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Original Article

Immunotherapy combined with targeted therapy and transcatheter arterial chemoembolization: a promising approach for advanced liver cancer

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Abstract: Objective: To investigate the clinical efficacy of combining immunotherapy and targeted therapy with transcatheter arterial chemoembolization (TACE) for advanced liver cancer. Methods: A retrospective analysis was performed on 144 patients with advanced liver cancer, divided into three groups based on treatment choice: TACE group, the TACE + immunotherapy group, and the TACE + immunotherapy + targeted therapy group, with 48 patients in each group. Short-term efficacy, T lymphocyte subsets (CD4+, CD8+, CD4+/CD8+), Th1/Th2 cytokines (interleukin-2 [IL-2], tumor necrosis factor-alpha [TNF-α], IL-4, IL-6), tumor markers (carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 199 [CA199], CA125), angiogenesis-related factors (vascular endothelial growth factor, vascular endothelial growth factor receptor, basic fibroblast growth factor, platelet-derived growth factor), and liver function indicators (alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin), adverse reactions, and long-term prognosis were compared. Results: Disease control rates for the three groups were 47.92%, 56.25%, and 77.08%, respectively. Objective response rates were 19.00%, 25.00%, and 45.83% (all $P < 0.05$). The combined therapy group showed significantly improved CD4+, CD8+, CD4+/CD8+, tumor markers, angiogenesis factors, and liver function indicators compared to the other groups (all $P < 0.05$). Progression-free and cumulative survival rates were also significantly better in the combined therapy group (both $P < 0.05$). Conclusion: Combining immunotherapy and targeted therapy with TACE offers significant advantages in treating advanced liver cancer, including improved tumor control, enhanced survival, better liver function, reduced tumor marker levels, and enhanced immune response, with a favorable safety profile.

Keywords: Immunotherapy, targeted therapy, transcatheter arterial chemoembolization, liver cancer

Introduction

Liver cancer is a prevalent malignant tumor, primarily affecting middle-aged and elderly individuals. According to the 2022 National Cancer Report, the incidence of primary liver cancer in China ranks fourth among all malignant tumors, with its mortality rate second only to lung cancer [1]. With societal development and lifestyle changes, the incidence of liver cancer has been rising, with an increasing trend among younger populations [2, 3].

The pathogenesis of liver cancer remains unclear, but risk factors include smoking, hepatitis virus infection, dietary exposure, and genetic predisposition. The disease often presents insidiously, with early-stage patients showing minimal clinical symptoms, leading to rapid progression. Due to low early screening rates in China, over 85% of patients are diagnosed at advanced stages, missing the optimal window for surgical treatment. This significantly limits treatment options and adversely affects life expectancy and quality of life [4, 5].

Transcatheter arterial chemoembolization (TACE) is the preferred treatment for intermediate to advanced liver cancer due to its minimal invasiveness and rapid postoperative recovery [6, 7]. However, survival benefits from TACE alone are not robust in some patients. Recent advancements in targeted therapies, molecular treatments, and immunotherapies offer new hope for these patients [8-11].

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The immune system plays a critical role in liver cancer progression. Programmed death-1 (PD-1), an immune checkpoint receptor, facilitates tumor immune escape, contributing to tumor development. Blocking PD-1 can elicit anti-tumor responses. Camrelizumab, a PD-1 inhibitor developed in China, enhances immune function by blocking the PD-1 pathway, showing promising results as a first-line treatment for liver cancer [12]. Lenvatinib, a multi-targeted tyrosine kinase inhibitor, demonstrates strong anti-angiogenic and anti-proliferative effects, although long-term use may lead to resistance [13].

Despite these advancements, monotherapies, including TACE, immunotherapy, or targeted therapy alone, often yield suboptimal survival outcomes. Therefore, combination therapies are increasingly utilized to enhance therapeutic efficacy [14]. The Chinese Society of Clinical Oncology guidelines recommend combination therapies for patients with advanced primary liver cancer [15]. Although recent studies have explored combined targeted and immunotherapy approaches, outcomes have varied.

This study explores the short-term clinical effects and long-term prognosis of combining TACE with camrelizumab and lenvatinib in treating advanced liver cancer. Additionally, it examines the treatment's effects on immune function, tumor markers, and angiogenesis, aiming to provide robust clinical evidence for optimizing advanced liver cancer management.

Materials and methods

Data collection

This retrospective study analyzed patients with advanced liver cancer treated at Harbin Medical University Cancer Hospital between November 2021 and November 2022. The study received approval from the Ethics Committee of the Harbin Medical University Cancer Hospital (Ethics Approval No.: YD2024-01).

Inclusion criteria: (1) Newly diagnosed patients meeting the diagnostic criteria for intermediate or advanced liver cancer [16]. (2) No prior treatment with targeted therapies, immunotherapies, or medications affecting study outcomes. (3) Age ≥ 18 years. (4) Complete clinical data available.

Exclusion criteria: (1) Concurrent immune or infectious diseases. (2) Neurological or psychiatric disorders. (3) Pregnant or breastfeeding women.

Treatment methods

Patients were categorized into three groups based on voluntary treatment choice: TACE group, TACE + immunotherapy group, and TACE + immunotherapy + targeted therapy group, with 50 patients per group. Due to dropout, 48 patients remained in each group.

TACE Group: Under anesthesia, the right femoral artery was punctured, and a 5F catheter was inserted for digital subtraction angiography to determine tumor location and size. Chemotherapy was administered through the feeding artery using carboplatin (Qilu Pharmaceutical Co., Ltd., National Drug Approval No.: H20020181) 200-300 mg, doxorubicin (Pfizer Pharmaceuticals (Wuxi) Co., Ltd., National Drug Approval No.: H20013334) 20-60 mg, and mitomycin (Zhejiang Hai Zheng Pharmaceutical Co., Ltd., National Drug Approval No.: H33020854) 10-20 mg. Embolization was performed with superfluid iodized oil, lobaplatin, and gelatin sponge particles. Postoperative care included gastric and liver protection.

TACE + Immunotherapy Group: Camrelizumab (Suzhou Shengdiya Biopharmaceutical Co., Ltd., National Drug Approval No.: S20190027) was added to TACE treatment, starting 7 days post-TACE and administered intravenously (3 mg/kg) every 21 days for 2 cycles.

TACE + Immunotherapy + Targeted Therapy Group: Lenvatinib (Eisai Co., Ltd., National Drug Approval No.: HJ20200044) was added to the treatment regimen, with oral administration beginning 7 days post-TACE in 3-week cycles for 2 cycles.

Observation indicators

Short-term clinical efficacy evaluation: Efficacy was assessed 6 months post-treatment. Complete remission (CR) indicated lesion disappearance; partial remission (PR) was a ≥ 30% reduction in lesion diameter; stable disease (SD) indicated a 20-30% reduction; and progressive disease (PD) failed to meet these criteria. Objective response rate was calculated as CR + PR, and disease control rate as CR + PR + SD [17].

Biomarker and cytokine analysis: Fasting venous blood samples (5 mL × 2) were collected before and 2 months after treatment. T lymphocyte subpopulations (CD4+, CD8+, CD4+/CD8+) were analyzed using flow cytometry (Beckman Coulter, USA). ELISA kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.) were used to measure:

Tumor Markers: carcinoembryonic antigen (CEA) (ml038471), alpha-fetoprotein (AFP) (ml092666), carbohydrate antigen 199 (CA199) (ml024075), CA125 (ml063596).

Angiogenesis Factors: basic fibroblast growth factor (bFGF) (ml062440), vascular endothelial growth factor (VEGF) (ml064281), vascular endothelial growth factor receptor (VEGFR) (ml062541), platelet-derived growth factor (PDGF) (ml063163).

Cytokines: interleukin 2 (IL-2) (ml098761), tumor necrosis factor alpha (TNF-α) (ml098760), IL-4 (ml058093), IL-6 (ml058097).

Liver function assessment: Liver function was evaluated before treatment (baseline) and 2 months post-treatment in all groups. Key indicators included alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), and total bilirubin (TBIL).

Adverse reaction evaluation: Adverse reactions during treatment were recorded, covering hematologic, gastrointestinal, urinary, circulatory, respiratory, skin, subcutaneous tissue, and immune system events. Adverse reactions were categorized by severity [18]:

Grade 1: Asymptomatic or mild symptoms. Grade 2: Requiring local or non-invasive treatment. Grade 3: Prolonged hospitalization needed. Grade 4: Life-threatening reactions. The incidence of adverse reactions in each group was analyzed.

Long-term prognosis assessment: Patients were followed up for 2 years through outpatient visits or telephone interviews. Disease progression or death served as primary outcomes.

Statistical analysis

Data were analyzed using SPSS 22.0. Measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and compared using one-way ANOVA (F-test). Count data were expressed as percentages and compared using the chi-square test (χ^2). Ordinal data were analyzed using the rank-sum test. Kaplan-Meier curves were used to compare overall survival, with $P < 0.05$ considered statistically significant.

Results

Comparison of general data

No significant differences were found among the three groups in age, gender, tumor size, pathological classification, or TNM stage (all $P > 0.05$). See **Table 1**.

Comparison of short-term efficacy

The TACE + immunotherapy + targeted therapy group showed significantly higher objective response and disease control rates than the TACE and TACE + immunotherapy groups (both $P < 0.05$). See **Table 2**.

Comparison of T lymphocyte subpopulation levels

Baseline levels of CD4+, CD8+, and CD4+/CD8+ were similar across all groups (all $P > 0.05$). Post-treatment, CD4+ and CD4+/CD8+ levels increased in all groups (all $P < 0.05$), with the TACE + immunotherapy + targeted therapy group showing the greatest improvement (all $P < 0.05$). See **Table 3**.

Comparison of liver function indicators

Before treatment, ALT, AST, TBIL, and ALB levels were comparable among groups (all $P > 0.05$). Post-treatment, ALT, AST, and TBIL levels decreased while ALB levels increased (all $P < 0.05$). The TACE + immunotherapy + targeted therapy group exhibited the most favorable liver function outcomes (all $P < 0.05$). See **Table 4**.

Comparison of Th1/Th2-related cytokines and angiogenesis-related factors

At baseline, there were no significant differences among the groups (all $P > 0.05$). Post-treatment, IL-4 and IL-6 levels increased, while IL-2, TNF-α, PDGF, bFGF, VEGF, and VEGFR levels decreased (all $P < 0.001$). The TACE + immunotherapy + targeted therapy group demon-

Table 1. Comparison of general data

Group	Age (years)	Gender (n)		Tumor size (n)		Pathological classification (n)		TNM staging (n)	
		Male	Female	≤ 5 cm	> 5 cm	Combined hepatocellular-cholangiocarcinoma	Intrahepatic cholangiocarcinoma	Stage III	Stage IV
TACE + immunotherapy + targeted therapy group (n=48)	58.9±9.4	30	18	12	36	1	47	29	19
TACE + immunotherapy group (n=48)	59.5±10.1	28	20	10	38	2	46	26	22
TACE group (n=48)	58.6±11.2	33	15	9	39	1	47	24	24
Statistics	0.096	1.135		0.576		0.514		1.066	
P	0.909	0.567		0.750		0.773		0.587	

Note: TACE: transcatheter arterial chemoembolization.

Table 2. Comparison of short-term efficacy

Group	CR (n)	PR (n)	SD (n)	PD (n)	Objective response rate (%)	Disease control rate (%)
TACE + immunotherapy + targeted therapy group (n=48)	4	18	15	11	45.83[a,b]	77.08[a,b]
TACE + immunotherapy group (n=48)	2	10	15	21	25.00[a]	56.25[a]
TACE group (n=48)	1	8	14	25	19	47.92
X^2					9.218	9.060
P					0.010	0.011

Note: CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease; TACE: transcatheter arterial chemoembolization. Compared to TACE group, [a]P < 0.05; Compared to TACE + immunotherapy group, [b]P < 0.05.

Table 3. Comparison of T lymphocyte subsets

Indicators	CD4+		CD8+		CD4+/CD8+	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
TACE + immunotherapy + targeted therapy group (n=48)	29.24±4.51	38.45±5.63[*,a,b]	28.35±4.64	29.16±3.49	1.01±0.21	1.33±0.24[*,a,b]
TACE + immunotherapy group (n=48)	30.12±5.34	32.12±4.01[*,a]	28.65±7.20	29.40±4.12	1.03±0.26	1.10±0.21[*,a]
TACE group (n=48)	29.46±4.49	30.08±3.71	28.19±4.25	29.01±4.47	1.01±0.33	1.06±0.31
t	0.438	44.570	0.086	0.113	0.087	15.458
P	0.646	< 0.001	0.918	0.893	0.917	< 0.001

Note: TACE: transcatheter arterial chemoembolization. Compared with before treatment within the group, [*]P < 0.05; Compared to TACE group, [a]P < 0.05; Compared to TACE + immunotherapy group, [b]P < 0.05.

Table 4. Comparison of liver function indicators

		TACE + immunotherapy + targeted therapy group (n=48)	TACE + immunotherapy group (n=48)	TACE group (n=48)	F	P
ALT (U/L)	Before treatment	98.27±15.44	97.79±14.38	97.49±17.23	0.030	0.970
	After treatment	41.04±10.19^{*,a,b}	58.33±9.21^{*,a}	64.67±8.25	83.905	< 0.001
AST (U/L)	Before treatment	58.79±9.23	59.22±11.49	58.59±10.21	0.046	0.955
	After treatment	40.56±7.27^{*,a,b}	43.45±6.31^{*,a}	48.90±6.28	19.737	< 0.001
ALB (g/L)	Before treatment	28.37±4.55	27.91±5.12	28.56±6.18	0.189	0.828
	After treatment	36.02±4.24^{*,a,b}	32.46±4.83^{*,a}	30.43±3.12	22.590	< 0.001
TBIL (μmol/L)	Before treatment	68.83±12.35	69.07±15.12	68.42±11.46	0.030	0.970
	After treatment	45.42±7.11^{*,a,b}	53.68±9.27^{*,a}	58.90±7.29	35.082	< 0.001

Note: Compared with before treatment within the group, *P < 0.05; Compared to TACE group, ^{a}P < 0.05; Compared to TACE + immunotherapy group, ^{b}P < 0.05. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; TBIL: total bilirubin; TACE: transcatheter arterial chemoembolization.

Table 5. Comparison of Th1/Th2 related cytokines and angiogenesis-related indicators

		TACE + immunotherapy + targeted therapy group (n=48)	TACE + immunotherapy group (n=48)	TACE group (n=48)	F	P
IL-2 (ng/L)	Before treatment	26.88±3.37	27.04±4.21	26.71±5.04	0.072	0.931
	After treatment	14.52±3.06^{*,a,b}	18.27±3.25^{*,a}	22.31±4.08	59.762	< 0.001
TNF-α (ng/L)	Before treatment	35.41±4.03	34.97±5.22	34.78±5.16	0.214	0.807
	After treatment	20.55±4.17^{*,a,b}	25.16±3.94^{*,a}	28.11±4.14	41.768	< 0.001
IL-4 (ng/L)	Before treatment	32.38±5.13	31.86±6.05	32.15±7.32	0.084	0.920
	After treatment	54.24±6.19^{*,a,b}	43.87±6.56^{*,a}	38.24±6.42	77.392	< 0.001
IL-6 (ng/L)	Before treatment	19.68±3.35	20.11±4.13	19.82±4.93	0.132	0.877
	After treatment	13.02±2.29^{*,a,b}	15.83±3.17^{*,a}	17.24±3.09	26.755	< 0.001
PDGF (μg/L)	Before treatment	2.11±0.24	2.19±0.31	2.28±0.49	2.645	0.075
	After treatment	1.16±0.25^{*,a,b}	1.54±0.28^{*,a}	1.85±0.21	92.964	< 0.001
bFGF (ng/L)	Before treatment	155.27±23.04	160.12±34.91	158.94±30.17	0.346	0.708
	After treatment	115.37±14.29^{*,a,b}	127.42±12.98^{*,a}	135.95±11.45	30.561	< 0.001
VEGF (ng/L)	Before treatment	452.49±37.50	446.72±49.74	453.10±51.33	0.274	0.761
	After treatment	374.01±24.45^{*,a,b}	407.63±27.85^{*,a}	424.19±23.51	48.476	< 0.001
VEGFR (ng/L)	Before treatment	7287.19±354.21	7308.41±421.07	7314.69±445.38	0.060	0.942
	After treatment	5832.34±219.24^{*,a,b}	6345.61±247.72^{*,a}	6541.18±223.64	121.041	< 0.001

Note: Compared with before treatment within the group, *P < 0.05; compared to TACE group, ^{a}P < 0.05; compared to TACE + immunotherapy group, ^{b}P < 0.05. IL: interleukin; TNF-α: tumor necrosis factor-alpha; TACE: transcatheter arterial chemoembolization; bFGF: basic fibroblast growth factor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; PDGF: platelet-derived growth factor.

strated significantly better cytokine and angiogenesis factor profiles than the other groups (all P < 0.001). See **Table 5**.

Comparison of tumor marker levels

There were no significant differences in CEA, AFP, CA199, and CA125 levels before treatment (all P > 0.05). After treatment, all groups showed reductions in these tumor markers (all P < 0.001). The TACE + immunotherapy + targeted therapy group had the most significant decrease in tumor marker levels (all P < 0.001). See **Table 6**.

Comparison of adverse reaction incidence

TACE + immunotherapy + targeted therapy group: 7 cases of gastrointestinal discomfort, 4 cases of fatigue, 1 case of hand-foot syndrome (25% incidence). TACE + immunotherapy group: 7 cases of gastrointestinal discomfort, 5 cases of fatigue, 4 cases of hand-foot syndrome (33.33% incidence). TACE group: 10 cases of gastrointestinal discomfort, 5 cases of hand-foot syndrome, 3 cases of fatigue (37.50% incidence). There was no statistically significant difference in the incidence of adverse reactions among the groups (P=0.961). See **Table 7**.

Comparison of progression-free survival and overall survival

At follow-up, the TACE + immunotherapy + targeted therapy group had 31 patients remaining progression-free, with a progression-free sur-

Table 6. Comparison of tumor marker levels

Group	CEA (μg/L)		AFP (μg/L)		CA199 (U/L)		CA125 (U/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
TACE + immunotherapy + targeted therapy group (n=48)	95.33±14.68	24.16±7.73^{*,a,b}	334.58±42.19	101.48±17.29^{*,a,b}	181.09±21.34	42.36±10.27^{*,a,b}	78.43±13.42	35.29±9.93^{*,a,b}
TACE + immunotherapy group (n=48)	96.01±15.24	30.22±8.51^{*,a}	328.64±43.17	130.42±22.31^{*,a}	178.44±29.36	61.19±12.38^{*,a}	80.21±15.12	42.16±10.21^{*,a}
TACE group (n=48)	95.20±12.47	53.99±10.24	330.18±49.22	178.93±25.97	177.26±30.14	112.36±24.29	80.34±16.77	61.04±12.56
F	0.045	151.025	0.226	149.914	0.249	222.624	0.238	70.995
P	0.956	< 0.001	0.798	< 0.001	0.780	< 0.001	0.789	< 0.001

Note: Compared with before treatment within the group, $^{*}P < 0.05$; compared to TACE group, $^{a}P < 0.05$; compared to TACE + immunotherapy group, $^{b}P < 0.05$. CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; CA: carbohydrate antigen; TACE: transcatheter arterial chemoembolization.

Table 7. Comparison of incidence of adverse reactions

Group	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Total incidence (%)
TACE + immunotherapy + targeted therapy group (n=48)	7	3	2	0	25
TACE + immunotherapy group (n=48)	9	4	2	1	33.33
TACE group (n=48)	10	4	3	1	37.50
U					0.080
P					0.961

Note: TACE: transcatheter arterial chemoembolization.

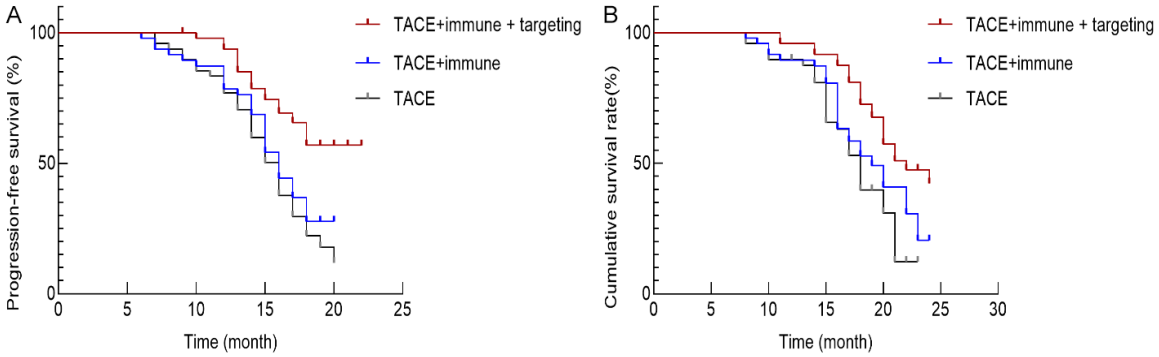

Figure 1. Kaplan-Meier curve among groups. A: Comparison of progression-free survival; B: Comparison of overall survival.

vival rate of 64.60% and a median progression-free survival time of 18.90 (17.72, 20.08) months. The TACE + immunotherapy group had 26 progression-free patients, with a rate of 54.20% and a time of 15.61 (14.35, 16.88) months. The TACE group had 13 progression-free patients, with a rate of 27.10% and a time of 15.13 (14.04, 16.22) months. These differences were statistically significant (Log Rank =13.753, P=0.001; **Figure 1A**).

Regarding overall survival, 25 patients in the TACE + immunotherapy + targeted therapy group remained alive at the time of study, with a cumulative survival rate of 52.10% and a median survival time of 20.83 (19.73, 21.93) months. In the TACE + immunotherapy group, 21 patients survived, with a survival rate of 43.80% and a time of 18.79 (17.43, 20.15) months. The TACE group had 17 surviving patients, with a rate of 35.40% and a time of 17.46 (16.26, 18.65) months. These differences were also statistically significant (Log Rank =12.314, P=0.002; **Figure 1B**).

Discussion

Liver cancer typically presents with an insidious onset, leading to late-stage diagnoses in most patients. Fewer than 30% of patients are eligible for surgical intervention, and even among those, the postoperative recurrence rate remains high. Thus, enhancing the survival and prognosis of advanced liver cancer patients is a critical clinical challenge.

TACE offers several benefits, including minimal invasiveness and a favorable safety profile. It effectively controls tumor progression and prolongs survival, establishing itself as a primary treatment for advanced liver cancer. However, studies indicate that TACE may reduce chemotherapy sensitivity, limiting its efficacy in eradicating residual tumor cells around the lesion. Additionally, TACE can induce tumor cell ischemia and hypoxia, triggering the secretion of VEGF-related factors, which promotes tumor angiogenesis and recurrence, complicating treatment [19-21]. Therefore, combining TACE with other therapies is often necessary to achieve improved therapeutic outcomes.

In recent years, immunotherapy, particularly the blockade of the PD-1/PD-L1 pathway, has shown promise in inhibiting tumor progression [22]. Camrelizumab, a PD-1 inhibitor developed in China, enhances T lymphocyte function and has been proposed as a first-line treatment for

liver cancer [23]. Previous studies reported a short-term efficacy rate of 56.9% and a survival rate of 64.3% for camrelizumab in combination with TACE for intermediate to advanced liver cancer [24]. In this study, the short-term efficacy was 56.25% and the survival rate was 43.80%. The discrepancies may result from differences in patient populations, disease severity, and treatment regimens across studies.

Targeted therapies inhibit tumor cell proliferation and angiogenesis. Clinical guidelines recommend lenvatinib, sorafenib, and donafenib as first-line treatments for advanced liver cancer. Lenvatinib, in particular, effectively suppresses microvascular regeneration following TACE. A retrospective study involving 61 advanced liver cancer patients demonstrated that lenvatinib provided significant clinical benefits with a favorable safety profile [25]. However, some studies have reported acquired resistance to lenvatinib within six months of treatment, leading to poor long-term outcomes [26]. This resistance likely arises because while most tumor cells are eliminated by lenvatinib, surviving cells adapt to the drug, fostering potential tumor recurrence and metastasis. Thus, combining lenvatinib with other therapies is necessary to achieve sustained clinical benefits.

In tumor tissues, the blood vessels differ structurally and functionally from normal vessels. Anti-angiogenic therapies can remodel the tumor microenvironment. Since angiogenesis is closely linked to immune regulation, targeted therapies not only inhibit tumor cell proliferation and neovascularization but also modulate the immune landscape of the tumor microenvironment. By combining PD-1/PD-L1 pathway inhibition with VEGF inhibitors, these therapies can reduce immune suppression and improve the efficacy of immunotherapy [27, 28]. Previous studies have shown that combining lenvatinib with camrelizumab offers high therapeutic efficacy and safety in patients undergoing TACE [29].

This study found that patients receiving TACE combined with lenvatinib and camrelizumab had significantly higher objective response and disease control rates than those receiving TACE alone or TACE with camrelizumab. The disease control rate reached 77.06%, indicating that combining immunotherapy with targeted therapy enhances tumor control and achieves better short-term survival outcomes. Additionally, the combination therapy group exhibited improved liver function and lower tumor marker levels, further supporting these findings.

Angiogenesis-related factors, including PDGF, bFGF, VEGF, and VEGFR, supply nutrients to tumors, promoting tumor proliferation and differentiation [30]. This study showed that combining TACE with lenvatinib and camrelizumab significantly reduced these factors' levels, demonstrating strong anti-angiogenic effects.

T lymphocyte levels are critical in tumor progression. Previous studies indicated that camrelizumab could boost T lymphocyte activity, exerting a potent anti-tumor effect [31]. This study expanded on these findings by demonstrating that combined immunotherapy and targeted therapy not only increased T lymphocyte subpopulation levels but also improved Th1/Th2-related cytokine profiles. These immune enhancements were significantly greater than those observed in the TACE or TACE + camrelizumab groups, highlighting the immune-boosting potential of the combination therapy.

Patients receiving combined immunotherapy and targeted therapy showed significantly improved progression-free survival and overall survival compared to those treated with TACE alone or TACE + camrelizumab. Importantly, no Grade 4 or higher adverse reactions occurred in the combination therapy group. Adverse reactions were generally mild and resolved with symptomatic treatment, underscoring the safety of this therapeutic strategy.

This study has several limitations: The study's single-center approach and small sample size may introduce bias. The clinical effects of TACE combined with immunotherapy and targeted therapy on different liver cancer types were not evaluated, necessitating further research to obtain more accurate efficacy data.

In conclusion, the combination of immunotherapy, targeted therapy, and TACE demonstrates significant advantages in treating advanced liver cancer, including better tumor control, enhanced survival outcomes, improved liver function, reduced tumor marker levels, strengthened immune function, and a strong safety profile. These findings provide valuable insights for

clinical practice and warrant broader clinical application.

Disclosure of conflict of interest

None.

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