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The efficacy and safety analysis of D-TACE combined with donafenib and tislelizumab in recurrent hepatocellular carcinoma after surgery

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This retrospective study evaluated the efficacy and safety of drug-eluting bead transarterial chemoembolization (D-TACE) combined with Donafenib and Tislelizumab versus D-TACE with Sorafenib in 105 patients with recurrent hepatocellular carcinoma (HCC) after surgical resection (January 2019–June 2023). Patients were divided into D-TACE + Donafenib + Tislelizumab ($N=51$) and D-TACE + Sorafenib ($N=54$) groups. The D-TACE + Donafenib + Tislelizumab group demonstrated significantly higher objective response rate (62.7% vs. 40.7%, $P<0.05$) and disease control rate (84.3% vs. 64.8%, $P<0.05$), along with prolonged median progression-free survival (8.7 vs. 5.7 months, $P<0.001$) and overall survival (19.2 vs. 12.3 months, $P<0.001$). While hypothyroidism incidence was higher in the D-TACE + Donafenib + Tislelizumab group (21.6% vs. 7.4%, $P=0.051$), the D-TACE + Sorafenib group exhibited increased fatigue (35.2% vs. 11.8%, $P=0.006$) and anorexia (35.2% vs. 13.7%, $P=0.013$). These findings suggest that D-TACE combined with Donafenib and Tislelizumab offers superior tumor control and survival benefits with a manageable safety profile, representing a promising therapeutic strategy for postoperative recurrent HCC.

Keywords Hepatocellular carcinoma, Postoperative recurrence, Interventional therapy, Targeted therapy, Immunotherapy, Transarterial chemoembolization (TACE), Immune checkpoint inhibitors

Hepatocellular carcinoma (HCC) is currently the fifth most common malignant tumor worldwide and the third leading cause of cancer-related deaths^{1,2}. According to the global epidemiological analysis of liver cancer in 2020, there were approximately 900,000 new cases of liver cancer globally, with over 390,000 deaths annually, posing a serious threat to human life³. Due to the lack of specific symptoms and signs in the early stages of HCC, many patients are diagnosed at an intermediate or advanced stage of the disease⁴. Studies have reported that less than 30% of HCC patients have the opportunity to undergo surgical resection⁵. Although surgical resection has been considered one of the curative treatments for HCC, the postoperative 5-year recurrence rate remains as high as 70%, with the majority of recurrences occurring within two years after surgery^{6,7}. Recurrence of HCC is one of the leading causes of patient mortality and has become a critical factor affecting the efficacy of surgery and long-term survival in HCC patients^{8,9}. Therefore, how to effectively treat recurrent HCC after surgery is a major challenge in the field of HCC treatment and a focus of research for many scholars. Since patients with recurrent HCC have often undergone previous surgical treatment, many are unable or unwilling to undergo repeat surgical intervention upon recurrence. Transarterial chemoembolization (TACE) is one of the effective treatment modalities for intermediate and advanced HCC¹⁰. Studies have shown that TACE can significantly improve the survival of patients with unresectable HCC^{11,12}. TACE includes conventional TACE (C-TACE)¹³ and drug-eluting bead TACE (D-TACE)¹⁴. As most drug-eluting beads are permanent embolic agents, they can more effectively reach the distal tumor-feeding arteries and exert embolization effects. Additionally, drug-eluting beads loaded with chemotherapeutic drugs can slowly and continuously release the drugs locally within the tumor, maintaining high concentrations of chemotherapeutic agents over an extended period, thereby achieving better tumor eradication. CalliSpheres® drug-loaded embolic microspheres have a unique network

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structure, with high drug loading capacity and efficiency, and can be loaded with multiple drugs^{15,16}. They exhibit good biocompatibility and high vascular compliance, achieving satisfactory clinical efficacy¹⁷. A study by Hua Xiang et al.¹⁸ reported on 73 patients with HCC treated with either D-TACE (using CalliSpheres[®]) or C-TACE. The results showed that D-TACE with CalliSpheres[®] achieved better treatment responses and progression-free survival (PFS). Another study by Song Liu et al.¹⁹ examined the clinical data of 90 patients with large HCC. The experimental group received D-TACE (CalliSpheres[®]) combined with sorafenib, while the control group received D-TACE (CalliSpheres[®]) alone. The median overall survival (OS) and time to progression (TTP) were significantly longer in the experimental group compared to the control group (18.6 months vs. 12.7 months, 8.3 months vs. 6.9 months).

However, TACE has its limitations. The post-embolization tumor tissue is subjected to an ischemic and hypoxic microenvironment, which upregulates hypoxia-inducible factor-1 α (HIF-1 α), consequently inducing the upregulation of VEGF, FGF, and other factors that may further lead to residual tumor recurrence and metastasis²⁰⁻²². Elisa Pinto et al.²³ reported that VEGF and HIF-1 α can serve as biological indicators of the prognosis of HCC treated with TACE, with lower HIF-1 α levels correlating with better outcomes. A study by L Y Guo et al.²⁴ demonstrated that both HIF-1 α and VEGF are significantly associated with overall survival (OS) in HCC patients ($P < 0.05$). Therefore, many researchers have explored combination treatment strategies based on TACE to improve the survival time of HCC patients. TACE combined with targeted therapy and immunotherapy is currently one of the commonly employed treatment strategies^{25,26}. Clinically, molecular targeted drugs commonly used for HCC include sorafenib²⁷, lenvatinib²⁸, donafenib, apatinib, regorafenib²⁹, and cabozantinib³⁰. Donafenib, a multi-targeted tyrosine kinase inhibitor, exerts antitumor effects by inhibiting tumor cell proliferation and angiogenesis^{31,32}. A randomized, open-label, parallel-controlled phase II-III trial involving 668 patients with unresectable or metastatic HCC showed that the OS in the donafenib group was superior to that in the sorafenib group, with good safety and tolerability³³. Immune checkpoint inhibitors are also commonly used in the treatment of advanced HCC. A multicenter phase I/II study published by Anthony B. El-Khoueiry et al.³⁴ demonstrated that nivolumab, a human anti-PD-1 monoclonal antibody, achieved an objective response rate (ORR) of 15% during the dose-escalation phase and 20% during the dose-expansion phase in patients with advanced HCC. Similarly, the results of a non-randomized, open-label phase II trial published by Andrew X. Zhu et al.³⁵ showed an ORR of 17% for pembrolizumab in the treatment of advanced HCC. Tislelizumab, a PD-1 inhibitor, works by blocking the PD-1/PD-L1 signaling pathway, thereby activating the patient's immune system to exert antitumor effects³⁶⁻³⁸. In the RATIONALE-301 (phase III randomized clinical trial), tislelizumab demonstrated non-inferior OS benefits compared to sorafenib, with higher ORR, longer duration of response, and a superior safety profile³⁹. The theoretical rationale for employing D-TACE with Donafenib and Tislelizumab in recurrent HCC lies in the direct tumor necrosis induced by D-TACE's chemotherapeutic and embolic effects, synergistically enhanced by Donafenib's anti-angiogenic properties and Tislelizumab's immunomodulatory actions, thereby achieving synergistic efficacy with TACE. This study aims to evaluate the efficacy and safety of D-TACE combined with donafenib and tislelizumab in treating recurrent HCC by retrospectively analyzing the clinical data of recurrent HCC patients from our center. The goal is to understand the advantages and limitations of this treatment strategy in improving patient survival, controlling tumor progression, and reducing the incidence of adverse events. These findings will provide further evidence to guide the treatment choices for postoperative recurrent HCC and have significant implications for improving the prognosis of this patient population.

Materials and methods

General information

We collected the clinical data of 105 patients with recurrent HCC after surgery who were treated at the Department of Interventional Radiology, Union Hospital, affiliated with Tongji Medical College, Huazhong University of Science and Technology, between January 2019 and June 2023. Inclusion Criteria: (1) Age between 18 and 75 years. (2) Previous surgical resection for HCC with a pathological diagnosis confirming HCC. (3) No history of radiotherapy, chemotherapy, targeted therapy, or immunotherapy related to HCC after surgery. (4) Liver function classified as Child-Pugh grade A-B, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. (5) Complete clinical follow-up data. Exclusion Criteria: (1) Presence of other primary or secondary malignant tumors. (2) Severe abnormalities in the heart, lungs, kidneys, hematologic system, nervous system, or coagulation function. (3) Tumor thrombus involving both first-order branches of the portal vein or the main trunk of the portal vein with poor collateral circulation. (4) Allergy to iodinated contrast agents, donafenib, sorafenib, or tislelizumab. (5) Expected survival time of less than 3 months. Patients were divided into two groups based on their treatment strategies: the D-TACE + Donafenib + Tislelizumab group ($N = 51$) and the TACE + Sorafenib group ($N = 54$). Baseline data collected included gender, age, etiology of liver cirrhosis, preoperative liver function classified by Child-Pugh grade⁴⁰, ECOG performance status, Barcelona Clinic Liver Cancer (BCLC) stage⁴¹, pre-treatment levels of total bilirubin, ALT, AST, white blood cell count(WBC), red blood cell count(RBC), and platelet count(PLT).

Methods

D-TACE procedure⁴²

A 5 F Yashiro catheter was inserted via the femoral artery into the celiac trunk and superior mesenteric artery (and, if necessary, other aberrant feeding arteries) to perform angiography and identify the tumor-feeding arteries. A 2.7 F microcatheter was then used to superselectively catheterize the feeding arteries of the hepatocellular carcinoma, followed by the injection of drug-eluting beads. The drug-eluting beads used during the procedure were 100–300 μm CalliSpheres[®], loaded with 80 mg of epirubicin, and injected at a rate of 1 ml/min. If angiography revealed significant arterioportal or arteriovenous shunting, PVA particles were used to

embolize the shunts before injecting the drug-eluting beads. In cases of large tumors, if significant tumor staining was still visible after embolizing with one vial of drug-eluting beads, additional embolization was performed using 300–500 μm 8Spheres beads(blank microspheres). The endpoint of D-TACE treatment was defined as the interruption of blood flow to the tumor-feeding arteries.

Materials and Drugs Used for TACE: 5 F vascular sheath (TERUMO5F-10CM, Terumo, Japan), 0.035-inch guidewire (RFGA35153M, Terumo, Japan), 5 F Yashiro catheter (Terumo, Japan), 2.7 F microcatheter (Terumo, Japan), Epirubicin (GYZZ H19990280, Zhejiang Hisun Pharmaceutical Co., Ltd.), CalliSpheres® and 8Spheres beads (Suzhou Hengrui Jialisheng Biotechnology Co., Ltd., Suzhou, China).

Donafenib and tislelizumab administration

Donafenib: 200 mg orally, twice daily. Tislelizumab: 200 mg via intravenous infusion, administered once every three weeks.

Sorafenib administration

Dosage: Sorafenib was administered at a dose of 400 mg orally, twice daily.

Patients underwent follow-up with contrast-enhanced CT or MRI every 4–6 weeks. Based on the results of these follow-up scans, the need for additional TACE treatments was determined. After disease progression, both groups of patients were switched to Regorafenib tablet therapy.

Outcome measures

Primary Endpoints: (1) Tumor Response Evaluation: The efficacy of tumor treatment in both groups was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST)^{43,44}. The assessment categories included Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD). (2) Objective Response Rate (ORR) and Disease Control Rate (DCR): The ORR and DCR were calculated for both groups to evaluate the overall effectiveness of the treatments. (3) Overall Survival (OS) and Progression-Free Survival (PFS): The OS and PFS were recorded and compared between the two groups to determine the long-term efficacy of the treatments.

Secondary Endpoints: (1) Liver Function and Hematologic Changes: Changes in liver function and blood count were monitored in both groups before treatment and three months after treatment. (2) Treatment-Related Adverse Events (AEs): The incidence of AEs related to treatment was recorded for both groups. AEs were evaluated using version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) published by the U.S. Department of Health and Human Services⁴⁵.

The assessment of tumor response based on the mRECIST criteria was conducted through joint interpretation by two Chief Physicians in the Radiology Department, yielding unanimous consensus.

Statistical methods

Statistical analysis was performed using SPSS version 27.0 software. Frequencies and percentages were used to present categorical data. Differences between groups were assessed using the chi-square test, including Pearson Chi-Square and Fisher's Exact Test. Means \pm standard deviations were used for continuous data. Differences between groups were analyzed using the t-test. Kaplan-Meier curves were used to display OS and PFS. The Log-Rank test was used to compare OS and PFS between the two groups. Univariate analyses were conducted using the log-rank test. Variables demonstrating statistical significance ($p < 0.1$) in univariate analysis were entered into multivariate analysis. A multivariate Cox proportional hazards regression model was subsequently employed to screen for prognostic factors independently associated with progression-free survival (PFS) and overall survival (OS). A P value of < 0.05 was defined as statistically significant.

Results

Comparison of baseline characteristics between groups

There were no significant statistical differences between the two groups in terms of gender, age, etiology of liver cirrhosis, preoperative liver function classified by Child-Pugh grade, ECOG performance status, presence of portal vein tumor thrombus(PVTT), AFP levels, BCLC stage, pre-treatment levels of total bilirubin, ALT, AST, WBC, RBC, and PLT($P > 0.05$, Table 1).

Comparison of blood parameters three months after treatment

There were no significant differences between the two groups in total bilirubin, ALT, AST, WBC, RBC, and PLT three months after treatment ($P > 0.05$, Table 2).

Tumor response assessment after treatment

The proportion of patients achieving CR was higher in the TACE + Donafenib + Tislelizumab group compared to the TACE + Sorafenib group, and the proportion of patients with PD was lower in the TACE + Donafenib + Tislelizumab group ($P = 0.041$, Table 3). The ORR and DCR were both higher in the TACE + Donafenib + Tislelizumab group compared to the TACE + Sorafenib group ($P < 0.05$, Table 3).

Comparison of OS and PFS between groups

The mPFS was longer in the TACE + Donafenib + Tislelizumab group compared to the TACE + Sorafenib group (8.7 months vs. 5.7 months, $P < 0.001$, Fig. 1; Table 4). The mOS was longer in the TACE + Donafenib + Tislelizumab group compared to the TACE + Sorafenib group (19.2 months vs. 12.3 months, $P < 0.001$, Fig. 2; Table 4).

			Group		Chi-Square Tests(<i>p</i> -value)		
			D-TACE + Donafenib + Tislelizumab group (N=51)	D-TACE + Sorafenib group (N=54)	Fisher's Exact Test	Pearson Chi-Square	t-test(<i>p</i> -value)
Gender	Female	Count(%)	12(23.5%)	11(20.4%)	0.814		
	Male	Count(%)	39(76.5%)	43(79.6%)			
Etiology of cirrhosis	Hepatitis B	Count(%)	42(82.4%)	43(79.6%)	0.797		
	Hepatitis C	Count(%)	5(9.8%)	6(11.1%)			
	Alcoholic	Count(%)	2(3.9%)	4(7.4%)			
	others	Count(%)	2(3.9%)	1(1.9%)			
Pre-treatment ECOG	0	Count(%)	16(31.4%)	20(37.0%)	0.811		
	1	Count(%)	26(51.0%)	26(48.1%)			
	2	Count(%)	9(17.6%)	8(14.8%)			
Pre-treatment liver function	Child A	Count(%)	29(56.9%)	32(59.3%)	0.845		
	Child B	Count(%)	22(43.1%)	22(40.7%)			
BCLC staging	B	Count(%)	14(27.5%)	17(31.5%)	0.675		
	C	Count(%)	37(72.5%)	37(68.5%)			
Portal vein tumor thrombus	No	Count(%)	20(39.2%)	25(46.3%)	0.555		
	Yes	Count(%)	31(60.8%)	29(53.7%)			
AFP	< 400ug/L	Count(%)	13(25.5%)	10(18.5%)	0.481		
	≥ 400ug/L	Count(%)	38(74.5%)	44(81.5%)			
Age(Years)	Mean ± SD		56.6 ± 11.5	52.8 ± 12.1			0.109
Pre-treatment bilirubin(μmol/L)	Mean ± SD		15.84 ± 6.50	14.54 ± 6.88			0.321
Pretreatment AST(U/L)	Mean ± SD		49.9 ± 27.0	46.9 ± 23.3			0.538
Pretreatment ALT(U/L)	Mean ± SD		50.6 ± 25.1	53.1 ± 26.2			0.618
Pretreatment WBC(G/L)	Mean ± SD		4.61 ± 1.66	4.33 ± 1.25			0.321
Pretreatment RBC(T/L)	Mean ± SD		3.68 ± 1.55	3.55 ± 1.47			0.657
Pretreatment PLT(G/L)	Mean ± SD		108.0 ± 56.7	111.8 ± 39.8			0.691

Table 1. Comparison of baseline characteristics between the two Groups.

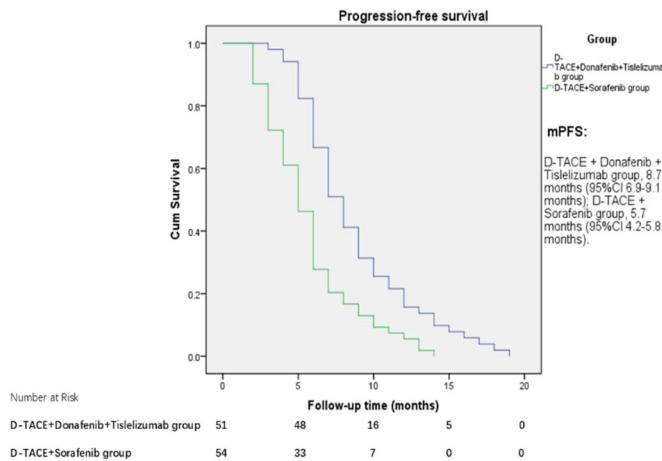
Group			D-TACE + Donafenib + Tislelizumab group (N=51)		D-TACE + Sorafenib group (N=54)		t-test(<i>p</i> -value)
Post-treatment bilirubin(μmol/L)	Mean ± SD		18.03 ± 6.46		21.11 ± 13.82		0.150
Post-treatment AST(U/L)	Mean ± SD		61.8 ± 38.5		63.6 ± 39.9		0.814
Post-treatment ALT(U/L)	Mean ± SD		47.0 ± 21.8		69.4 ± 37.7		< 0.001
Post-Treatment WBC(G/L)	Mean ± SD		3.50 ± 0.83		3.67 ± 0.82		0.289
Post-Treatment RBC(T/L)	Mean ± SD		3.47 ± 0.74		3.28 ± 0.66		0.146
Post-Treatment PLT(G/L)	Mean ± SD		84.7 ± 20.6		79.0 ± 30.5		0.272

Table 2. Comparison of blood parameters at 3 months Post-Treatment between the two Groups.

Incidence of treatment-related adverse events

The incidence of fatigue (all grades) was higher in the TACE + Sorafenib group compared to the TACE + Donafenib + Tislelizumab group (35.2% vs. 11.8%, $P=0.006$, Table 5). The incidence of anorexia (all grades) was higher in the TACE + Sorafenib group compared to the TACE + Donafenib + Tislelizumab group (35.2% vs. 13.7%, $P=0.013$, Table 5). There were no significant differences between the two groups in terms of abdominal pain, fever, vomiting, hypertension, diarrhea, hand-foot syndrome, rash, or proteinuria ($P>0.05$, Table 5). The incidence of hypothyroidism (all grades) was higher in the TACE + Donafenib + Tislelizumab group compared to the TACE + Sorafenib group (21.6% vs. 7.4%), but this difference was not statistically significant ($P=0.051$, Table 5).

			Group		Chi-Square Tests(<i>p</i> -value)	
			D-TACE + Donafenib + Tislelizumab group (N=51)		D-TACE + Sorafenib group (N=54)	
Tumor response	CR	Count(%)	13(25.5%)		5(9.3%)	0.041
	PR	Count(%)	19(37.3%)		17(31.5%)	
	SD	Count(%)	11(21.6%)		13(24.1%)	
	PD	Count(%)	8(15.7%)		19(35.2%)	
ORR		Count(%)	32(62.7%)		22(40.7%)	0.032
DCR		Count(%)	43(84.3%)		35(64.8%)	0.027

Table 3. Tumor efficacy evaluation in the two Groups.**Fig. 1.** Progression-free survival time in the two groups mPFS: D-TACE + Donafenib + Tislelizumab group, 8.7 months (95%CI 6.9–9.1 months); D-TACE + Sorafenib group, 5.7 months (95%CI 4.2–5.8 months).

	Gruop	Median(months)	95% Confidence interval		Log rank (Mantel-Cox) (p-value)
			Lower bound	Upper bound	
PFS	D-TACE + Donafenib + Tislelizumab group	8.7	6.9	9.1	<0.001
	D-TACE + Sorafenib group	5.7	4.2	5.8	
OS	D-TACE + Donafenib + Tislelizumab group	19.2	16.7	21.3	<0.001
	D-TACE + Sorafenib group	12.3	7.4	14.6	

Table 4. Comparison of overall survival (OS) and Progression-Free survival (PFS) between the two Groups.

Prognostic factors affecting PFS and OS

Multivariate analysis demonstrated that AFP (<400 μ g/L vs. $\geq 400 \mu$ g/L) (Hazard Ratio [HR] = 0.110; 95% Confidence Interval [CI]: 0.032–0.383; $P = 0.001$) and treatment (D-TACE + Donafenib + Tislelizumab vs. D-TACE + Sorafenib) (HR = 0.180; 95% CI: 0.104–0.313; $P < 0.001$) were independent predictors of OS (Table 6). Additionally, portal vein tumor thrombus (No vs. Yes) (HR = 0.422; 95% CI: 0.209–0.853; $P = 0.016$) and treatment (D-TACE + Donafenib + Tislelizumab vs. D-TACE + Sorafenib) (HR = 0.323; 95% CI: 0.206–0.508; $P < 0.001$) emerged as independent prognostic factors for PFS (Table 7).

Discussion

Although surgical resection remains one of the primary curative treatments for HCC, the postoperative recurrence rate remains high⁴⁶. Carla Fuster-Anglada⁴⁷ conducted a retrospective study of 218 patients with solitary HCC undergoing hepatectomy. The results demonstrated that microvascular invasion (mVI) and/or satellitosis were the sole independent risk factors for aggressive recurrence and mortality post-surgery. Tumor recurrence after surgery is a major factor affecting long-term survival in HCC patients^{48–50}. Currently, the treatment of postoperative recurrent HCC remains a significant challenge in clinical practice^{51–53}. Therefore, we initiated a treatment protocol combining D-TACE with targeted therapy and immunotherapy for postoperative recurrent HCC. D-TACE exerts synergistic antitumor effects through two primary mechanisms: (1) the cytotoxic effects of chemotherapeutic agents loaded onto drug-eluting beads, and (2) ischemia and hypoxia induced by embolization of tumor-feeding arteries^{54,55}. TACE is one of the most widely used treatments for

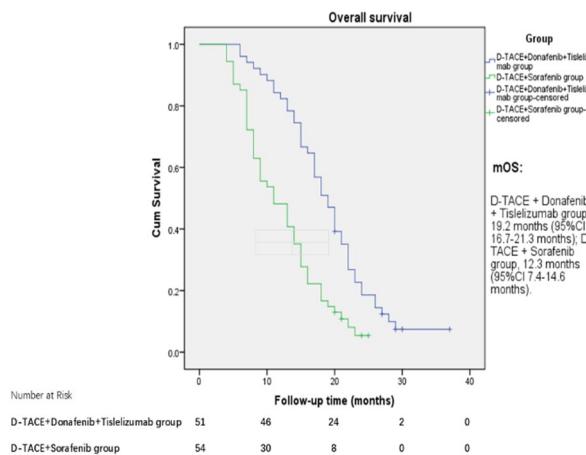


Fig. 2. Overall survival of patients in two groups mOS: D-TACE + Donafenib + Tisleizumab group, 19.2 months (95%CI 16.7–21.3 months); D-TACE + Sorafenib group, 12.3 months (95%CI 7.4–14.6 months).

Adverse events	Group				Chi-Square Tests(p-value)	
	D-TACE + Donafenib + Tisleizumab group (N=51)		D-TACE + Sorafenib group (N=54)			
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)	All grades	Grade 3/4
Abdominal pain	22(43.1%)	10(19.6%)	26(48.1%)	12(22.2%)	0.696	0.813
Fever	18(35.3%)	9(17.6%)	23(42.6%)	9(16.7%)	0.549	1.000
Vomiting	19(37.3%)	5(9.8%)	19(35.2%)	7(13.0%)	0.842	0.762
Hypertension	14(27.5%)	4(7.8%)	19(35.2%)	7(13.0%)	0.410	0.528
Diarrhea	8(15.7%)	3(5.9%)	8(14.8%)	2(3.7%)	1.000	0.672
Hand-foot syndrome	14(27.5%)	3(5.9%)	23(42.6%)	9(16.7%)	0.152	0.124
Rash	5(9.8%)	0(0.0%)	7(13.0%)	1(1.9%)	0.762	1.000
Proteinuria	7(13.7%)	2(3.9%)	10(18.5%)	5(9.3%)	0.600	0.438
Fatigue	6(11.8%)	1(2.0%)	19(35.2%)	4(7.4%)	0.006	0.364
Anorexia	7(13.7%)	3(5.9%)	19(35.2%)	5(9.3%)	0.013	0.717
Hypothyroidism	11(21.6%)	5(9.8%)	4(7.4%)	2(3.7%)	0.051	0.261

Table 5. Comparison of adverse events (AEs) between the two groups after Treatment.

postoperative recurrent HCC, with approximately 60% of patients undergoing TACE⁵⁶. Yiming Liu et al.⁵⁷ reported that the mOS and mPFS for recurrent HCC patients treated with TACE were 24 months and 9 months. TACE is particularly effective in improving survival rates in patients with multiple intrahepatic recurrences after resection⁵⁸. Studies have reported that TACE may represent a more effective therapeutic option than surgical resection or RFA for recurrent HCC patients with MVI positivity^{59,60}. Research indicates comparable efficacy between TACE combined with RFA and repeat surgery in treating recurrent HCC following hepatectomy⁶¹. Yonghua Bi et al.⁶² reported on 29 patients with unresectable or recurrent HCC treated with D-TACE, showing a mPFS of 25.7 months and a mOS of 33.9 months. Although TACE induces tumor necrosis, the embolization creates an ischemic and hypoxic microenvironment within the tumor, which can upregulate levels of hypoxia-inducible factor 1-alpha (HIF-1 α), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF), potentially leading to tumor recurrence and metastasis^{63–65}. To enhance the therapeutic efficacy of TACE, some studies have investigated TACE-based combination strategies. Among these, TACE combined with targeted therapy has emerged as a predominant therapeutic approach⁶⁶. Current targeted therapies for HCC predominantly utilize tyrosine kinase inhibitors (TKIs), which exert antitumor effects by suppressing tumor angiogenesis⁶⁷. Donafenib, a multi-targeted TKI, inhibits various receptor tyrosine kinases such as VEGFR and PDGFR, and directly suppresses several Raf kinases, thereby blocking the Raf/MEK/ERK signaling pathway. This dual inhibition and multi-target blocking provide anti-tumor effects^{68,69}. Mechanistically, donafenib can synergize with TACE to enhance therapeutic efficacy. Hao Li et al.⁷⁰ reported on clinical data from 388 HCC patients, comparing 157 patients treated with TACE plus donafenib and 166 patients treated with TACE plus donafenib and a PD-1 inhibitor. The mOS for the two groups was 13.2 months and 18.1 months, respectively, while the mPFS was 7.9 months and 10.6 months.

Immune checkpoint inhibitors (ICIs) are one of the commonly used treatments for HCC^{71–73}. PD-1 inhibitors and PD-L1 inhibitors^{74,75} can block the binding of immune checkpoint receptors on the surface of tumor cells with their ligands, restoring the function of immune cells. TACE combined with ICIs can achieve a synergistic

Characteristics	Univariate regression analysis		Multivariate regression analysis	
	P value	P value	HR (95%CI)	
Group/Treatment	<0.001	<0.001	0.180(0.104,0.313)	
Gender	0.587			
Age	0.950			
Etiology of cirrhosis	0.112			
Portal vein tumor thrombus	0.012	0.312	1.197(0.455,3.147)	
BCLC staging	0.023	0.169	0.458(0.173,1.359)	
Pre-treatment ECOG	0.041	0.220	1.275(0.641,2.535)	
AFP	0.036	0.001	0.110(0.032,0.383)	
Pre-treatment liver function	0.623			
Pre-treatment bilirubin	0.074	0.427	1.017(0.976,1.059)	
Pretreatment AST	0.755			
Pretreatment ALT	0.576			
Pretreatment WBC	0.887			
Pretreatment RBC	0.103			
Pretreatment PLT	0.308			

Table 6. Univariate regression analysis and multivariate regression analysis for OS.

Characteristics	Univariate regression analysis		Multivariate regression analysis	
	P value	P value	HR (95%CI)	
Group/Treatment	<0.001	<0.001	0.323(0.206,0.508)	
Gender	0.398			
Age	0.367			
Etiology of cirrhosis	0.245			
Portal vein tumor thrombus	0.048	0.016	0.422(0.209,0.853)	
BCLC staging	0.035	0.311	1.089(0.542,2.189)	
Pre-treatment ECOG	0.064	0.309	0.712(0.388,1.309)	
AFP	0.251			
Pre-treatment liver function	0.875			
Pre-treatment bilirubin	0.085	0.613	0.995(0.956,1.036)	
Pretreatment AST	0.162			
Pretreatment ALT	0.803			
Pretreatment WBC	0.507			
Pretreatment RBC	0.398			
Pretreatment PLT	0.071	0.274	0.622(0.339,1.142)	

Table 7. Univariate regression analysis and multivariate regression analysis for PFS.

effect⁷⁶. Following TACE, the release of tumor-associated antigens (TAAs) and inflammatory mediators facilitates immune system activation. However, TACE-induced hypoxia creates an immunosuppressive tumor microenvironment while upregulating PD-L1 expression in tumor tissues⁷⁷. Consequently, combining TACE with immune checkpoint inhibitors (ICIs) may reverse immunosuppression, enhance antigen-specific immune responses against HCC, and improve therapeutic efficacy. Qing-Qing Liu et al.⁷⁸ reported satisfactory therapeutic outcomes in 42 patients with uHCC treated with TACE combined with ICIs. Our previous study involving 169 patients with unresectable HCC compared 81 patients receiving TACE + Donafenib + Toripalimab with 88 patients receiving TACE + Sorafenib. The TACE + Donafenib + Toripalimab group exhibited longer OS and PFS⁷⁹.

The clinical efficacy of tislelizumab has been validated in multiple clinical studies^{80,81}. Current applications of TACE combined with targeted therapy and immunotherapy in HCC treatment demonstrate favorable therapeutic outcomes. Li Xu et al.⁸² reported on 64 patients with unresectable HCC treated with tislelizumab combined with lenvatinib, showing an ORR of 38.7% and a DCR of 90.3%, demonstrating promising anti-tumor activity and good tolerability. However, there are various targeted drugs and immune checkpoint inhibitors available for treating HCC, and different drug combinations present varying therapeutic effects. Identifying the optimal combination to maximize survival benefits for patients with postoperative recurrent HCC remains a key focus. In this study, we employed D-TACE combined with Donafenib and Tislelizumab for treating postoperative

recurrent HCC. The results indicated that the D-TACE + Donafenib + Tislelizumab group had higher ORR and DCR compared to the D-TACE + Sorafenib group ($P < 0.05$, Table 3). Furthermore, the D-TACE + Donafenib + Tislelizumab group demonstrated longer mPFS and mOS compared to the D-TACE + Sorafenib group ($P < 0.001$, Table 4). These findings suggest that this combined treatment approach more effectively controls tumor growth and disease progression in recurrent HCC and significantly extends patient survival. In this study, the D-TACE + sorafenib group demonstrated relatively shorter mPFS and mOS, which were generally consistent with findings from previous studies⁸³. Dailong Li et al.⁸⁴ found in a meta-analysis that while Sorafenib combined with TACE offers some clinical benefits compared to TACE alone, it does not seem to extend OS in HCC patients and is associated with a higher incidence of adverse events. Therefore, our study further confirms the effectiveness of D-TACE combined with Donafenib and Tislelizumab for treating postoperative recurrent HCC.

Three months after treatment, there were no statistically significant differences in liver function or blood routine indicators between the two groups. Compared to the TACE + Sorafenib group, the TACE + Donafenib + Tislelizumab group had a higher incidence of fatigue and anorexia (all grades), but there were no statistically significant differences in other adverse events (Table 5). One possible explanation for this is that Donafenib, a deuterated derivative of Sorafenib, has enhanced stability and reduced susceptibility to liver drug-metabolizing enzymes. This may result in higher plasma exposure and decreased toxic metabolites^{21,22}. In Phase II/III clinical studies³³, pharmacokinetic results of donafenib (200 mg, bid) and sorafenib (400 mg, bid) demonstrated that the plasma accumulation ratios of donafenib's parent drug and M2 metabolite were approximately 3.5- and 6-fold higher than those of sorafenib, respectively. This indicates that a lower dose of donafenib achieves comparable or superior pharmacodynamic effects to standard-dose sorafenib. Metabolites are critical contributors to drug toxicity. Phase I trials of donafenib revealed that its active metabolite M2 was significantly elevated compared to sorafenib, while other metabolites (M4, M6, M7) showed reduced systemic exposure⁸⁵. These pharmacokinetic differences may underlie the enhanced safety profile of donafenib. This may also contribute to the safety advantage of Donafenib. The TACE + Donafenib + Tislelizumab group had a higher incidence of thyroid dysfunction (all grades), but this was not statistically significant (Table 5). Thyroid dysfunction is a common adverse effect of targeted therapies and immunotherapies⁸⁶. Katalin Gabora et al.⁸⁷ reported that 33% of patients receiving tyrosine kinase inhibitors (TKIs) experienced clinical thyroid dysfunction. However, our study indicates that despite the addition of more medications, the TACE + Donafenib + Tislelizumab regimen did not significantly increase overall treatment-related AEs. This may be because, although the risk of immune therapy-related AEs increased, the reduced dose of the targeted drug did not significantly raise the overall risk of treatment-related AEs.

It is important to note that this study has several limitations. The study was only conducted in a single center, the sample size was relatively small, and the included patients may have certain regional and medical resource dependence, which limits the generalizability and external validity of the study results. Future research could employ a multi-center, prospective design to further validate our findings.

Conclusion

Compared to the D-TACE + Sorafenib group, the D-TACE + Donafenib + Tislelizumab group demonstrated higher ORR and DCR, as well as longer mPFS and mOS. In summary, the results of this study indicate that the combination of D-TACE with Donafenib and Tislelizumab shows promising efficacy and safety in treating postoperative recurrent HCC patients. This combined treatment regimen may offer a safe and viable strategy to improve the prognosis of patients with postoperative recurrent HCC. However, further research is necessary to more comprehensively evaluate its efficacy and safety and to optimize treatment strategies.

Data availability

The datasets used during the current study are available from the corresponding author upon request.

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Author contributions

Haohao Lu contributed to the conception and design of the work, the acquisition, analysis of data, as well as manuscript writing. Bin Liang and Xiangwen Xia contributed to the design of the work. Xuefeng Kan contributed to the acquisition, analysis of data. Chuansheng Zheng contributed to analysis, interpretation of data, and manuscript writing.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The medical ethics committee at Union Hospital, Tongji Medical College, Huazhong University of science and technology, Wuhan, Hubei Province approved the retrospective study. The requirement for informed consent was waived by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of science and technology due to the retrospective nature of the study. During follow-up, we informed patients about the study and they agreed to use their data. We confirmed that all methods were performed in accordance with the relevant guidelines and Declaration of Helsinki.

Additional information

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