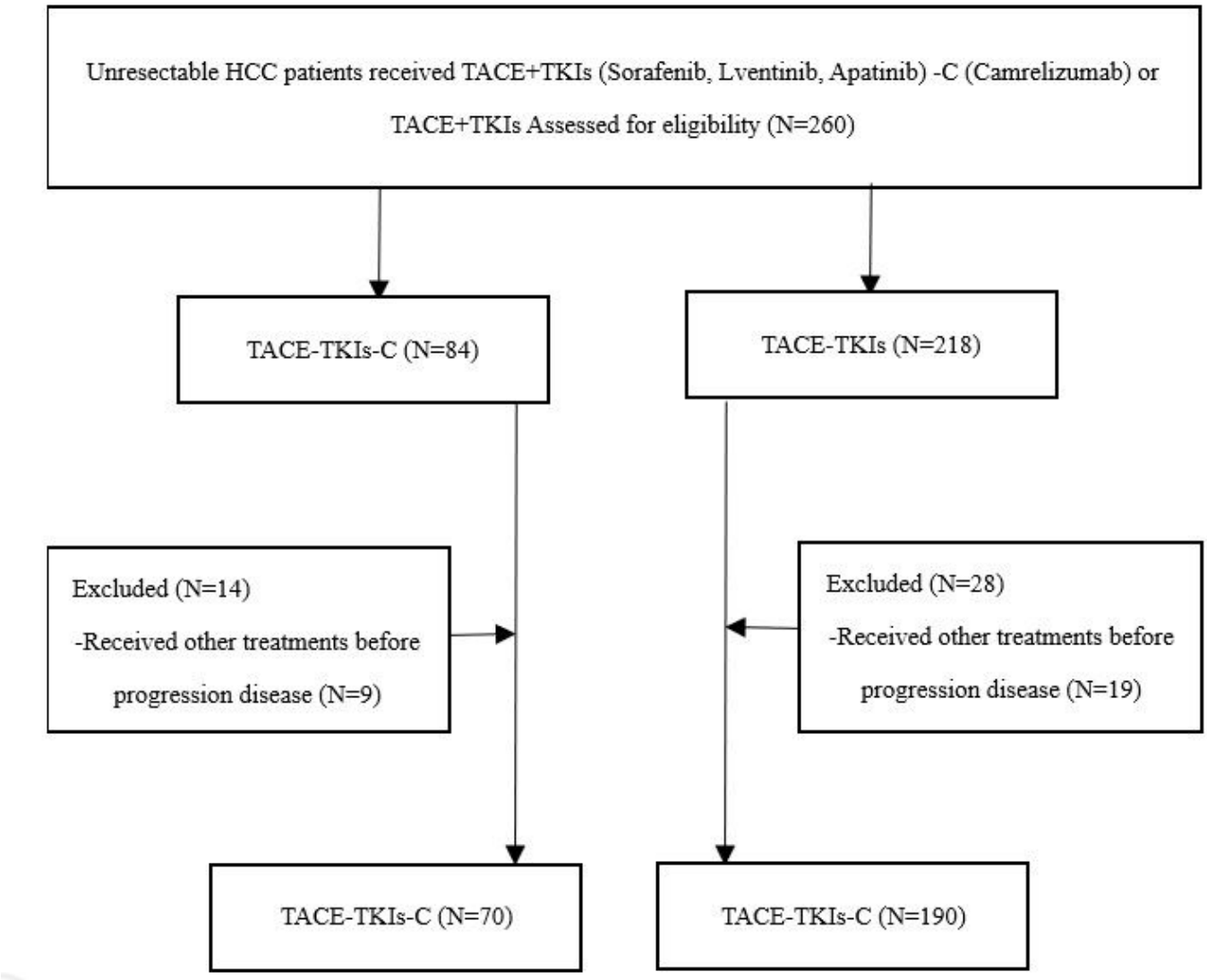

Figure 1

Flow chart illustrating the selection of patients. HCC, hepatocellular carcinoma; TACE-TKIs-C, transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab; TACE-TKIs, transcatheter arterial chemoembolization with tyrosine kinase inhibitors.

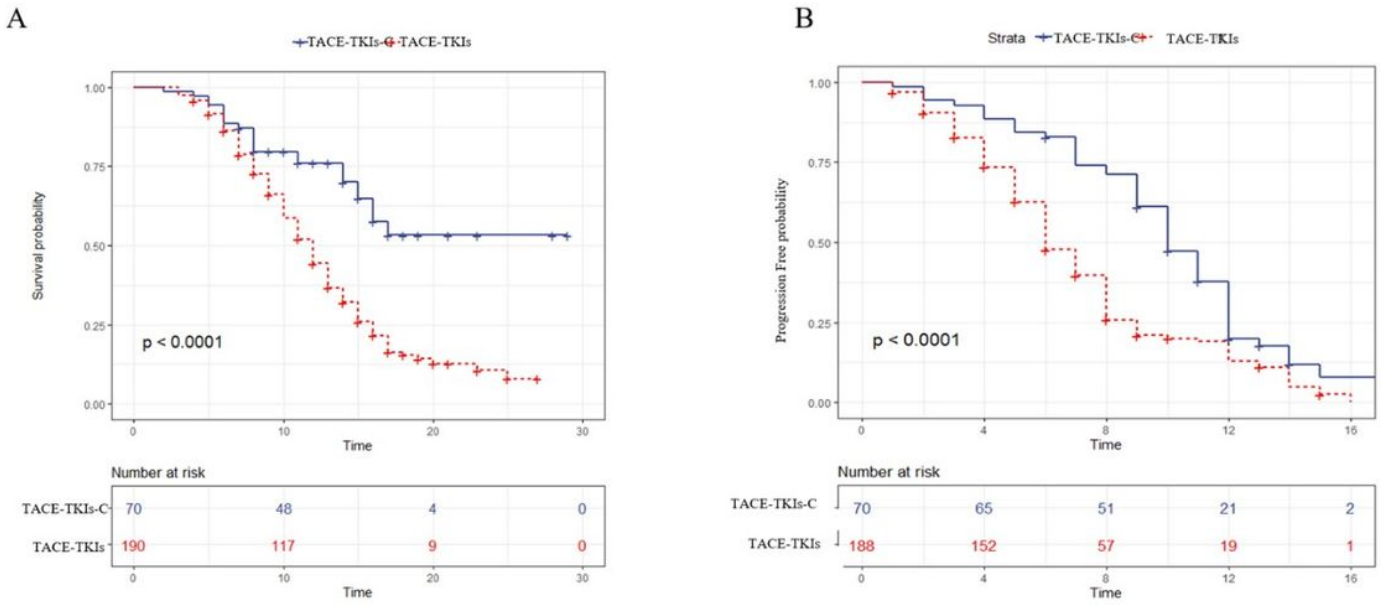

Figure 2

The Kaplan–Meier (KM) curves for patients with unresectable hepatocellular carcinoma who received the treatment of transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab (TACE-TKIs-C) or transcatheter arterial chemoembolization with tyrosine kinase inhibitors (TACE-TKIs): (A) the KM curves of overall survival time; (B) the KM curves of time to progression.

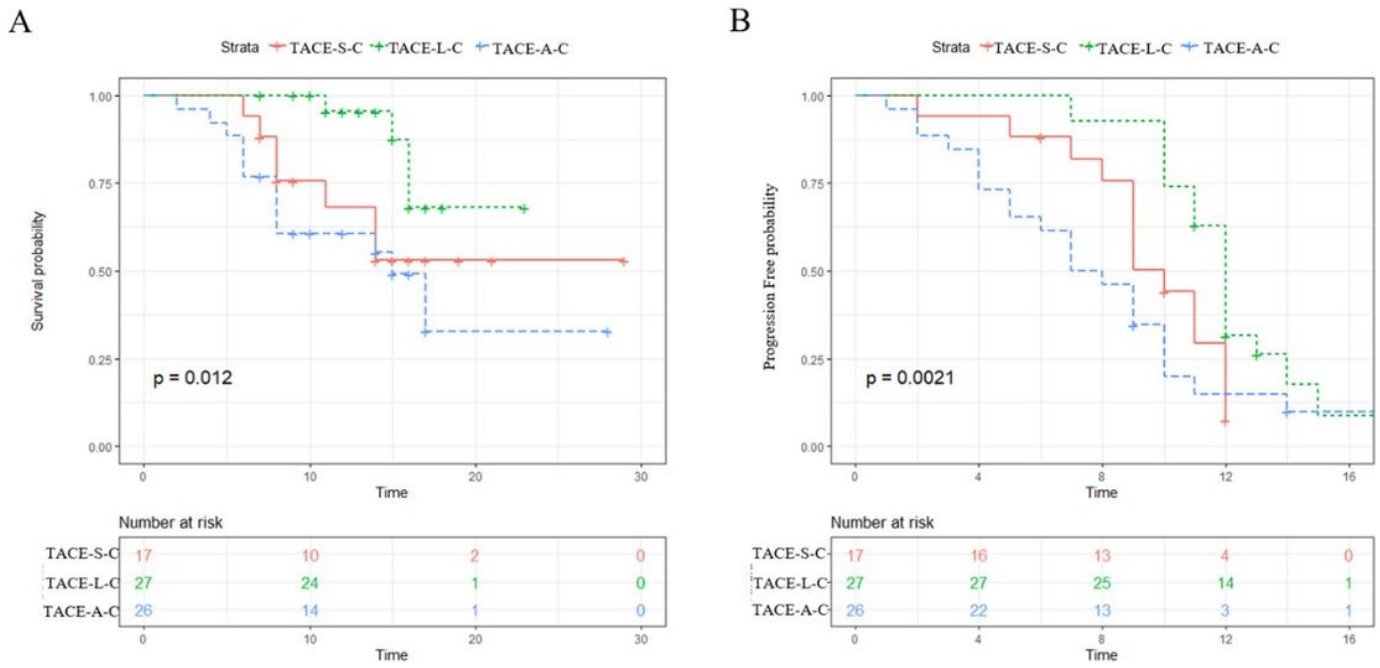

Figure 3

The Kaplan–Meier (KM) curves for patients with unresectable hepatocellular carcinoma who received the treatment of transcatheter arterial chemoembolization with tyrosine kinase inhibitors plus camrelizumab (TACE-TKIs-C): (A) the KM curves of overall survival time for TACE-S-C, TACE-L-C, and TACE-A-C; (B) the KM curves of progression-free time TACE-S-C, TACE-L-C, and TACE-A-C. TACE-S-C TACE with sorafenib plus camrelizumab; TACE-L-C TACE with lenvatinib plus camrelizumab; TACE-A-C TACE with apatinib plus camrelizumab.