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ORIGINAL RESEARCH

Efficacy and Safety of Transarterial Chemoembolization Plus Lenvatinib with or Without Tislelizumab as the First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Propensity Score Matching Analysis

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Purpose: To compare the efficacy and safety of transarterial chemoembolization (TACE) plus lenvatinib and tislelizumab (TACE-Len-T) versus TACE plus lenvatinib (TACE-Len) as the first-line treatment for patients with unresectable hepatocellular carcinoma (uHCC).

Patients and Methods: This retrospective study included 136 uHCC patients treated with TACE-Len-T or TACE-Len from January 1, 2021, to June 30, 2023. Clinical outcomes including overall survival (OS), progression-free survival (PFS), tumor response and adverse events (AEs) were compared between the two groups. The risk factors affecting OS and PFS were also analyzed.

Results: The median OS and PFS of the TACE-Len-T group were significantly longer than those of the TACE-Len group (Median OS: not reached vs 13.8 months, P<0.001; Median PFS: 13.0 months vs 2.7 months, P<0.001). The best overall objective response rate (ORR) was also better with TACE-Len-T treatment (ORR: 72.1% vs 29.4%, P<0.001), and the disease control rate (DCR) significantly increased in the TACE-Len-T group (88.2% vs 48.5%, P<0.001). Multivariate analyses revealed that TACE-Len treatment, tumor number >3, and cTACE were independent risk factors for OS, whereas TACE-Len treatment was the only independent risk factor for PFS. The frequency and severity of AEs in the TACE-Len-T group were comparable to those in the TACE-Len group (any grade: 92.6% vs 91.2%, P=0.753; grade 3 or 4: 33.8% vs 32.3%, P=0.855).

Conclusion: TACE-Len-T treatment significantly improved OS, PFS, ORR, and DCR over TACE-Len treatment, with a manageable safety profile in uHCC.

Keywords: unresectable hepatocellular carcinoma, transarterial chemoembolization, lenvatinib, tislelizumab, immunotherapy

Introduction

Primary liver cancer is the sixth most common and fourth most lethal malignancy worldwide. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for approximately 90% of all cases.[1] Although surgical resection, radiofrequency ablation, and liver transplantation can provide curative potential for HCC, a large proportion of patients with HCC are diagnosed with advanced disease that is not suitable for these treatments; thus, the prognosis of most HCC remains poor.[2,3] Recently, systemic therapies for advanced HCC have attracted considerable attention.[4]

Tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib, are recommended as the first-line treatment for advanced HCC, but the efficacy of TKI monotherapy is far from satisfactory. Recent randomized trials demonstrated that

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sorafenib only achieved 2.8 months survival benefits compared to placebo.[5,6] Despite implementing a high response rate, lenvatinib only exhibited non-inferiority and provided limited overall survival benefits compared with sorafenib.[7] In this setting, transcatheter arterial chemoembolization (TACE) is applied to provide local disease control for advanced HCC with preserved liver function and encouraging survival outcomes.[8] However, TACE can also aggravate hypoxia in residual tumors,[9] resulting in the upregulation of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which facilitates tumor angiogenesis.[10,11] Thus, the combination of TACE with antiangiogenic agents may effectively offset hypoxia-induced angiogenesis after TACE and improve the survival outcomes of advanced HCC. A randomized, multicenter prospective trial reported that TACE plus sorafenib significantly improved progression-free survival (PFS) in patients with unresectable HCC compared with TACE alone.[12] Another randomized clinical trial (LAUNCH) indicated that TACE combined with lenvatinib improved the clinical efficacy of lenvatinib monotherapy in patients with advanced HCC.[13] These studies suggest that the combination of TACE with TKIs significantly improves clinical outcomes compared with monotherapy for advanced HCC. However, other studies found that the combination of TACE with TKIs, such as sorafenib, brivanib, and olantinib, did not improve clinical outcomes in advanced HCC compared to TACE alone.[14–16]

Recently, immune checkpoint inhibitors (ICIs), including programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, have shown promising clinical benefits as second-line treatment for advanced HCC based on Phase I/II clinical trials (CheckMate040, KEYNOTE-224).[4,17,18] However, in the Phase III trials, nivolumab and pembrolizumab both failed to significantly improve clinical outcomes compared to the standard of care.[19,20] These studies showed that the benefits of monotherapy with ICIs were limited. Previous studies have shown that lenvatinib can alleviate immunosuppressive tumor microenvironment (TME) by inhibiting VEGF and increasing populations of tumor-infiltrating T lymphocytes, indicating its potential synergistic effect with ICIs.[21,22] Combined immunotherapy with other therapies such as TACE may be a potential strategy to improve the efficacy of immunotherapy, where combination strategies might include two types of ICIs (anti-PD-1/PD-L1 and CTLA-4 antibodies), anti-PD-1/PD-L1 antibody with TKIs, and anti-PD-1/PD-L1 or CTLA-4 antibodies, along with TACE.[23] Although phase III trials for anti-PD-1 monotherapy failed to improve overall survival (OS), the combination of PD-1/PD-L1 inhibitors with TKIs exhibited encouraging results. In a recent phase Ib study evaluating the efficacy and safety of lenvatinib and pembrolizumab in unresectable HCC (uHCC), an objective response rate (ORR) of 46.0% and a median OS of 22 months were achieved.[24] Another study (IMbrave150) indicated that the combination of PD-L1 antibodies with bevacizumab has reached a remarkable outcome and has been approved as the first-line therapy for advanced HCC.[25]

In addition to lenvatinib, TACE has potential in combination with immunotherapy. As a locoregional therapy, TACE causes embolization of the tumor microcirculation, resulting in necrosis of tumor tissues, and release of tumor antigens, which could enhance immunotherapy efficacy by reinforcing anti-tumor immunity.[26] Previous research indicated that the hypoxic response induced by TACE not only upregulated the expression of VEGF but also stimulated immune responses, and the post-TACE TME correlated with less intratumoral exhausted effector T cells ($CD8^+PD\text{-}1^+$) and T regulatory cells ($CD4^+FOXP3^+$).[27] Based on this theory, TACE, lenvatinib and tislelizumab may achieve a synergistic effect in combination. Combination therapy may be a promising complement to TACE for patients with advanced TACE-refractory HCC. However, whether patients with uHCC can obtain survival benefits from TACE combined with lenvatinib plus tislelizumab (TACE-Len-T) remains unclear. Therefore, it is worth studying whether TACE-Len-T treatment could be beneficial in patients with uHCC compared to TACE in combination with lenvatinib (TACE-Len).

During the past three years, a subset of patients with uHCC undergoing TACE also received oral TKIs (eg, sorafenib, lenvatinib) or a combination of TKIs (eg, sorafenib, lenvatinib) with ICIs (eg, pembrolizumab, sintilimab, camrelizumab and tislelizumab) in our hospital. And we especially concerned clinical outcomes of TACE-Len-T in the treatment of uHCC. Therefore, we comprehensively evaluated the efficacy and safety of triple combination TACE-Len-T versus double combination TACE-Len in uHCC in this retrospective comparative study.

Material and methods

Study Design and Patients

From January 1, 2021, to June 30, 2023, the data of consecutive patients with uHCC treated with TACE at our center were collected and analyzed. Among these patients, those treated with TACE in combination with lenvatinib and tislelizumab were assigned to the TACE-Len-T group. Patients who underwent TACE combined with lenvatinib were classified into the TACE-Len group. All patients were histologically or clinically diagnosed with HCC according to the standards of the American Association for the Study of Liver Diseases (AASLD). This retrospective study was approved by the ethics committee of Southwest Hospital, Army Medical University. The number of ethics approval was (B) KY2024005. The study was registered on https://www.chictr.org.cn and the research registration number was ChiCTR2400079715. The data in the article were anonymous, and the requirement for written informed consent was waived due to the retrospective nature of the study. This study was performed in accordance with the principles of the Declaration of Helsinki. The work has been reported in line with the STROCSS criteria.[28]

The inclusion criteria were as follows: (1) age between 18 and 75 years; (2) histologically or clinically confirmed diagnosis of HCC; (3) one or more measurable tumor lesions on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) using the modified Response Evaluation Criteria in Solid Tumors (mRECIST criteria); (4) Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC; (5) HCC were considered unresectable either because they were already intermediate or advanced stage HCC or because of insufficient remnant liver volume after surgical resection (<40% for patients with liver cirrhosis; <30% for patients without liver cirrhosis);[29] (6) Child-Pugh class A or B; (7) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0–1; (8) prior resection, radiofrequency ablation or TACE; (9) no previous systemic therapy.

The exclusion criteria were as follows: (1) secondary malignant tumor in addition to HCC; (2) Child-Pugh class C; (3) any contraindication to TACE, lenvatinib, or tislelizumab; (4) presence of severe comorbidities, including severe cardiac, pulmonary, renal or coagulation dysfunction; and (5) incomplete clinical or follow-up information.

TACE Procedure

All patients underwent standard conventional TACE (cTACE) or drug-eluting bead TACE (DEB-TACE) according to the treatment plans formulated by multidisciplinary consultation including hepatobiliary surgeons, oncologists, radiologists, and interventionalists. The procedures were performed by interventionalists with more than 5 years of experience. TACE was performed by puncturing the right femoral artery. Under the guidance of digital subtraction angiography (DSA), a 5-F catheter was placed into the hepatic artery and a 3-F microcatheter was inserted selectively into the tumor-supplying artery. For cTACE, an emulsion of 2–20 mL lipiodol and 20–60 mg epirubicin was administered into the tumor-feeding arteries, followed by embolization with polyvinyl alcohol particles. For DEB-TACE, CalliSpheres (Hengrui Medical, Suzhou, China) or DC Bead (Biocompatibles, Farnham, Surrey, UK) 100–300 μm in diameter, were used as the drug carrier and embolization agent. One vial of beads was loaded with 60 mg of epirubicin. Gelatin sponge particles (350–710 μm, Alicon, Hangzhou, China) were used to completely embolize the tumor-feeding arteries. Finally, hepatic artery angiography was performed to validate complete embolism of the tumor-feeding arteries.

TACE was repeated based on evidence of viable residual tumor or recurrence on contrast-enhanced CT or MRI. TACE was discontinued if hepatic function deteriorated to Child-Pugh class C, ECOG PS >2, or if the tumor continued progressed after three TACEs.

Lenvatinib and Tislelizumab Administration

Lenvatinib and tislelizumab were administrated within seven days after TACE. For patients receiving TACE-Len-T or TACE-Len treatment, lenvatinib was recommended at a dose of 8 mg (<60 kg) or 12 mg (≥60 kg) once daily, based on body weight. Tislelizumab (BeiGene, Shanghai, China) was injected intravenously at a dose of 200 mg every three weeks. Dose reduction was allowed when grade 3 or 4 of adverse events occurred. Drug administration was continued until disease progression or unacceptable toxicity was observed. The interruption and discontinuation of drug administration depended on the presence and severity of adverse events (AEs) according to the drug direction.

Follow-Up and Assessments

The first follow-up was conducted at 4-week intervals after TACE therapy, and routine follow-up was recommended every 6–9 weeks. Each follow-up included physical examination, laboratory investigations (complete blood count, biochemistry test, coagulation panel, α-fetoprotein (AFP), protein induced by vitamin K absence-II (PIVKA-II), thyroid function test, myocardial enzymes, and contrast CT or MRI). All AEs were recorded and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Tumor responses were evaluated by two independent radiologists with more than five years of experience, based on contrast-enhanced CT or MRI. Tumor responses were categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), according to the mRECIST criteria. Patients were followed-up regularly until death or at the end of the study (September 30, 2023).

Outcomes

The primary endpoints were OS and PFS. The OS and PFS were compared between the TACE-Len-T and TACE-Len group. OS was defined as the time from the first TACE procedure to death for any reason or the last follow-up. PFS was defined as the time from the first TACE procedure to disease progression or last follow-up. The secondary endpoints were ORR, DCR, and safety. The ORR was defined as the percentage of patients with CR or PR, and DCR was defined as the percentage of patients with CR, PR, or SD. The incidence and severity of AEs were recorded and assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).

Propensity Score Matching (PSM) Analysis

PSM analysis was conducted to reduce bias in patient selection and to compare the differences between the TACE-Len-T and TACE-Len group. Variables including sex, age, Child-Pugh class were matched in our model. One-to-one matching without replacement was applied, and the caliper value was 0.05.

Statistical Analysis

To compare the differences in baseline characteristics between the two groups, Fisher's exact test or $\chi 2$ test was used to compare categorical variables, presented as numbers (percentages), and Student's *t*-test was performed for continuous variables, presented as mean ± standard deviation (SD). Kaplan–Meier analysis was used to plot the OS and PFS curves, and significance was calculated using the Log rank test. Cox proportional regression analysis was used to calculate potential factors that might influence OS or PFS in all patients. Factors with p-values no more than 0.05 in the univariable analysis were included in the multivariate analysis. Differences were considered statistically significant when the p-value was less than 0.05 (two-tailed). All statistical analyses were conducted using the SPSS software (version 26.0; IBM, Armonk, NY, USA).

Results

Patient Characteristics

During the study period, 149 patients with uHCC who received TACE-Len-T or TACE-Len were screened and included in the study. Among these, 13 were excluded based on the exclusion criteria (Figure 1). After PSM analysis, 136 patients remained (68 in each group). The detailed baseline characteristics of the patients are listed in Table 1. In each group, about half of the patients had vascular invasion and one-quarter had extrahepatic metastasis. Other parameters were also comparable between the two groups. There were no significant differences in the baseline demographic, clinical and tumor characteristics. In the TACE-Len-T group, the number of cycles of tislelizumab ranged from 1 to 35, with a median of 6.

Survival

The follow-up duration ranged from 2.5 to 32.2 months, with a median of 11.1 months. At the clinical cut-off date, 14 patients (20.6%) in the TACE-Len-T group and 30 patients (44.1%) in the TACE-Len group died. The median OS was not reached in the TACE-Len-T group and was significantly longer than that in the TACE-Len group (13.8 months, 95% confidence interval

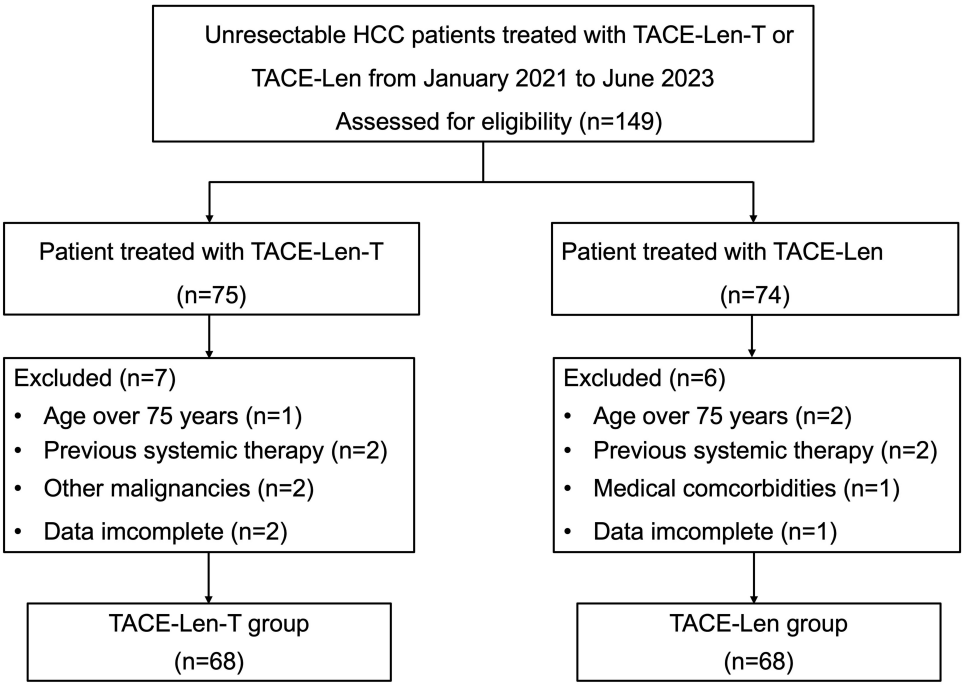


Figure 1 Flow diagram of patient enrollment. HCC, Hepatocellular carcinoma; TACE+Len+T, transarterial chemoembolization combined with lenvatinib plus tislelizumab; TACE+Len, transarterial chemoembolization combined with lenvatinib; TACE, transarterial chemoembolization.

(CI), 7.5–20.1), P<0.001) (Figure 2). The median PFS was also significantly longer in the TACE-Len-T group than in the TACE-Len group (median, 13.0 months, 95% CI, 7.6–18.4) vs 2.7 months, 95% CI 1.9–3.5) (P<0.001). These results indicated that TACE-Len-T group had better OS and PFS than TACE-Len group.

Table 1 The Baseline Characteristics of Patients Enrolled

Characteristics	TACE+Len+T group (n=68)	TACE+Len group (n=68)	P value
Gender			
Male	59 (86.8)	58 (85.3)	0.805
Female	9 (13.2)	10 (14.7)	
Age (mean±SD, years)	55.3±9.1	55.2±12.3	0.949
<60	51 (75.0)	43 (63.2)	0.138
≥60	17 (25.0)	25 (36.8)	
Etiology			
HBV	60 (88.2)	61 (89.7)	0.784
Others	8 (11.8)	7 (10.3)	
ECOG PS			0.834
0	54 (79.4)	53 (77.9)	
1	14 (20.6)	15 (22.1)	

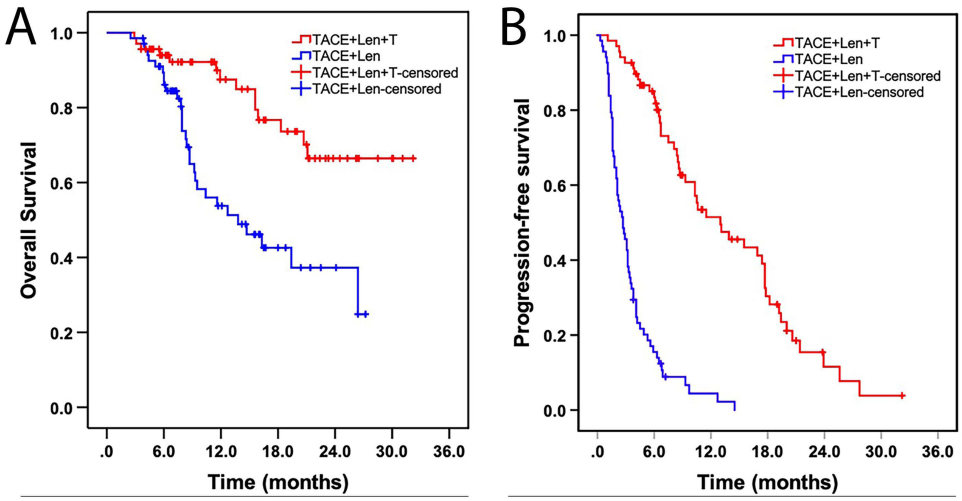
(*Continued*)

Table 1 (Continued).

Characteristics	TACE+Len+T group (n=68)	TACE+Len group (n=68)	P value
Child-Pugh class			
A	61 (89.7)	59 (86.8)	0.595
B	7 (10.3)	9 (13.2)	
BCLC stage			0.855
B	23 (33.8)	22 (32.4)	
C	45 (66.2)	46 (67.6)	
Tumor size (cm)			0.114
<5	31 (45.6)	22 (32.4)	
≥5	37 (54.4)	46 (67.6)	
Number of tumors			0.121
≤3	35(51.5)	26(38.2)	
>3	33(48.5)	42(61.8)	
Vascular invasion			0.298
Yes	36 (52.9)	42 (61.8)	
No	32 (47.1)	26 (38.2)	
Extrahepatic metastasis			0.317
Yes	14 (20.6)	19 (27.9)	
No	54 (79.4)	49 (72.1)	
AFP (μg/L)			0.397
<400	44 (64.7)	39 (57.4)	
≥400	24 (35.3)	29 (42.6)	
PIVKA-II (mAU/mL)			0.385
<400	31 (45.6)	26 (38.2)	
≥400	37 (54.4)	42 (61.8)	
TACE times			0.097
<3	61 (89.7)	54 (79.4)	
≥3	7 (10.3)	14 (20.6)	
TACE technique			0.480
cTACE	24 (35.3)	28 (41.2)	
DEB-TACE	44 (64.7)	40 (58.8)	

Notes: Data were presented as n (%) or mean ± standard deviation.

Abbreviations: TACE+Len+T, transarterial chemoembolization combined with lenvatinib plus tislelizumab; TACE+Len, transarterial chemoembolization combined with lenvatinib; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, Hepatitis B virus; BCLC, Barcelona clinic liver cancer; AFP, α-fetoprotein; PIVKA-II, Protein induced by vitamin K absence-II; TACE, transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization.



Number at risk

Months	0	6	12	18	24	30	36
TACE-Len-T	68	56	35	25	10	3	0
TACE-Len	68	53	23	9	4	0	0

Number at risk

Months	0	3	6	9	12	15	18
TACE-Len-T	68	63	51	34	26	21	14
TACE-Len	68	31	10	4	2	0	0

Figure 2 Kaplan-Meier analysis of overall survival (**A**) and progression-free survival (**B**) according to treatment groups. TACE+Len+T, transarterial chemoembolization combined with lenvatinib plus tislelizumab; TACE+Len, transarterial chemoembolization combined with lenvatinib.

Prognostic Factors Analysis

Based on the results of univariate and multivariate analyses, we identified independent prognostic factors associated with OS and PFS. Univariate analysis showed that treatment options (TACE-Len-T vs TACE-Len, Hazard ratio [HR]= 0.318; 95% CI, 0.167–0.604; P < 0.001), number of tumors (> 3 vs ≤3, HR = 1.898, 95% CI: 1.004–3.586; P = 0.049), AFP levels (> 400 vs ≤400, HR =1.901, 95% CI: 1.047–3.454; P = 0.035), and TACE technique type (DEB-TACE vs cTACE, HR = 0.397, 95% CI: 0.190–0.826; P = 0.013) were independent factors for OS. Moreover, multivariate analyses showed that only the treatment option (TACE-Len-T vs TACE-Len, HR=0.309, 95% CI, 0.161–0.595; P < 0.001), tumor number (> 3 vs ≤3, HR =2.068, 95% CI: 1.086–3.936; P = 0.027) and type of TACE technique (DEB-TACE vs cTACE, HR = 0.333, 95% CI: 0.158–0.699; P = 0.004) were significantly independent factors for OS. Similarly, univariate analysis revealed that treatment options (TACE-Len-T vs TACE-Len, HR=0.144; 95% CI, 0.091–0.229; P < 0.001) and TACE times (≥3 vs < 3, HR= 1.849; 95% CI, 1.140–3.000; P = 0.013) were independent prognostic factors for PFS. In addition, multivariate analyses showed that only the treatment option (TACE-Len-T vs TACE-Len, HR=0.145; 95% CI, 0.091–0.232; P < 0.001) was a significant independent factor for PFS (Table 2).

Subgroup analyses showed that TACE-Len-T group had better OS and PFS than TACE-Len group (Figure 3). Subgroup analyses of factors for OS indicated that TACE-Len-T treatment could provide a superior survival benefit in patients with hepatitis B virus (HBV), BCLC C stage, tumor number > 3, TACE times < 3 or DEB-TACE treatment, but failed to have a clinical benefit in patients with extrahepatic metastasis. Subgroup analyses of factors for PFS indicated that TACE-Len-T treatment had better survival benefits in HBV patients.

Tumor Response

The best tumor responses of all patients in the two groups are shown in Figure 4. The durations of treatment response range from 0.1 to 32.2 months with a median of 5.2 months in the TACE-Len-T group and 0.9 to 24.1 months with a median of 5.8 months in the TACE-Len group. The ORR of the overall tumor was 72.1% in the TACE-Len-T group, which was significantly higher than the ORR of 29.4% in the TACE-Len group (P<0.001), according to the mRECIST criteria (Supplement Table 1). DCRs in the TACE-Len-T and TACE-Len groups were 88.2% and 48.5%, respectively (P<0.001). When stratified by BCLC stage, ORR and DCR differed between the two groups (Supplement Table 2). The

Table 2 Analyses of Prognostic Factors for Over Survival and Progression-Free Survival

	Overall survival				Progression-free survival			
Factors	**Univariate analyses**		**Multivariate analyses**		**Univariate analyses**		**Multivariate analyses**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Gender (Male vs Female)	0.743 (0.313–1.763)	0.501			0.963 (0.565–1.644)	0.891		
Age (≥60 vs <60)	0.686 (0.346–1.358)	0.279			1.000 (0.983–1.017)	0.983		
Etiology (HBV vs others)	1.135 (0.405–3.176)	0.810			1.107 (0.620–1.977)	0.732		
ECOG PS (1 vs 0)	1.011 (0.467–2.187)	0.978			1.284 (0.828–1.990)	0.264		
Child Pugh class (B vs A)	0.771 (0.304–1.957)	0.584			0.977 (0.566–1.685)	0.932		
BCLC stage (C vs B)	1.174 (0.626–2.200)	0.617			1.121 (0.748–1.680)	0.581		
Tumor size (>5cm vs ≤5cm)	1.363 (0.734–2.531)	0.326			1.257 (0.852–1.852)	0.249		
Number of tumors (>3 vs ≤3)	1.898 (1.004–3.586)	0.049	2.068 (1.086–3.936)	0.027	1.312 (0.897–1.920)	0.161		
Vascular invasion (present vs absent)	1.059 (0.583–1.924)	0.850			1.148 (0.781–1.687)	0.482		
Extrahepatic metastasis (present vs absent)	1.689 (0.881–3.240)	0.115			1.287 (0.844–1.960)	0.241		
AFP (>400 vs ≤400)	1.901 (1.047–3.454)	0.035	1.734 (0.952–3.160)	0.072	1.370 (0.930–2.017)	0.111		
PIVKA-II (>400 vs ≤400)	1.587 (0.856–2.942)	0.142			1.339 (0.912–1.967)	0.136		
TACE times (≥3 vs <3)	1.553 (0.784–3.076)	0.207			1.849 (1.140–3.000)	0.013	1.619 (0.987–2.655)	0.056
Treatment option (TACE-Len-T vs TACE-Len)	0.318 (0.167–0.604)	<0.001	0.309 (0.161–0.595)	<0.001	0.144 (0.091–0.229)	<0.001	0.145 (0.091–0.232)	<0.001
TACE technique (DEB-TACE vs cTACE)	0.397 (0.190–0.826)	0.013	0.333 (0.158–0.699)	0.004	1.096 (0.747–1.610)	0.639		

Notes: Analyses were performed using Cox proportional hazard regression model.

Abbreviations: HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona clinic liver cancer; AFP, α-fetoprotein; PIVKA-II, Protein induced by vitamin K absence-II; TACE, transarterial chemoembolization. TACE+Len+T, transarterial chemoembolization combined with lenvatinib plus tislelizumab; TACE+Len, transarterial chemoembolization combined with lenvatinib.

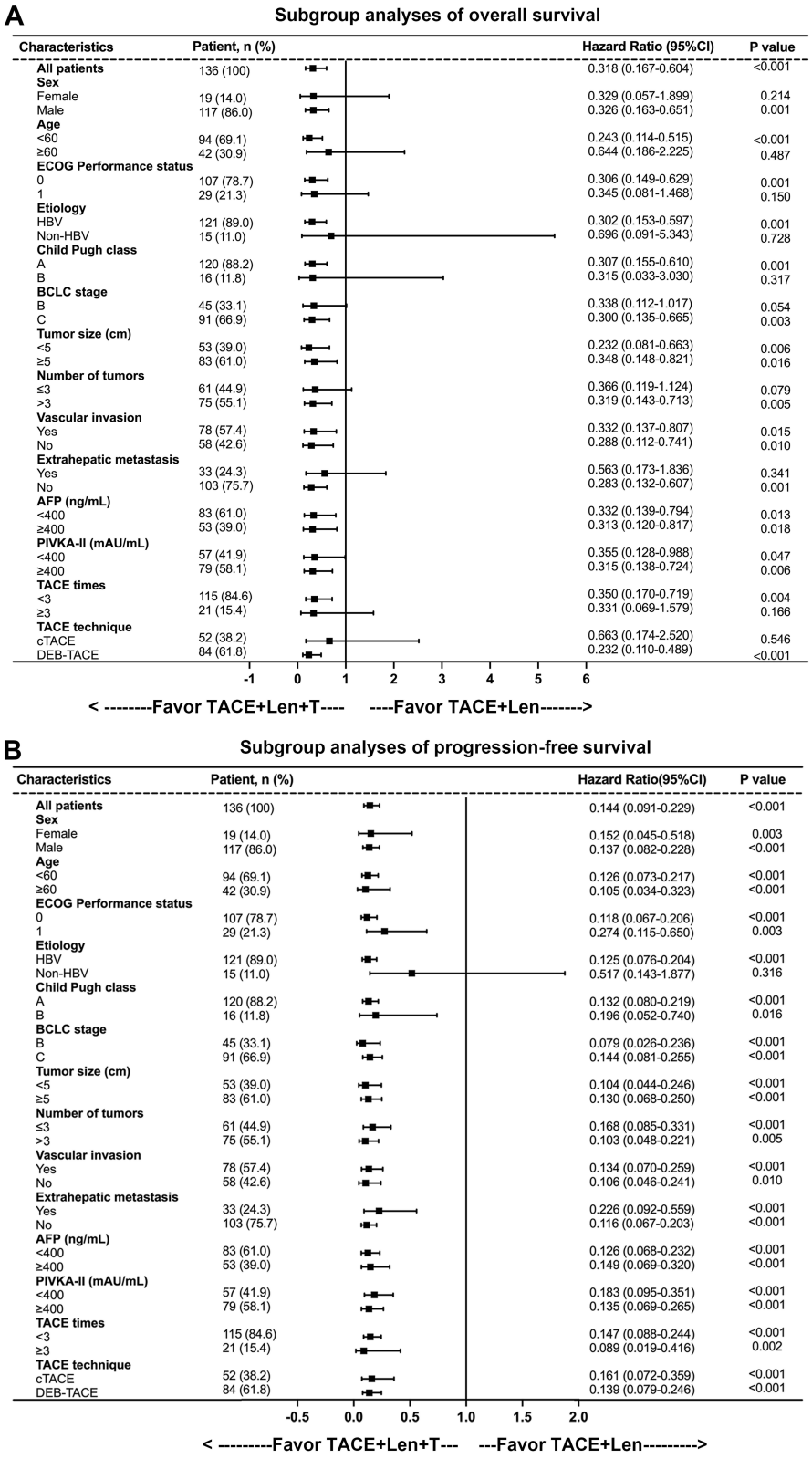


Figure 3 Subgroup analysis of overall survival (**A**) and progression-free survival (**B**). HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; cTACE conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads transarterial chemoembolization; HCC, hepatocellular carcinoma.

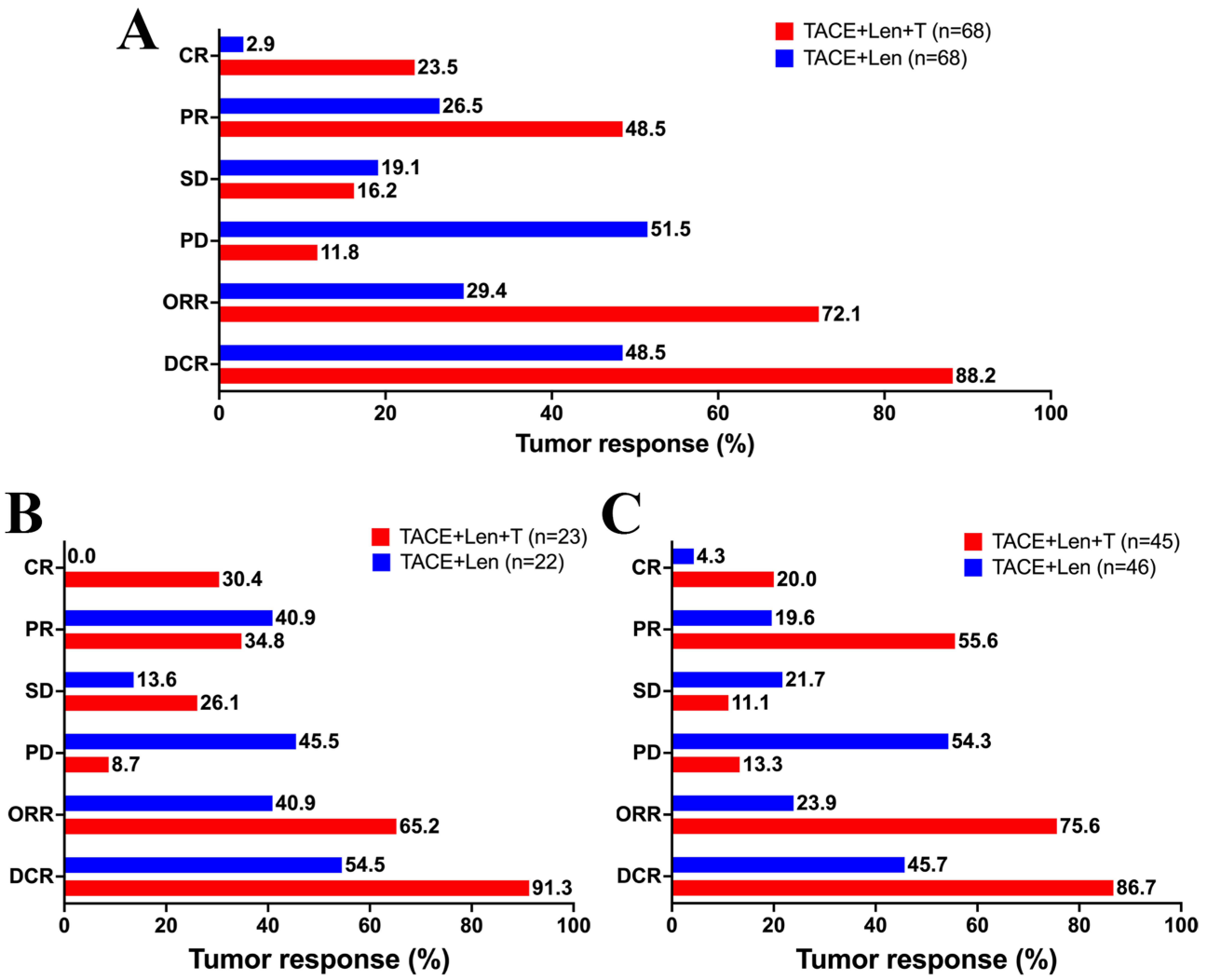


Figure 4 Treatment responses of overall tumor in all patients (**A**), patients with BCLC B stage (**B**), patients with BCLC C stage patients (**C**). TACE+Len+T, transarterial chemoembolization combined with lenvatinib plus tislelizumab; TACE+Len, transarterial chemoembolization combined with lenvatinib; BCLC, Barcelona clinic liver cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

disease progression patterns may be hepatic or extrahepatic. In our study, we observed 5 patients with hepatic progression and 3 patients with extrahepatic progression in the TACE-Len-T group, while 23 patients with hepatic progression and 12 patients with extrahepatic progression in the TACE-Len group. These results indicate that TACE in combination with lenvatinib and tislelizumab may result in a better tumor response in the early stages of uHCC.

Typical Case Presentation

In this study, 16 patients achieved CR in the TACE-Len-T group, whereas only two patients achieved CR in TACE-Len group. Here, we present a typical case of uHCC patient who received TACE-Len-T treatment and achieved CR. The patient was a 51-year-old man with huge HCC and portal vein tumor thrombosis (PVTT) in the right hemi-liver. He has about 20 years history of HBV infection. The patient had not received any therapy prior to admission. Liver function tests showed abnormal liver function with a Child Pugh score of 5 (grade A). The tumor stage was BCLC C. After consultation with a multidisciplinary team (MDT), this patient was confirmed to have both technical and oncological uHCC. The patient was recommended TACE-Len-T treatment. Detailed treatment information and clinical course are shown in Figure 5. The patient received one dose of DEB-TACE, lenvatinib (12 mg once daily), and tislelizumab (200 mg intravenously every 3 weeks). After four months of combination treatment, the lesion and PVTT shrank

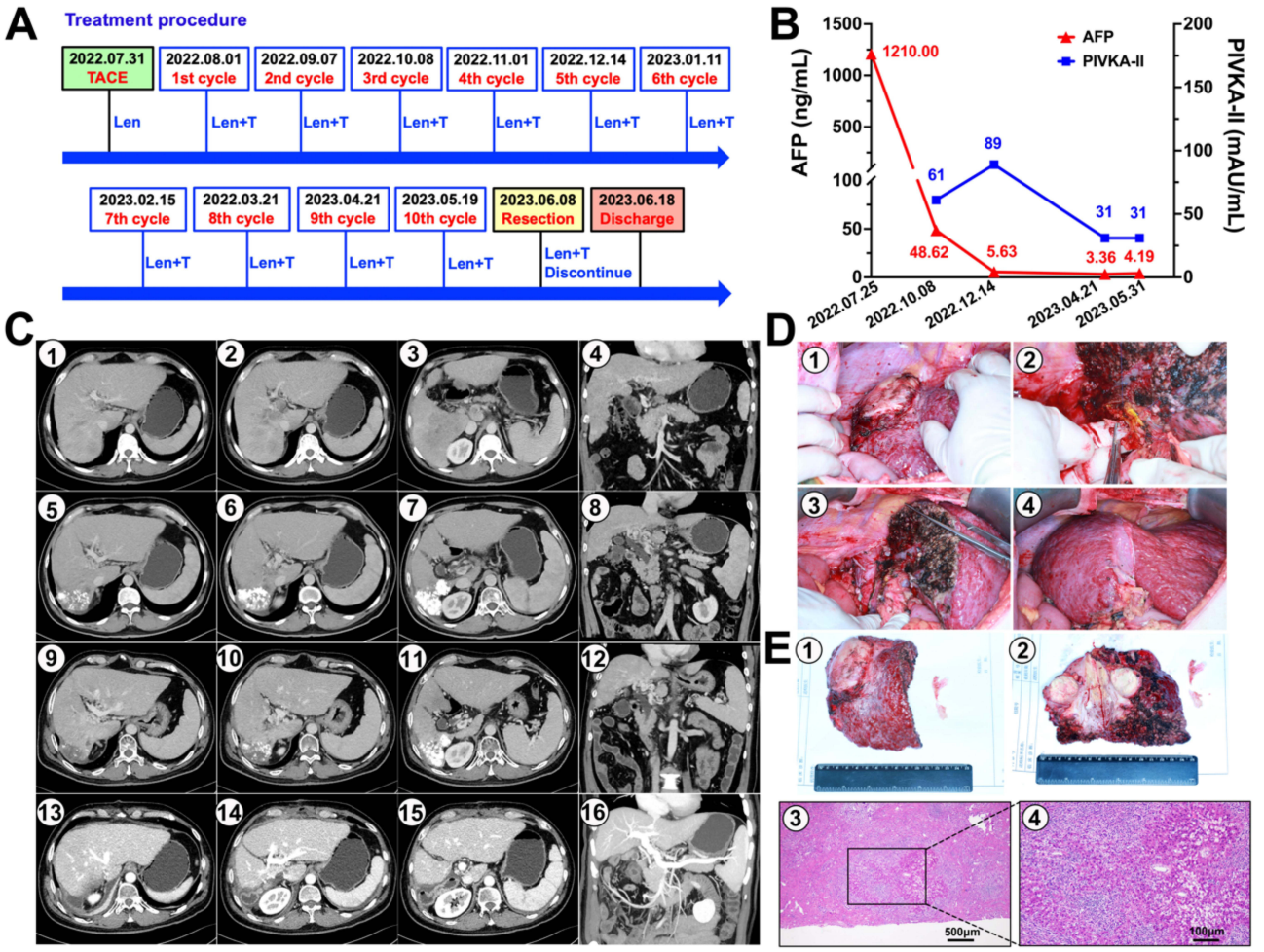


Figure 5 Typical case of a 51-year-old man diagnosed with uHCC with portal vein tumor thrombosis (PVTT) (BCLC C stage) received TACE-Len-T treatment. (**A**) The treatment procedure diagram of the patient throughout the conversion therapy; (**B**) The levels of tumor biomarker AFP and PIVKA-II changed during the treatment; (**C**) Representative computed tomography (CT) images of the lesion and PVTT throughout the conversion therapy. ①-④ The patient was diagnosed with uHCC with PVTT on July 25, 2022; ⑤-⑧ About four months after first TACE treatment (December 14, 2022), the lesion and PVTT shrank significantly; ⑨-⑫ After 10 cycles of tislelizumab treatment, the lesion showed inactive and tumor response reached CR on enhanced CT (May 31, 2023); ⑬-⑯ The remnant liver appeared normal and the blood flow of portal vein was patent after right hemi-hepatectomy (June 8, 2023); (**D**) Images of intraoperative during the right hemi-hepatectomy; (**E**) The images of resected specimen and representative pathological hematoxylin-eosin (HE) staining. ①-② The images of resected specimen showed inactive; ③-④ The images of HE staining of the resected tumor showed complete tumor necrosis with massive lymphocyte infiltration and a pathological complete response was achieved. Left, magnification 40X; Right, magnification 200X.

significantly and the AFP level returned to normal. After 10 cycles of tislelizumab treatment, contrast-enhanced CT revealed that the tumor was inactive. No severe AEs were observed during conversion therapy. After successful downstaging, the patient was deemed eligible for surgical resection. Finally, the patient underwent right hemi-hepatectomy without any severe perioperative complications. The PVTT was also removed and was organized and necrotic. Complete tumor necrosis with massive lymphocyte infiltration was confirmed and a pathological complete response (pCR) was achieved. In addition, lenvatinib and tislelizumab were discontinued postoperatively, and no tumor recurrence occurred during the 6-months follow-up. These results suggest that TACE-Len-T treatment is a safe and effective conversion therapy for uHCC.

Safety

Treatment-related AEs of any grade were observed in 125 of 136 patients (91.9%), with 63 patients (92.6%) in the TACE-Len-T group and 62 patients (91.2%) in the TACE-Len group, respectively. No grade 5 AEs were observed (Table 3). In the TACE-Len-T group, the most frequent treatment-related AEs of any grade (>10%) were elevated

Table 3 Treatment-Related Adverse Events in the Two Groups

Adverse events	Any grade			Grade 3 / 4		
	TACE+Len+T (n=68)	TACE+Len (n=68)	P	TACE+Len+T (n=68)	TACE+Len (n=68)	P
Elevated AST	60 (88.2)	60 (88.2)	1.000	15 (22.1)	18 (26.5)	0.548
Abdominal pain	55 (80.9)	53 (77.9)	0.671	0 (0.0)	0 (0.0)	–
Elevated ALT	53 (77.9)	48 (70.6)	0.327	9 (13.2)	10 (14.7)	0.586
Rash	43 (63.2)	39 (57.4)	0.483	3 (4.4)	2 (2.9)	1.000
Hand-foot syndrome	43 (63.2)	43 (63.2)	1.000	2 (2.9)	3 (4.4)	1.000
Elevated TBIL	42 (61.8)	49 (72.1)	0.202	2 (2.9)	3 (4.4)	1.000
Pruritus	34 (50.0)	28 (41.2)	0.302	2 (2.9)	1 (1.5)	1.000
Diarrhea	34 (50.0)	29 (42.6)	0.390	1 (1.5)	1 (1.5)	1.000
Fatigue	32 (47.1)	32 (47.1)	1.000	1 (1.5)	1 (1.5)	1.000
Nausea	25 (36.8)	23 (33.8)	0.720	0 (0.0)	0 (0.0)	–
Vomiting	21 (30.9)	19 (27.9)	0.707	0 (0.0)	0 (0.0)	–
Hypertension	18 (26.5)	13 (19.1)	0.307	2 (2.9)	1 (1.5)	1.000
Fever	13 (19.1)	21 (30.9)	0.113	0 (0.0)	0 (0.0)	–
Dental ulcer	8 (11.8)	3 (4.4)	0.116	0 (0.0)	0 (0.0)	–
Gingival bleeding	6 (8.8)	4 (5.9)	0.706	0 (0.0)	0 (0.0)	–
Gastrointestinal hemorrhage	3 (4.4)	3 (4.4)	1.000	0 (0.0)	0 (0.0)	–
Hypothyroidism	3 (4.4)	0 (0.0)	0.243	0 (0.0)	0 (0.0)	–
Chest distress	2 (2.9)	0 (0.0)	0.476	0 (0.0)	0 (0.0)	–
Dysphonia	2 (2.9)	2 (2.9)	1.000	0 (0.0)	0 (0.0)	–
Arthralgia	2 (2.9)	0 (0.0)	0.496	0 (0.0)	0 (0.0)	–
Alopecia	1 (1.5)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	–
Haemoptysis	1 (1.5)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	–
Constipation	0 (0.0)	3 (4.4)	0.243	0 (0.0)	0 (0.0)	–
Xerostomia	0 (0.0)	3 (4.4)	0.243	0 (0.0)	0 (0.0)	–
Decreased platelet count	0 (0.0)	1 (1.5)	1.000	0 (0.0)	0 (0.0)	–
Blepharoptosis	0 (0.0)	1 (1.5)	1.000	0 (0.0)	0 (0.0)	–

Notes: Data were presented as n (%).

Abbreviations: TACE, transarterial chemoembolization; TACE+Len+T, transarterial chemoembolization combined with lenvatinib plus tislelizumab; TACE+Len, transarterial chemoembolization combined with lenvatinib; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin.

aspartate aminotransferase (AST), abdominal pain, elevated alanine aminotransferase (ALT), rash, hand-foot syndrome, elevated bilirubin, pruritus, diarrhea, fatigue, nausea, vomiting, hypertension, fever and dental ulcer. In the TACE-Len group, the most frequent treatment-related AEs of any grade (>10%) were elevated AST, abdominal pain, elevated bilirubin, elevated ALT, hand-foot syndrome, rash, fatigue, diarrhea, pruritus, nausea, fever, vomiting and hypertension.

Grade 3 or 4 AEs occurred in 23 patients (33.8%) in the TACE-Len-T group and in 22 patients (32.3%) in the TACE-Len group. Elevated AST, elevated ALT, rash, hypertension, hand-foot syndrome, pruritus and elevated bilirubin were the most frequent grade 3/4 AEs in the TACE-Len-T group. Elevated AST, elevated ALT, elevated bilirubin, hand-foot syndrome and rash were the most frequent grade 3/4 AEs in the TACE-Len group. The frequency and severity of AEs were similar between the two groups.

Treatment-related AEs lead to treatment discontinuation, interruption, dose reduction of lenvatinib in 11 (16.2%), 9 (13.2%), 2 (2.9%) patients, respectively, in the TACE-Len-T group, and in 9 (13.2%), 8 (11.8%), 6 (8.8%) patients, respectively, in the TACE-Len group. The most common reasons for dose interruption and cessation of lenvatinib were tumor progression, gastrointestinal bleeding, gums bleeding, diarrhea, loss of appetite, rash and hepatic insufficiency. Most of these adverse reactions can be quickly recovered after drug withdrawal and symptomatic treatment. Treatment-related AEs led to treatment discontinuation and interruption of tislelizumab in six (8.8%) and seven (10.3%) patients, respectively, in the TACE-Len-T group. The most common reasons for dose interruption and cessation of tislelizumab were hypothyroidism, immune-related pneumonia and rash. Discontinuation of both lenvatinib and tislelizumab due to AEs occurred in 5 patients (7.4%). The total treatment time of lenvatinib range from 0.8 to 30.1 months with a median of 11.0 months in the TACE-Len-T group and 1.0 to 26.8 months with a median of 6.9 months in the TACE-Len group (P=0.094, Mann–Whitney Test). There was no significance in the total treatment time of lenvatinib between TACE-Len-T group and TACE-Len group. The total treatment time of tislelizumab range from 0.7 to 24.5 months with a median of 4.2 months in the TACE-Len-T group.

Discussion

Our study indicated that combined TACE with lenvatinib plus tislelizumab resulted in significantly improved clinical outcomes in patients with uHCC compared to TACE-Len. Patients in the TACE-Len-T group had better OS and PFS than those in the TACE-Len group (median OS: not reached vs 13.8 months, P<0.001; median PFS: 13.0 months vs 2.7 months, P<0.001), which might attribute to the higher ORR and DCR achieved in patients receiving TACE-Len-T treatment rather than TACE-Len. Subsequent univariate and multivariate analyses confirmed that the treatment option of TACE-Len-T was an independent prognostic risk factor for prolonged OS and PFS. In addition, the frequencies of treatment-related AEs were slightly higher in TACE-Len-T group than that in TACE-Len group, but all AEs were easily managed with mild-to-moderate severity. These results suggest that the triple combination treatment with TACE-Len-T might be a superior treatment option for patients with uHCC.

A reasonable explanation for TACE-Len-T treatment is that the triple combination treatment of TACE with TKIs plus PD-1 inhibitor could obtain more benefits for uHCC.[30,31] The reasons for this may be as follows: First, TACE causes necrosis of tumor tissues, promotes the release of tumor antigens and proinflammatory cytokines, and subsequently activates antitumor immune responses that may be further boosted by the PD-1 inhibitor, tislelizumab.[26,32] Second, lenvatinib exhibits antiproliferative and antiangiogenic activities, which may inhibit TACE-induced angiogenesis and enhance the effects of tislelizumab by regulating the tumor immune microenvironment.[22,33,34] Therefore, the combination of TACE with lenvatinib plus tislelizumab may provide synergistic antitumor activity in uHCC.

Previous studies have indicated that TACE combined with TKIs does not yield the desired results. The TACTICS trial reported that TACE combined with sorafenib achieved better PFS compared with TACE alone, but without OS benefits in later data.[12,35] Although the PFS of TACE combined with sorafenib in the TACTICS trial was 25.2 months, which was much longer than that of TACE-Len group in our study, the occurrences of new intrahepatic lesions were not recognized as PD in the TACTICS trial. In addition, compared with the TACE-Len group, the combination of TACE with lenvatinib plus tislelizumab significantly improved the clinical survival of patients with uHCC. To compare our results with other researchers', we reviewed a large number of relevant literatures on the he efficacy and safety of TACE combined with lenvatinib and PD-1 such as pembrolizumab and sintilimab in uHCC. We found that our results were similar to most of the results reported in literatures.[36,37] These results indicated that the combination treatment of TACE and lenvatinib plus tislelizumab significantly prolonged the survival of patients with uHCC.

In univariate and multivariate analyses, TACE-Len treatment, tumor number >3, and cTACE were identified as independent risk factors affecting OS. In subgroup analyses, prolonged OS was observed following treatment with

TACE-Len-T. Furthermore, TACE-Len-T provided better OS than TACE-Len in patients with HBV, BCLC C stage, tumor number > 3, vascular invasion, TACE times < 3 or DEB-TACE treatment, but not in patients with extrahepatic metastasis. One reasonable explanation is that TACE exhibits antitumor activity mainly by controlling intrahepatic lesions rather than extrahepatic metastases, and its effect on multiple tumors is limited. Subsequent multivariate analysis showed that the treatment option was also an independent risk factor for PFS. Early combination of TACE with lenvatinib and tislelizumab prolonged the PFS of patients with uHCC. These results suggest that the early combination of TACE with lenvatinib plus tislelizumab is a promising treatment option for patients with uHCC, especially those with vascular invasion or multiple tumors.

The incidence of AEs of any grade was comparable between the TACE-Len-T and TACE-Len groups. Most AEs were of mild to moderate and were easily managed in this study. No unexpected AEs observed. The most frequent AEs after TACE is postembolization syndrome.[8] Postembolization syndrome occurred in 92.6% and 91.2% of the patients in the TACE-Len-T and TACE-Len groups, respectively. The most common AEs in the TACE-Len-T group were elevated ASL, abdominal pain, elevated ALT, hand-foot syndrome, elevated bilirubin, pruritus and diarrhea. Although the incidence of grade 3/4 AEs in the TACE-Len-T group was much higher than that in the TACE-Len group, these AEs, including elevated ASL, elevated ALT, rash, hypertension, hand-foot syndrome, pruritus, and elevated bilirubin, significantly improved after timely monitoring and symptomatic treatment. No grade 5 AEs were observed in either of the groups. The triple combination treatment did not increase the risk of AEs compared with TACE-Len treatment. These results indicate that the combination of TACE with lenvatinib plus tislelizumab for uHCC is effective and safe.

The present study has some limitations. First, this was a retrospective study, and the treatment option was determined by the attending physician and patient, which inevitably led to a selection bias. Second, the follow-up time was short, and long-term survival results were not available. Third, the sample size was small. The results of subgroup analyses should be interpreted cautiously. Therefore, multicenter, large-scale, prospective, randomized controlled trials are needed to confirm our findings.

Conclusion

In conclusion, our study indicated that the combination of TACE with lenvatinib plus tislelizumab resulted in significantly better outcomes for uHCC patients than TACE-Len treatment, with an acceptable safety profile. These patients could benefit from the triple combination treatment and had a better treatment response and improved survival compared with TACE-Len treatment. Thus, early combination of lenvatinib and tislelizumab may be a promising treatment strategy for patients with uHCC.

Data Sharing Statement

No further data will be shared. More information can be acquired by contacting the corresponding author for reasonable reasons.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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