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ORIGINAL RESEARCH

Atezolizumab Plus Bevacizumab Combined with or without Transarterial Chemoembolization in the Treatment of Advanced Hepatocellular Carcinoma: A Single-Center Retrospective Study

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Purpose: This study aimed to compare the efficacy and safety of atezolizumab plus bevacizumab (T+A) in combination with transarterial chemoembolization (TACE) (T+A+TACE) and T+A for patients with advanced hepatocellular carcinoma (HCC).

Patients and Methods: From December 2020 to August 2024, 83 patients with advanced HCC who received T+A+TACE treatment or T+A treatment in our hospital were included, and these patients were categorized into TACE+T+A group (n=52) and T+A group (n=31). The clinical outcomes between the two groups were analyzed and compared, and the prognostic factors that affected the efficacy were analyzed.

Results: The median overall survival (OS) and median progression-free survival (PFS) in the T+A+TACE group were significantly longer than those of in the T+A group (OS: 22.8 vs 16.9 months, $P = 0.015$; PFS: 7.1 vs 4.9 months, $P = 0.006$). A significantly higher objective response rate (ORR) and disease control rate (DCR) that are based on the modified RECIST were achieved in the T+A +TACE group than those of in the T+A group (ORR: 51.9% vs 6.5%, $P < 0.001$; DCR: 88.5% vs 54.8%, $P < 0.001$). No significant differences in adverse events (AEs) were observed between the two groups ($P > 0.05$). The T+A+TACE treatment was identified as a protective factor for OS and PFS.

Conclusion: TACE further improved the efficacy of T+A treatment for patients with advanced HCC, and it did not increase the incidence of AEs. T+A+TACE treatment is a promising treatment option for patients with advanced HCC.

Keywords: hepatocellular carcinoma, atezolizumab, bevacizumab, TACE

Introduction

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide.[1] Hepatocellular carcinoma (HCC) is the most common form of liver cancer and accounts for about 90% of cases.[2] HCC often presents with no symptoms in its early stage and is typically in an advanced stage by the time it is diagnosed, leading to an unfavorable prognosis.[3,4] In recent years, the molecular targeted therapy and immune checkpoint inhibitors (ICIs) were widely used as the systemic treatment for advanced HCC.[4] Oral multi kinase inhibitors, represented by sorafenib, can target vascular endothelial growth factor (VEGF) receptors to inhibit tumor growth.[5] ICIs can promote the anti-tumor response of cytotoxic T cells (CTLs) by blocking the activation of immune checkpoints and inhibiting immune escape, thereby exerting an anti-tumor effect.[6,7] Atezolizumab works by antagonizing the programmed cell

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death-ligand 1 (PD-L1) protein expressed on tumor cells. The PD-L1 protein on tumor cells exerts an immunosuppressive effect by binding to the programmed cell death-1 (PD-1) receptor on T cells and antigen-presenting (APC) cells, atezolizumab allows T cells to exhibit greater tumor cells killing effects by antagonizing this inhibitory effect.[8] Bevacizumab is a monoclonal antibody that selectively targets VEGF receptors, a key protein that promotes angiogenesis, and thus effectively inhibits tumor-supplying vessels formation.[9] Overall, atezolizumab enhances the ability of T cells to recognize and eliminate tumor cells, and bevacizumab reduces the supply of nutrients and oxygen to the tumor cells. The convergence of these two mechanisms allows the combination of the two drugs to produce better efficacy than alone. The Phase III clinical trial (IMbrave150 trial) showed that atezolizumab plus bevacizumab (T+A) significantly prolonged the median overall survival (OS) and median progression-free survival (PFS) of patients with advanced HCC compared to sorafenib treatment, and reduced the risk of death by 34%. Due to this reason, it was approved by Food and Drug Administration as the first-line treatment for advanced HCC.[10,11]

Transarterial chemoembolization (TACE) is currently widely used in the treatment of unresectable HCC and could also be applied for the prevention of tumor recurrences after resection of HCC.[12–14] It can block the tumor blood supply, increase the local concentration of chemotherapy drugs, and promote the immunogenic death of tumor cells. However, TACE treatment has some limitations. TACE treatment could lead to upregulations of hypoxia-inducible factor 1-α (HIF-1α) and VEGF,[15] which could lead to tumor hypoxia and a tumor immune suppressive microenvironment, and thus increasing the risk of tumor recurrence and metastasis.[16–18] Furthermore, after TACE treatment, the expression of the immunosuppressive PD-L1 increases in HCC, which enhances immune escape of tumor cells.[19] So in theory, TACE has a good synergistic effect with targeted therapy and immunotherapy for advanced HCC,[20–22] and the combination of TACE with atezolizumab (an anti-PD-L1 antibody) and bevacizumab (an anti-VEGF antibody) in patients with advanced HCC may yield promising results. However, researches on this topic are limited. In the present study, we evaluated the efficacy and safety of "T+A" in combination with TACE (T+A+TACE) as a first-line treatment for patients with advanced HCC.

Materials and Methods

Patients

From December 2020 to August 2024, 99 advanced HCC patients who received "T+A" in combination with or without TACE treatment in our hospital were retrospectively reviewed. The inclusion criteria of patients in this study were as follows: 1) age of patients were 18–80 years old; 2) patients were diagnosed with HCC according to a pathological examination or a noninvasive criteria in accordance with European Association for the Study of Liver;[23] 3) patients with HCC in Barcelona Clinic Liver Cancer (BCLC)[12] stage C; 4) patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤2; 5) patients had at least one measurable tumor lesion; 6) patients with liver function at Child-Pugh A or B. Patients were excluded if they had: 1) a complete occlusion of the main portal main; 2) previously undergone other treatments, such as oral sorafenib or lenvatinib, ablation, hepatic arterial infusion chemotherapy (HAIC), or radiotherapy; 3) a moderate or severe ascites; 4) patients lost to follow-up or whose clinical data were missing. This study protocol adhered to the ethical principles of the 1975 helsinki Declaration and was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (No: UHCT241070). A written informed consent was waived due to the retrospective nature of this study.

Treatment Protocol

The TACE procedures were performed by interventional physicians with over ten years of experience. After local anesthesia was applied to the femoral artery puncture point, a 5 French (F) Yashiro catheter (Terumo, Tokyo, Japan) was first placed into the celiac trunk and superior mesenteric artery for arteriography to identify the feeding artery of the tumor, then a 2.7 F microcatheter (Terumo, Tokyo, Japan) was inserted into the tumor supply artery to embolize the tumor super-selectively under digital subtraction angiography (DSA) guidance. The decision to receive conventional TACE (C-TACE) or drug-eluting beads TACE (DEB-TACE) was jointly made by physicians and patients. For C-TACE procedures, a mixture of iodide oil and doxorubicin emulsion was injected into the tumor supply arteries through the

microcatheter, and followed a complete embolization with gelatin sponge particles. The dosage of lipiodol mainly depended on the tumor size, number of tumors, and the abundance of arterial blood supply, and generally did not exceed 20 mL in a single session. Gelatin sponge particles (350–560 μm, Hangzhou Alicon Pharm SCI&TEC Co., Ltd, China) were used for supplemental embolization until near-stasis of blood flow was achieved, and the usage amount was mainly determined based on angiographic findings during TACE procedure. For DEB-TACE procedures, the drug-eluting bead microspheres (CalliSpheres, Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) with different diameters were loaded with epirubicin (60 mg) (Hanhui Pharmaceutical Co. Ltd. Zhejiang, China) and then injected through the microcatheter for embolization. The particle size and dosage of drug-eluting beads were mainly determined by the blood supply of tumors, the presence of arteriovenous fistula, and tumor size. For tumors with rich blood supply and without arteriovenous fistula, microspheres with a particle size of 100–300 μm were preferred for embolization. For large size tumors with arteriovenous fistula, a large size (300–500μm or 500–700μm) was usually used for embolization. When a single vial of drug-eluting beads was unable to completely embolize tumors with a diameter >10 cm, a second vial of drug-eluting beads was used for further embolization. Embolization was stopped when the blood flow became stagnant. Angiography was performed again to ensure the stain lesions disappeared.

If an endoscopic examination showed that patients had no moderate to severe esophageal and gastric varices or gastric and duodenal ulcers, intravenous injections of atezolizumab (1200 mg) and bevacizumab (15 mg/kg) were administered every three weeks. In the T+A+TACE group, atezolizumab and bevacizumab was administered at three to seven days after TACE. The treatments were discontinued until the occurrence of disease progression or intolerable toxic reactions. For patients with tumor progression in the two groups, the second-line treatment with oral regorafenib was administered.

Patients' Follow-up

All the patients received a series of follow-up, which included a live enhanced CT scan or a liver enhanced MRI scan, a lung CT scan, blood biochemistry analyses, urinalysis, and so on. The first follow-up was conducted around four weeks after the initial treatment. The liver contrast-enhanced CT or MR images and lung CT scan were performed every six to eight weeks. The blood biochemistry analyses and urinalysis, that included blood routine, urinary routine, liver and kidney function, and myocardial enzyme spectrum, were performed every three weeks. If a viable tumor in the liver was revealed by the CT or MRI imaging, a repeated TACE was performed if the patients had no contraindication to TACE in the T+A+TACE group.

Assessment

The tumor response was assessed by two radiologists with over 10 years of experience using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST 1.1. The objective response rate (ORR) was defined as the number of CR and PR among all patients, and the disease control rate (DRR) was defined as the number of patients with CR, PR, and SD. The OS was defined as the time from initial treatment to death or last follow-up. The PFS was defined as the time from initial treatment to tumor progression or death. The AEs were recorded and assessed based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

All data were analyzed using SPSS (version 26.0, IBM, NY, USA) and GraphPad Prism (version 8.0.0, San Diego, California USA). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were expressed as numbers (percentages). The comparison of categorical data was made by Chi-squared test, and continuous data were compared using Student's *t*-test. The Kaplan-Meier (KM) curves were plotted for different follow-up endpoints (OS and PFS), and a Log rank test was used to compare differences between the curves. When variables with the value of $P < 0.10$ at univariate analysis, the multi-univariate Cox proportional hazards regression analysis was used to evaluate the factors that affected the OS and PFS. A two-tailed P-value < 0.05 was considered statistically significant.

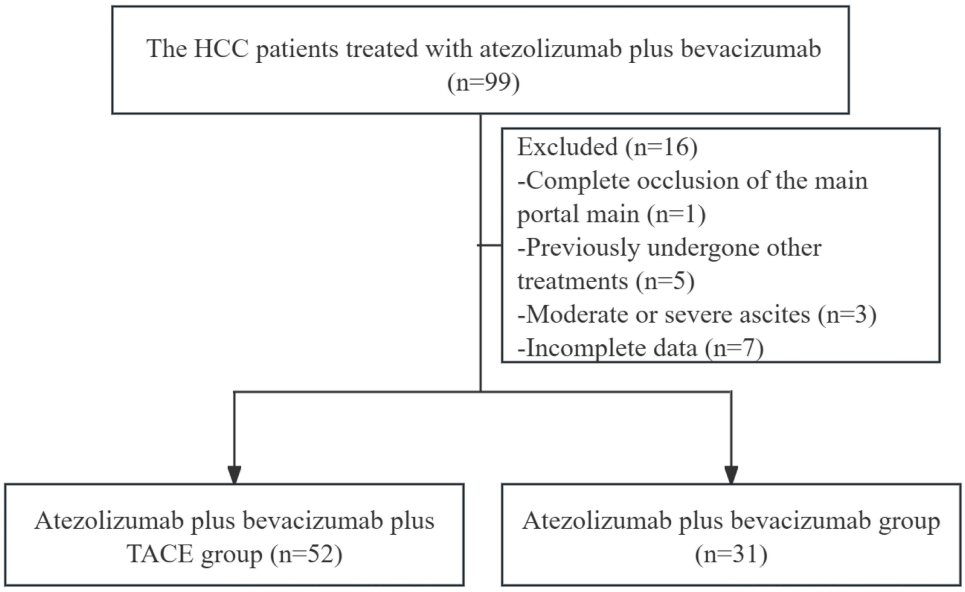

Figure 1 The patients' flowchart.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Results

Characteristics of the Study Patients

A total of 83 patients with advanced HCC were included in this study. All patients included in the study underwent endoscopy before receiving the T+A treatment. Out of 83 patients, 52 patients underwent atezolizumab plus bevacizumab in combination with TACE (T+A+TACE) treatment, and 31 patients received atezolizumab plus bevacizumab (T+A) therapy (Figure 1). The baseline characteristics of the patients are summarized in Table 1. The demographic data, tumor characteristics, and laboratory parameters between the two groups were comparable. In the T+A+TACE group, the mean number of TACE treatment was 3.1 times.

The Treatment Effects Between the Two Groups

The median OS in the T+A +TACE group was significantly longer than that of in the T+A group (22.8 months vs 16.9 months, $P = 0.015$), and the median PFS was significantly longer in the T+A +TACE group than in the T+A group (7.1 months vs 4.9 months, $P = 0.006$) (Figure 2). The univariate and multivariate analysis showed that the treatment method

Table 1 The Baseline Characteristics of Patients

Variables	T+A Group (n=31)	T+A+TACE Group (n=52)	*P*-value
Age, years	53.6 ± 13.5	52.6 ± 11.6	0.721
Gender, male	25 (80.6)	45 (86.5)	0.687
ECOG PS			
0	13 (41.9)	15 (28.8)	0.222
1	18 (58.1)	37 (71.2)	
Child–Pugh class			
A	19 (61.3)	40 (76.9)	0.129
B	12 (38.7)	12 (23.1)	

(*Continued*)

Table 1 (Continued).

Variables	T+A Group (n=31)	T+A+TACE Group (n=52)	*P*-value
ALBI grade			
1	6 (19.4)	15 (28.8)	0.11
2	22 (70.9)	25 (48.1)	
3	3 (9.7)	12 (23.1)	
Etiology			
Hepatitis B	28 (90.3)	40 (76.9)	0.075
Hepatitis C	2 (6.5)	2 (3.9)	
Non-B, non-C	1 (3.2)	10 (19.2)	
Liver cirrhosis	15 (48.4)	23 (44.2)	0.713
Macrovascular invasion	17 (54.8)	36 (69.2)	0.187
Extrahepatic spread	19 (61.3)	29 (55.8)	0.622
Ascites	7 (22.6)	6 (11.5)	0.181
Tumor size, ≥10 cm	10 (32.3)	21 (40.4)	0.459
Tumor distribution, Single	12 (38.7)	21 (40.4)	0.88
Laboratory parameters			
RBC, $\times 10^{12}$/L	4.17 ± 0.63	4.32 ± 0.61	0.308
Hb, g/L	132.0 ± 18.6	133.3 ± 20.1	0.76
Platelet, $\times 10^{9}$/L	158.4 ± 55.5	189.2 ± 89.3	0.087
PT, s	14.1 ± 1.3	13.8 ± 1.1	0.246
INR	1.12 ± 0.14	1.10 ± 0.13	0.534
WBC, $\times 10^{9}$/L	5.4 ± 3.3	6.2 ± 2.5	0.203
Neutrophils, $\times 10^{9}$/L	3.6 ± 3.0	4.1 ± 2.1	0.386
Lymphocyte, $\times 10^{9}$/L	1.81 ± 3.03	1.41 ± 0.71	0.376
NLR	3.2 ± 3.3	4.3 ± 7.3	0.461
ALT, U/L	61.6 ± 61.4	52.5 ± 52.3	0.472
AST, U/L	98.7 ± 127.9	71.0 ± 130.0	0.347
TBIL, μmol/L	28.3 ± 37.4	19.9 ± 23.3	0.267
ALP, U/L	156.5 ± 103.6	138.2 ± 96.6	0.42
TP, g/L	63.9 ± 6.1	66.1 ± 8.2	0.192
TBA, μmol/L	23.0 ± 30.1	15.9 ± 20.5	0.203
ALB, g/L	35.6 ± 5.4	37.8 ± 5.4	0.066
Cr, μmol/L	66.2 ± 15.5	67.5 ± 11.9	0.662
UA, μmol/L	312.8 ± 101.8	323.3 ± 86.8	0.619
AFP, ≥200 μg/L	18 (58.1)	25 (48.1)	0.378

Abbreviations: TACE, transarterial chemoembolization; T+A, atezolizumab plus bevacizumab; T+A+TACE, atezolizumab plus bevacizumab in combination with TACE; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; ALBI, Albumin-Bilirubin; RBC, red blood cell; Hb, hemoglobin; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; NLR, neutrophils/lymphocyte; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; TP, total protein; TBA, total bile acid; ALB, albumin; Cr, creatinine; UA, uric acid; AFP, alpha-fetoprotein.

(T+A+TACE) and a low alkaline phosphatase (ALP) level were the independent protective factors for OS (Table 2), and the treatment method (T+A+TACE), a low neutrophil-to-lymphocyte ratio (NLR) level, and a low alpha-fetoprotein (AFP) level (AFP < 200 μg/L) were the independent protective factors for PFS (Table 3). The ORR and DCR based on mRECIST and RECIST 1.1 in the T+A+TACE group were significantly higher than those of in the T+A group (Table 4). The forest plot that analyzed the OS of subgroups showed the combination of TACE with the T+A regimen was beneficial for all subgroups, and the subgroup of ALBI grade 0 was more benefit from the combination of TACE with systemic therapy (Figure 3). The subgroup analyses were performed based on the type of TACE received by patients

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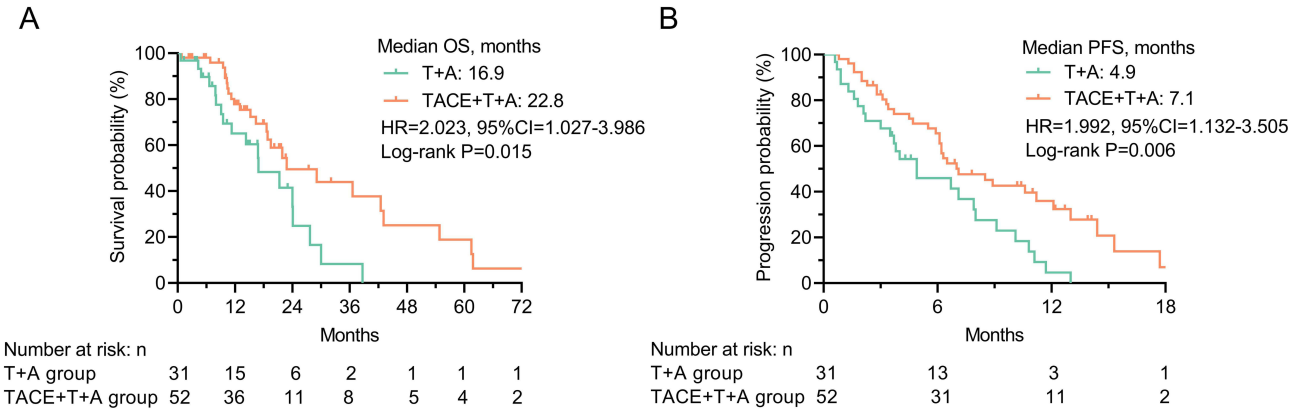

Figure 2 Kaplan–Meier curves between the two groups for median OS (**A**) and median PFS (**B**).
Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; TACE, transcatheter arterial chemoembolization; T+A, atezolizumab plus bevacizumab; TACE+T+A, TACE plus atezolizumab plus bevacizumab.

(C-TACE vs DEB-TACE) and Child-Pugh class (Figure 4). In the T+A+TACE group, there was no significant difference in the median OS between the C-TACE group and the D-TACE group (P=0.203), and no significant difference in the median OS between the Child-Pugh A group and the Child-Pugh B group (P=0.633) (Figure 4A and C). In T+A group, no significant difference was found between the Child-Pugh A group and the Child-Pugh B group (P=0.612) (Figure 4B).

Safety

As described in Table 5, the most common AEs in the two groups were diarrhea, fatigue, hand-foot skin reaction (HFSR), ALT elevation, hypertension, mouth ulcers, and hypothyroidism. AEs were observed in 28 patients (90.3%) in the T+A group and 49 patients (94.2%) in the TACE+T+A group, with no occurrence of grade 5 AEs in the two groups. There was no significant difference in the AEs incidence between the two groups ($P > 0.05$).

Table 2 Univariate and Multivariate Analysis for the OS

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Methods, T+A+TACE vs T+A	0.422	0.202–0.810	0.010	0.403	0.208–0.780	0.007
Age, years	0.997	0.972–1.022	0.795			
Gender, female vs male	0.651	0.313–1.353	0.251			
Liver cirrhosis, yes vs no	0.968	0.526–1.780	0.916			
Ascites, yes vs no	1.806	0.818–3.988	0.144			
Tumor size, ≥10 cm vs.<10 cm	1.108	0.561–2.185	0.768			
Tumor distribution, single vs multiple	1.360	0.721–2.566	0.342			
RBC, $\times 10^{12}$/L	0.726	0.445–1.186	0.201			
Hb, g/L	0.994	0.980–1.008	0.410			
Platelet, $\times 10^{9}$/L	1.000	0.995–1.004	0.931			
PT, s	1.359	1.058–1.746	0.016	–		
INR	11.458	1.175–111.757	0.036	–		
WBC, $\times 10^{9}$/L	1.044	0.928–1.174	0.475			
Neutrophils, $\times 10^{9}$/L	1.092	0.953–1.250	0.205			
Lymphocyte, $\times 10^{9}$/L	1.049	0.907–1.213	0.521			
NLR	1.037	1.001–1.074	0.042	–		
ALT, U/L	1.004	0.999–1.010	0.138			

(*Continued*)

Table 2 (Continued).

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
AST, U/L	1.001	1.000–1.003	0.133			
TBIL, μmol/L	1.007	0.995–1.018	0.249			
ALP, U/L	1.005	1.002–1.008	0.001	1.005	1.002–1.008	0.001
TP, g/L	0.971	0.934–1.010	0.139			
TBA, μmol/L	1.012	0.999–1.025	0.078	–		
ALB, g/L	0.954	0.909–1.002	0.061	–		
Cr, μmol/L	1.007	0.985–1.029	0.523			
UA, μmol/L	1.000	0.997–1.004	0.812			
AFP, ≥200 μg/L vs <200 μg/L	1.084	0.579–2.029	0.800			

Abbreviations: TACE, transarterial chemoembolization; T+A, atezolizumab plus bevacizumab; T+A+TACE, atezolizumab plus bevacizumab plus TACE; HR, hazard ratio; CI, confidence interval; RBC, red blood cell; Hb, hemoglobin; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; NLR, neutrophils/lymphocyte; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; TP, total protein; TBA, total bile acid; ALB, albumin; Cr, creatinine; UA, uric acid; AFP, alpha-fetoprotein.

Table 3 Univariate and Multivariate Analysis for PFS

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Methods, T+A+TACE vs T+A	0.483	0.284–0.819	0.007	0.482	0.283–0.822	0.007
Age, years	0.992	0.971–1.014	0.494			
Gender, female vs male	0.980	0.494–1.943	0.954			
Liver cirrhosis, yes vs no	0.866	0.519–1.445	0.583			
Ascites, yes vs no	1.348	0.790–2.300	0.273			
Tumor size, ≥10 cm vs.<10 cm	1.317	0.772–2.249	0.313			
Tumor distribution, single vs multiple	0.900	0.536–1.511	0.691			
RBC, $\times10^{12}$/L	0.984	0.626–1.546	0.943			
Hb, g/L	0.997	0.983–1.010	0.622			
Platelet, $\times10^{9}$/L	1.000	0.997–1.003	0.841			
PT, s	1.055	0.839–1.327	0.645			
INR	0.876	0.111–6.895	0.900			
WBC, $\times10^{9}$/L	0.961	0.871–1.059	0.418			
Neutrophils, $\times10^{9}$/L	0.989	0.887–1.102	0.842			
Lymphocyte, $\times10^{9}$/L	1.020	0.875–1.189	0.798			
NLR	1.039	1.001–1.079	0.045	1.05	1.009–1.093	0.017
ALT, U/L	1.004	1.000–1.009	0.075	–		
AST, U/L	1.001	1.000–1.003	0.098	–		
TBIL, μmol/L	1.003	0.995–1.011	0.402			
ALP, U/L	1.002	0.999–1.004	0.121			
TP, g/L	0.962	0.929–0.996	0.029	–		
TBA, μmol/L	0.994	0.983–1.004	0.227			
ALB, g/L	0.985	0.944–1.029	0.500			
Cr, μmol/L	0.989	0.969–1.009	0.278			
UA, μmol/L	0.999	0.996–1.002	0.678			
AFP, ≥200 μg/L vs <200 μg/L	1.833	1.081–3.108	0.024	1.851	1.083–3.2164	0.024

Abbreviations: TACE, transarterial chemoembolization; T+A, atezolizumab plus bevacizumab; T+A+TACE, atezolizumab plus bevacizumab plus TACE; HR, hazard ratio; CI, confidence interval; RBC, red blood cell; Hb, hemoglobin; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; NLR, neutrophils/lymphocyte; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; TP, total protein; TBA, total bile acid; ALB, albumin; Cr, creatinine; UA, uric acid; AFP, alpha-fetoprotein.

Table 4 Tumor Response Between the Two Groups

	RECIST 1.1			mRECIST		
	T+A Group (n=31)	T+A+ TACE Group (n=52)	*P*-value	T+A Group (n=31)	T+A+ TACE Group (n=52)	*P*-value
Tumor Response						
CR	1 (3.2)	3 (5.8)	0.002	1 (3.2)	4 (7.7)	<0.001
PR	2 (6.5)	21 (48.1)		1 (3.2)	23 (44.3)	
SD	17 (54.8)	20 (38.5)		15 (48.4)	19 (36.5)	
PD	11 (35.5)	8(15.4)		14 (45.2)	6 (11.5)	
ORR (CR+PR)	3 (9.8)	24 (46.2)	<0.001	2 (6.5)	27 (51.9)	<0.001
DCR (CR+PR+SD)	20 (64.5)	44 (84.6)	0.035	17 (54.8)	46 (88.5)	<0.001

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; T+A, atezolizumab plus bevacizumab; T+A+TACE, atezolizumab plus bevacizumab plus TACE; TACE, transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Discussion

The results of IMbrave150 trial[11] showed that atezolizumab in combination with bevacizumab for unresectable HCC was superior to the conventional systemic treatment of sorafenib in terms of OS and PFS, and the updated results of IMbrave150 trial[24] showed that the median OS in the T+A group was 19.2 months (95% CI: 17.0–23.7 months), and the median PFS in the T+A group was 6.9 months (95% CI: 5.7–8.6 months), which were shorter than those of in the T+A+TACE group of our study. Meanwhile, we found the median OS and median PFS in the T+A+TACE group were significantly longer than those of in T+A group, and ORR and DCR in the T+A+TACE group were significantly higher than those of in T+A group. These results demonstrated that TACE treatment can further improve the effect of T+A for advanced HCC patients. In addition, some previous studies[25,26] reported that cTACE plus sorafenib therapy did not improve OS for patients with advanced HCC compared with sorafenib alone treatment. Meanwhile, some previous studies[27,28] reported that TACE could improve the OS and PFS for advanced HCC patients who received ICIs plus VEGF antibody/tyrosine kinase inhibitors (TKIs) treatment, which was confirmed by our study.

The results of our study indicated that the triple combination treatment (T+A+TACE) could significantly prolong the OS of patients with advanced HCC. The possible reasons are that 1) TACE treatment can reduce the tumor blood supply and tumor hypoxia, which increases the expression of VEGF in tumor.[29] Bevacizumab (VEGF inhibitor) weakened this effect, and thus inhibiting the tumor recurrence; 2) TACE can increase tumor antigen release and subsequently trigger anti-cancer immune response, which may be further enhanced by atezolizumab (PD-L1 inhibitor);[19,30] 3) In addition to reducing VEGF expression, bevacizumab can reverse the immunosuppressive microenvironment and promote T cells infiltration to enhance the immune response triggered by PD-L1 inhibitors in HCC.[31,32] Therefore, in clinical practice, "T+A" in combination with TACE could improve the prognosis of patients with advanced HCC.

The results of our study showed the "T+A+TACE" treatment and a low ALP level were the independent protective factors for OS, and the "T+A+TACE" treatment, a low NLR level, and a low AFP (AFP < 200 μg/L) level were the independent protective factors for PFS, which suggested that use of T+A+TACE treatment may help improve the prognosis of these patients. Meanwhile, the forest plot that analyzed the OS of subgroup showed the subgroup of ALBI grade 0 was more benefit from the combination of TACE with systemic therapy, which indicated a well-preserved liver function may facilitate in improving the effect of T+A+TACE treatment.

In our study, the majority of AEs were grade 1–2, with no occurrence of grade 5 AEs. Moreover, no significant increase of AEs was observed when TACE was added to the "T+A" therapy, which indicated that the safety profile of the T+A+TACE treatment was acceptable.

This study had limitations. The small sample size may limit the statistical power, and the retrospective and single-center design may introduce potential biases. A large-scale, prospective, and multi-center randomized controlled trial is needed to validate the results and explore the underlying mechanisms of this study.

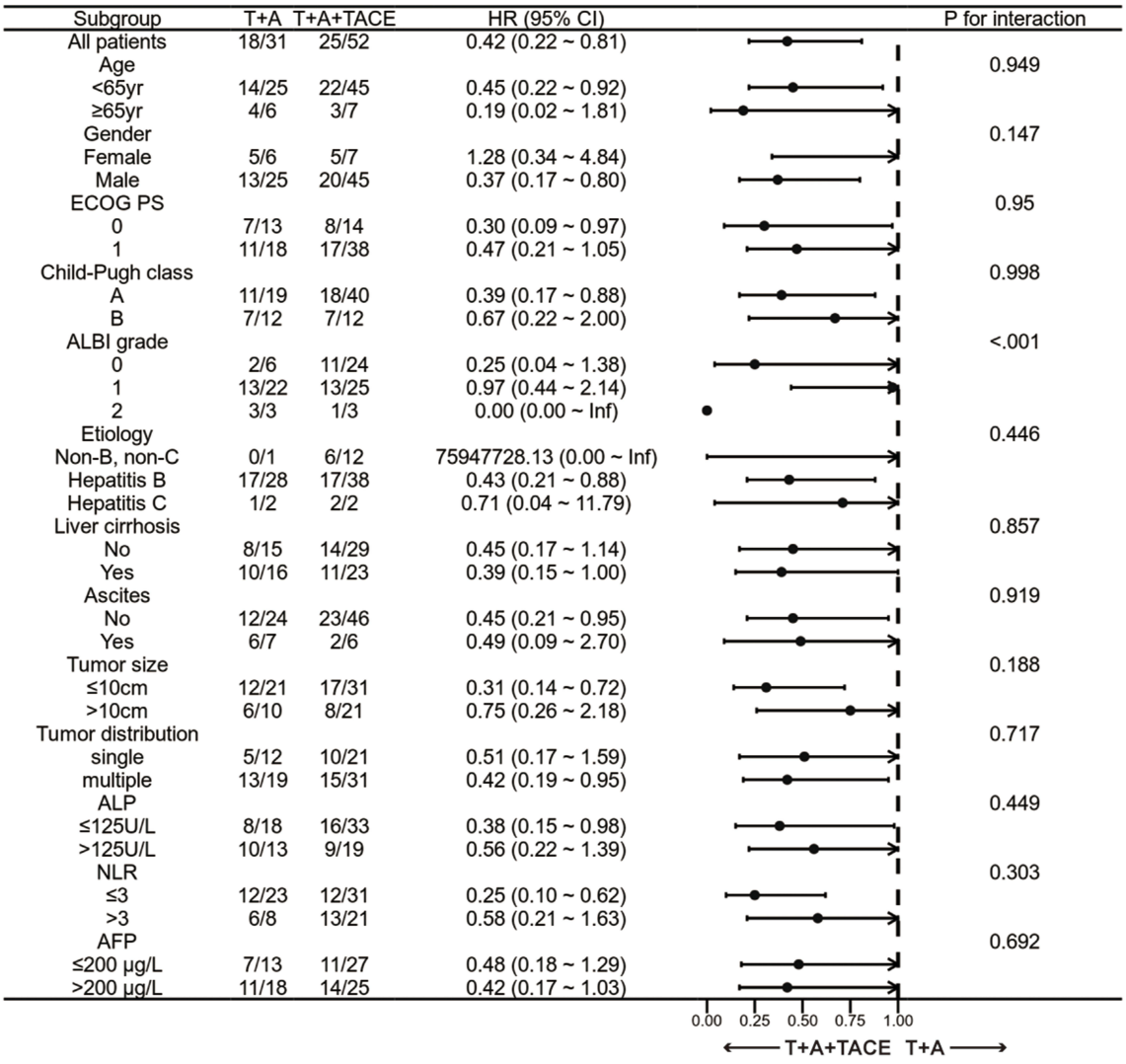

Figure 3 Forest plot demonstrated the subgroup analysis of overall survival.

Abbreviations: TACE, transarterial chemoembolization; T+A, atezolizumab plus bevacizumab; T+A+TACE, atezolizumab plus bevacizumab plus TACE; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ALBI, Albumin-Bilirubin; ALP, alkaline phosphatase; NLR, neutrophils/lymphocyte; AFP, alpha-fetoprotein.

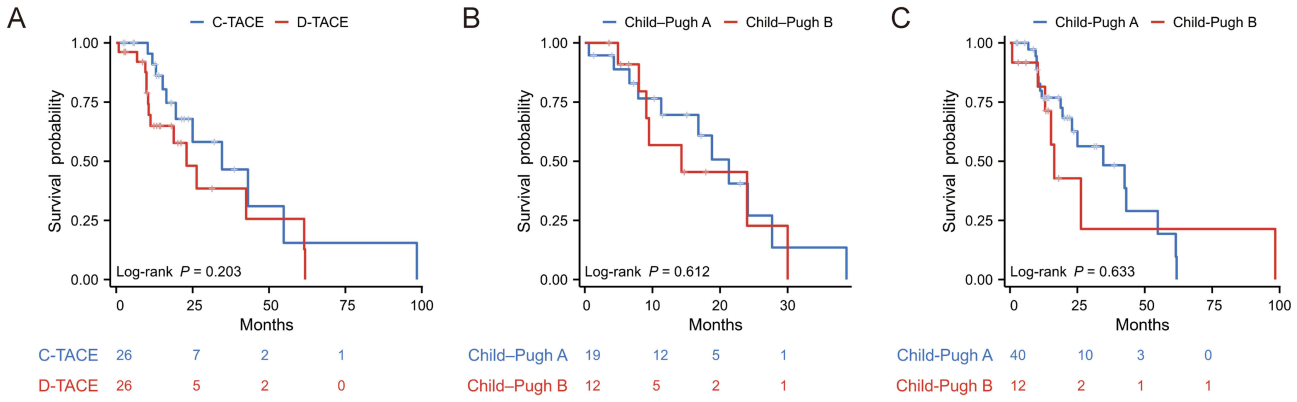

Figure 4 Kaplan-Meier curves from subgroup analyses. (**A**) Subgroup analysis according to different types of TACE. (**B**) Subgroup analysis according to different Child-Pugh classifications within the T+A group. (**C**) Subgroup analysis according to different Child-Pugh classifications in the T+A+TACE group.

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Table 5 Adverse Events Related to Treatments

	All Grade		Grade 3 or 4	
	T+A Group (n=31)	T+A+TACE Group (n=52)	T+A Group (n=31)	T+A+TACE Group (n=52)
Mouth ulcers	6 (19.4)	6 (11.5)	3 (9.7)	3 (5.8)
Hypertension	4 (12.9)	7 (13.5)	1 (3.2)	4 (7.7)
HFSR	5 (16.1)	8 (15.4)	2 (6.5)	5 (9.6)
Elevated bilirubin	4 (12.9)	5 (9.6)	1 (3.2)	2 (3.8)
Diarrhea	1 (3.2)	9 (17.3)	0	6 (11.5)
Rash	3 (9.7)	5 (9.6)	0	2 (3.8)
Fatigue	4 (12.9)	7 (13.5)	0	1 (1.9)
ALT elevation	4 (12.9)	10 (19.2)	1 (3.2)	2 (3.8)
Proteinuria	6 (19.4)	4 (7.7)	3 (9.7)	1 (1.9)
Hypothyroidism	5 (16.1)	6 (11.5)	2 (6.5)	3 (5.8)
RCCEP	4 (12.9)	4 (7.7)	1 (3.2)	1 (1.9)
Thrombocytopenia	4 (12.9)	3 (5.8)	2 (6.5)	0
Gastrointestinal hemorrhage	4 (12.9)	3 (5.8)	1 (3.2)	0
Pneumonitis	2 (6.5)	1 (1.9)	0	0

Abbreviations: T+A, atezolizumab plus bevacizumab; T+A+TACE, atezolizumab plus bevacizumab plus TACE; TACE, transarterial chemoembolization; HFSR, hand-foot skin reaction; ALT, alanine aminotransferase; RCCEP, reactive cutaneous capillary endothelial proliferation.

Conclusion

In summary, TACE could further improve the effect of "T+A" treatment for patients with advanced HCC, and it did not increase the incidence of AEs. "T+A+TACE" treatment is a promising treatment option for patients with advanced HCC.

Ethical Approval

This retrospective study was conducted in accordance with the principles of 1975 Declaration of Helsinki. The study received approval from the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Approval No.: UHCT241070). A written informed consent was waived by our ethics committee due to the retrospective nature of this study. All patients' data was handled with strict confidentiality and anonymity. The data used in this study was anonymized and securely encrypted to protect patients' privacy.

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Disclosure

The authors report no conflicts of interest in this work.

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