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Original Article

Lenvatinib plus sintilimab with or without transarterial chemoembolization for intermediate or advanced stage hepatocellular carcinoma: a propensity score-matching cohort study

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Abstract: In this retrospective study, we compared the efficacy and safety of lenvatinib plus sintilimab, with or without transarterial chemoembolization (TLS vs. LS), in patients with intermediate or advanced stage hepatocellular carcinoma (HCC). Eligible patients who received combination therapy with TLS or LS at Tianjin Medical University Cancer Institute & Hospital from December 2018 to October 2020 were propensity score matched (PSM) to correct for potential confounding biases between the two groups. The primary endpoint was progression-free survival (PFS) and secondary endpoints were overall survival (OS), overall response rate (ORR) and treatment-related adverse events (TRAEs). Cox proportional hazards models were used to identify prognostic factors. The study included 152 patients (LS group, n=54, TLS group, n=98). After PSM, patients in the TLS group had significantly longer PFS (11.1 versus 5.1 months, *P*=0.033), OS (not reached versus 14.0 months, *P*=0.0039) and ORR (modified Response Evaluation Criteria in Solid Tumors: 44.0% versus 23.1%; *P*=0.028) than those in the LS group. In the multivariate Cox regression analysis, the treatment regimen (TLS versus LS) was an independent predictor for both PFS (HR=0.551; 95% CI: 0.334-0.912; *P*=0.020) and OS (HR=0.349; 95% CI: 0.176-0.692; *P*=0.003) and CA19-9 level was an independent predictor for OS (HR=1.005; 95% CI: 1.002-1.008; *P*=0.000). No significant differences in the incidence of grade ≥3 TRAEs were reported between the two treatment groups. In conclusion, triple combination therapy with TLS improved survival with an acceptable safety profile compared with LS in patients with intermediate or advanced stage HCC.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization, lenvatinib, sintilimab

Introduction

Hepatocellular carcinoma (HCC) is the fifth-most-common malignancy and the second leading cause of cancer-related death worldwide [1]. Newly-diagnosed cases of HCC in China account for approximately half of all cases worldwide, and approximately 300-400,000 Chinese people die from HCC each year [2]. In addition, the early symptoms of HCC can be difficult to detect and, as a result, nearly 70% of patients in China are diagnosed at an intermediate to advanced stage, thereby missing the opportunity for radical treatment [3].

Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor 1-4, and platelet-derived growth factor receptor α, resulting in potent antiangiogenic properties [4]. In a phase 3 clinical trial in patients with unresectable HCC, compared to sorafenib (the first marketed multikinase-targeted drug for HCC), lenvatinib was not inferior

in prolonging overall survival (OS) and was associated with significantly improved progression-free survival (PFS) and overall response rate (ORR) [5]. Based on these results, lenvatinib has been approved for the first-line treatment of unresectable advanced HCC in the USA, the European Union, Japan, and China [6].

Programmed cell death-1 (PD-1) and its main ligand, programmed death-ligand 1 (PD-L1) are expressed on tumor cells and on T cells, B cells, and bone marrow cells, respectively [7]. Blocking this pathway disrupts the ability of tumor cells to evade immune surveillance and can exert an antitumor effect [8]. ORRs following treatment with PD-1 inhibitors as monotherapy in patients with advanced stage HCC have been reported to be only 14.7-18.3% [9-13]. However, the combined use of PD-1 inhibitors with tyrosine kinase inhibitors (TKIs) has the potential for an enhanced antitumor effect due to synergy in improving the immune microenvironment and promoting the normalization of immunoreactive cell function [14, 15]. In addition, combining TKIs and PD-1 inhibitors may reprogram the immunosuppressive microenvironment into an immunostimulatory microenvironment [16]. In clinical trials, combination therapy with lenvatinib and the PD-1 inhibitor nivolumab resulted in an ORR of 54.2% when used as a first-line treatment regimen for patients with advanced HCC, and combining lenvatinib and pembrolizumab prolonged OS to 22 months in patients with intermediate or advanced stage HCC [17]. Similarly, in a real-world study, a numerically higher ORR, disease control rate (DCR), and PFS were reported in patients treated with lenvatinib combined with a PD-1 inhibitor compared with lenvatinib monotherapy [18]. The novel PD-1 inhibitor sintilimab has also shown promising results in HCC when combined with a bevacizumab biosimilar [19].

Transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) are recommended locoregional treatments for patients with intermediate or advanced stage HCC [20, 21]. However, treatment with TACE or HAIC alone can cause hypoxia in tumor tissue, leading to upregulation of hypoxia-inducible factor 1-α expression, elevation of local VEGF and ultimately tumor progression and metastasis [22]. These effects can potentially be mitigated by combined treatment with lenvatinib, with or without a PD-1 inhibitor. This hypothesis is now being evaluated in the clinic, with promising data reported for several recently completed studies [6, 23-25].

To date, no study has evaluated the benefits of adding TACE to lenvatinib plus sintilimab in the first-line treatment of patients with intermediate to advanced stage HCC. Therefore, we performed this retrospective study using propensity score matching (PSM) to determine whether triple combination therapy with TACE, lenvatinib and sintilimab could provide a survival benefit and be a valuable approach for the management of patients with intermediate or advanced stage HCC.

Material and methods

Study design and patients

This was a single-center study that retrospectively analysed data from all patients with intermediate or advanced stage HCC who received TACE, lenvatinib and sintilimab triple combination therapy (TLS) or lenvatinib and sintilimab double combination therapy (LS) at Tianjin Medical University Cancer Institute & Hospital, Tianjin, China between December 2018 and October 2020. The study was conducted in accordance with the ethical standards of the Research Committee of Tianjin Medical University Cancer Institute & Hospital and the recently revised Declaration of Helsinki. Informed consent was obtained from all patients before inclusion.

Eligible patients had a pathological or imaging diagnosis of intermediate or advanced stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage B or C, as defined by the European Association for the Study of Liver Cancer or the American Association for the Study of Liver Diseases [26]) with a measurable target lesion and had received treatment with at least two cycles of lenvatinib and sintilimab with or without TACE. Other inclusion criteria were age ≥18 years, Child-Pugh class A or B liver function, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2, and adequate organ function. Patients were excluded if they had secondary HCC, had received other systemic therapies before or during treatment, had Child-Pugh grade C liver disease or BCLC

stage A cancer, active bleeding, or had incomplete clinical data.

Procedures

All patients included in this study received lenvatinib (Levima®, Eisai, Tokyo, Japan) at a dose of 8 mg once per day plus sintilimab (Tyvyt®, Innovent Biologics, Suzhou, China) at a dose of 200 mg every 3 weeks. For the TLS group, TACE was performed once every four weeks. Patients were required to interrupt lenvatinib treatment for 2 days before and after receiving TACE. TACE was performed under local anesthesia by three interventional radiologists with over ten years of experience. The TACE procedure involved the introduction of an RH catheter to the right femoral artery via a catheter sheath and selective insertion into the common hepatic artery under the guidance of an ultra-smooth guidewire for imaging of the intrahepatic tumor. A microcatheter was then introduced through the RH catheter and super-selectively inserted into the arteries feeding the tumor and 0.3 g of 300-500 μm microspheres was injected for embolization. Approximately 200 mL of a 300 mg diluted solution of carboplatin or lobaplatin was also slowly injected through the RH catheter. The catheter and catheter sheath were removed at the end of the procedure. All treatments were discontinued upon disease progression, intolerable side effects, patient withdrawal of consent, or modifications to the treatment strategy. As this was a retrospective study, all treatment decisions were made at the discretion of each patient's physician.

Evaluation of therapeutic response and follow-up

Data from laboratory blood tests were collected three days prior to the start of therapy. Patients underwent enhanced computed tomography or magnetic resonance imaging every 4-6 weeks after initiation of treatment, followed by assessments every 2-3 months. Blood tests including liver and kidney function, tumor markers, and coagulation parameters were performed every month, until death or study discontinuation.

The Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) [27] and Modified RECIST (mRECIST) [28] were used to assess tumor response. The ORR was calculated as the percentage of patients who achieved a best overall response of either complete response (CR) or partial response (PR). The DCR was calculated as the percentage of patients who achieved a best overall response of either CR, PR or stable disease. The primary endpoint of the study was PFS, defined as time from treatment initiation until tumor progression or death from any cause. Secondary endpoints were OS (time from treatment initiation until death from any cause), ORR, and safety. Treatment-related adverse events (TRAEs) were monitored and recorded during the treatment period using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) [29]. For patients experiencing any unacceptable TRAE of grade ≥3, the drug dose was reduced or discontinued until the adverse effect had resolved.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA). A two-tailed *P* value <0.05 was considered statistically significant. All categorical variables were summarized as numbers and percentages. An independent sample t test, Wilcoxon rank-sum test, Pearson's χ^2 test or Fisher's exact test were used for between group comparisons. The Kaplan-Meier method was used to estimate survival times with two-sided 95% confidence intervals (CIs) calculated for the medians. The log-rank test was used to assess the significance of between-group differences in survival. Univariate and multivariate Cox regression analyses were used to explore independent prognostic factors for PFS and OS. Variables with *P*<0.05 in univariate analyses, or clinically relevant variables, were incorporated into the multivariate analyses.

Propensity score matching (PSM) was performed to reduce differences in baseline characteristics between the two treatment groups. The following covariates were included in the PSM model: age, sex, hepatitis status, liver cirrhosis, alpha fetoprotein (AFP) level (≤ vs. >400 ng/mL), Child-Pugh class, BCLC stage, ECOG PS, presence of metastases, vascular invasion, tumor size, tumor number, and history of local treatment. Nearest neighbor matching (1:2) was used, with a caliper width equal to 0.1 of the standard deviation.

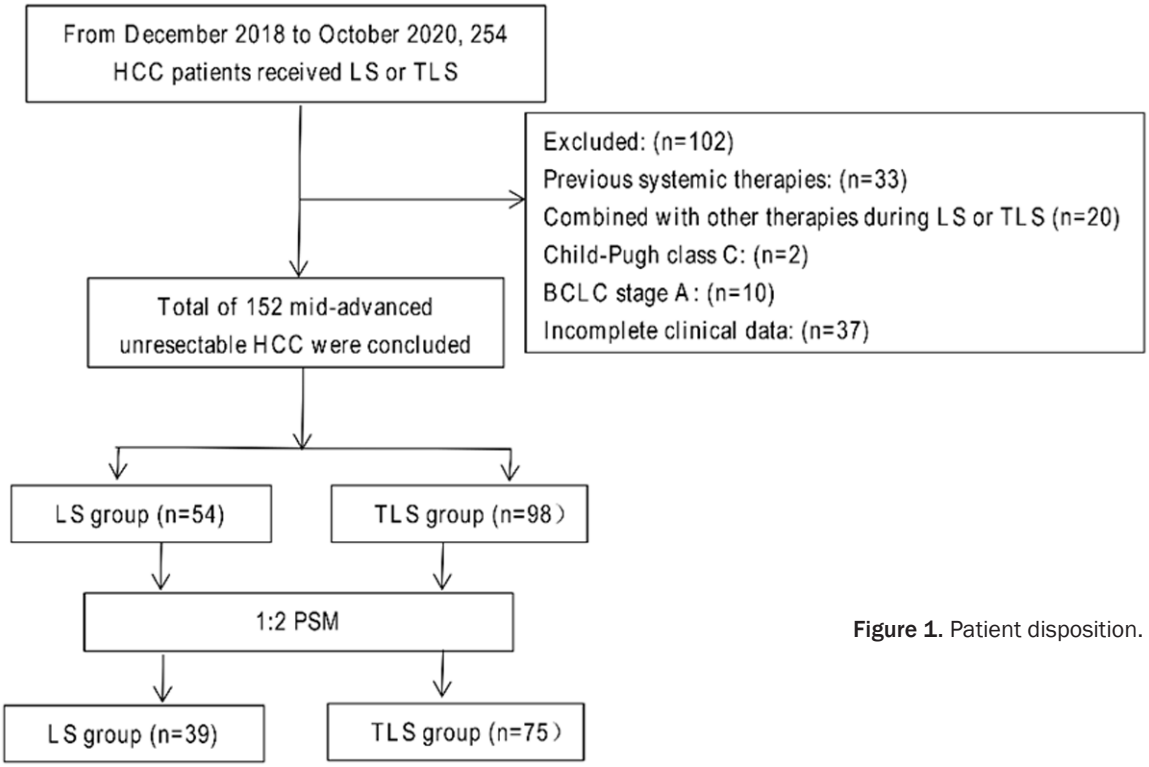

Figure 1. Patient disposition.

Results

Patient characteristics

During the study period, 254 patients with HCC received either LS or TLS at the Tianjin Medical University Cancer Institute & Hospital. Of these, 102 were excluded from the study, either because they received other systemic therapies before LS or TLS (n=33), received other therapies during LS or TLS (n=20), were classified as Child-Pugh class C (n=2) or BCLC stage A (n=10), or did not have complete clinical data (n=37). Overall, 152 patients with intermediate or advanced stage HCC met the study inclusion criteria; of these, 54 received LS treatment, and 98 received TLS treatment (**Figure 1**).

In the unmatched cohort, baseline characteristics were broadly similar between the two groups (**Table 1**), with the only statistically significant difference being that patients in the LS group were more likely to have metastases than those in the TLS group (61.1% vs. 26.5%; $P<0.001$). Patients in the LS group were also more likely to have advanced (BCLC stage C) HCC than those in the TLS group (70.4% vs. 57.1%; $P=0.152$) and to have a history of local treatment such as surgical resection or radiofrequency ablation (53.7% vs. 38.8%; $P=0.109$).

A total of 114 patients were included in the PSM-matched cohort, including 39 in the LS group and 75 in the TLS group. The clinical characteristics of patients in the PSM-matched groups were well balanced (**Table 1**). Most patients were ≤65 years of age (74.4% in the LS group and 76.0% in the TLS group) and male (87.2% in the LS group and 88.8% in the TLS group). The majority of patients were classified as Child-Pugh class A (76.9% in the LS group and 78.7% in the TLS group) and BCLC stage C (64.1% in the LS group and 57.3% in the TLS group). A similar proportion of patients in the LS and TLS groups had received local treatment before treatment (46.2% vs. 44.0%). As per the eligibility criteria, no patients received any other systemic therapies before or during LS or TLS treatment. In the LS and TLS groups, the median number of cycles of sintilimab plus lenvatinib was 6 (range: 1-19) and 9 (range: 1-29), respectively. TACE was performed on a median of 3 occasions in the TLS group (range: 1-10).

Table 1. Patient clinical characteristics before and after propensity score matching

Variable	Before PSM			After PSM		
	LS n=54	TLS n=98	*P* value	LS n=39	TLS n=75	*P* value
Age, n (%)			0.615			1.000
≤65 years	44 (81.5)	75 (76.5)		29 (74.4)	57 (76.0)	
>65 years	10 (18.5)	23 (23.5)		10 (25.6)	18 (24.0)	
Sex, n (%)			0.528			1.000
Female	7 (13.0)	18 (18.4)		5 (12.8)	9 (12.0)	
Male	47 (87.0)	80 (81.6)		34 (87.2)	66 (88.0)	
Hepatitis, n (%)			0.903			0.958
None	2 (3.7)	4 (4.1)		1 (2.6)	2 (2.7)	
HBV	48 (88.9)	85 (86.7)		35 (89.7)	69 (92.0)	
HCV	3 (5.6)	5 (5.1)		2 (5.1)	3 (4.0)	
Both HBV and HCV	1 (1.9)	4 (4.1)		1 (2.6)	1 (1.3)	
Liver cirrhosis, n (%)			0.598			1.000
Positive	35 (64.8)	69 (70.4)		27 (69.2)	53 (70.7)	
AFP group, n (%)			0.149			1.000
≤400 (ng/ml)	37 (68.5)	54 (55.1)		23 (59.0)	45 (60.0)	
>400 (ng/ml)	17 (31.5)	45 (45.9)		16 (41.0)	30 (40.0)	
Child-Pugh class, n (%)			0.563			1.000
A	40 (74.1)	78 (79.6)		30 (76.9)	59 (78.7)	
B	14 (25.9)	20 (20.4)		9 (23.1)	16 (21.3)	
BCLC stage, n (%)			0.152			0.619
B	16 (29.6)	42 (42.9)		14 (35.9)	32 (42.7)	
C	38 (70.4)	56 (57.1)		25 (64.1)	43 (57.3)	
ECOG PS, n (%)			0.296			0.349
0	37 (68.5)	61 (62.2)		28 (71.8)	48 (64.0)	
1	12 (22.2)	32 (32.7)		8 (20.5)	24 (32.0)	
2	5 (9.3)	5 (5.1)		3 (7.7)	3 (4.0)	
Metastases, n (%)			<0.001			0.210
Present	33 (61.1)	26 (26.5)		19 (48.7)	26 (34.7)	
Vascular invasion, n (%)			0.057			0.525
Present	11 (20.4)	36 (36.7)		9 (23.1)	23 (30.7)	
Tumor size, cm, n (%)			0.510			0.915
≤10	42 (77.8)	70 (71.4)		28 (71.8)	56 (74.7)	
>10	12 (22.2)	28 (28.6)		11 (28.2)	19 (25.3)	
Tumor number, n (%)			0.088			0.707
≤3	35 (64.8)	48 (49.0)		23 (59.0)	40 (53.3)	
>3	19 (35.2)	50 (51.0)		16 (41.0)	35 (46.7)	
History of local treatment, n (%)			0.109			0.983
Yes	29 (53.7)	38 (38.8)		18 (46.2)	33 (44.0)	

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; LS, lenvatinib plus sintilimab; PSM, propensity score matching; TLS, transarterial chemoembolization combined with lenvatinib plus sintilimab.

Survival

In both the unmatched and PSM-matched cohorts, the median follow-up time for all patients was 10.0 months. Patients in the TLS group had significantly longer PFS and OS than those in the LS group, both in the unmatched cohort (**Figure 2A** and **2B**; PFS: *P*=0.037; OS:

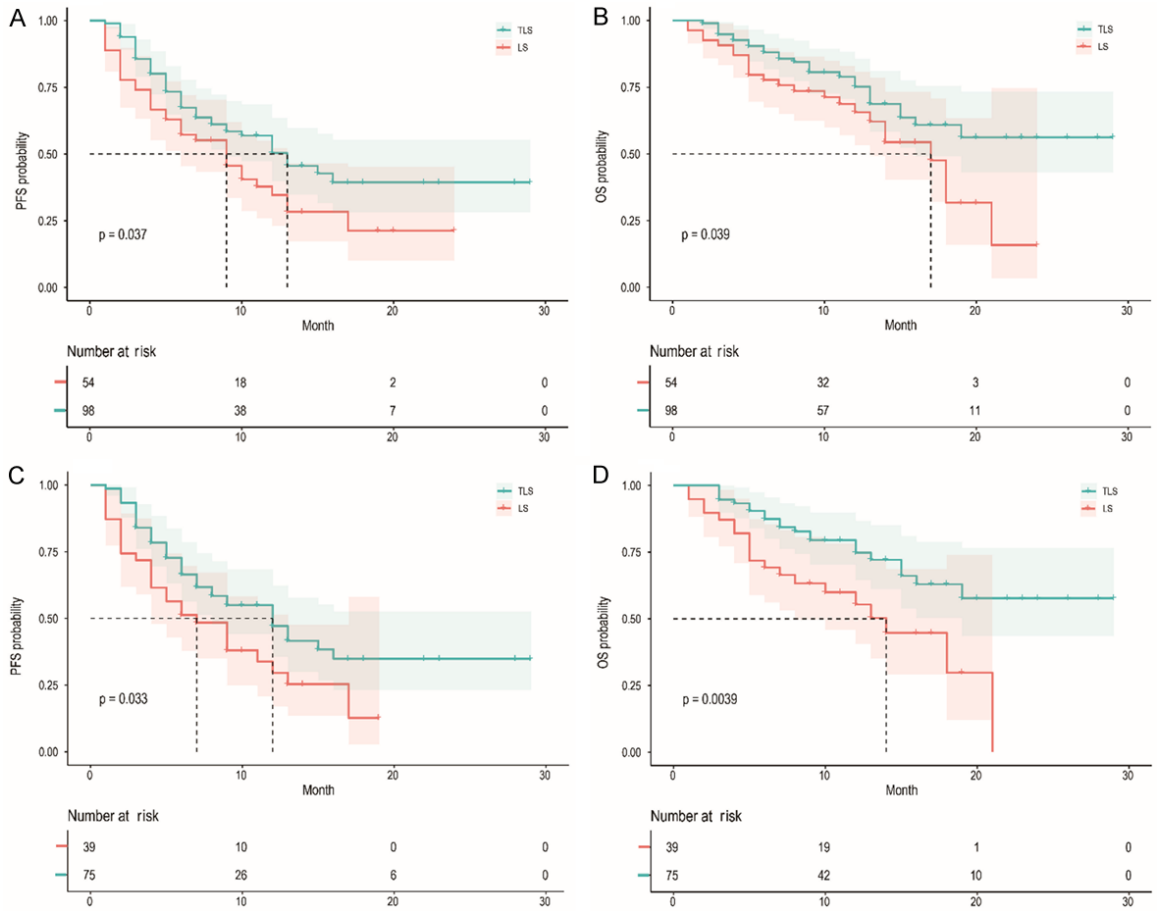

Figure 2. Kaplan-Meier estimates of PFS and OS before (A, B) and after (C, D) propensity score matching. Abbreviations: OS, overall survival; PFS, progress-free survival.

P=0.039) and in the PSM-matched cohort (**Figure 2C** and **2D**; PFS: *P*=0.033; OS: *P*=0.0039). In the PSM-matched cohort, the 6-, and 12-month PFS rates were 66.5% and 47.1% in the TLS group, and 51.3% and 29.6% in the LS group. The median PFS was 12.0 months in the TLS group (95% CI: 8.1-16.0) and 7.0 months in the LS group (95% CI: 3.6-10.4). The 6-, and 12-month OS rates were 87.4% and 74.8% in the TLS group, and 69.2% and 55.4% in the LS group. The median OS was 14.0 months in the LS group (95% CI: 10.4-17.6) and was not reached in the TLS group.

Prognostic factor analysis

Analysis of potential prognostic factors for PFS and OS are shown in **Tables 2** and **3**, respectively. Treatment with TLS vs. LS was an independent predictor of both PFS (HR: 0.551; 95% CI: 0.334-0.912; *P*=0.020) and OS (HR: 0.349; 95% CI: 0.176-0.692; *P*=0.003) in multivariate Cox regression analyses. CA19-9 level was also an independent predictor of OS in this population of patients with intermediate or advanced stage HCC (HR: 1.005; 95% CI: 1.002-1.008; *P*=0.000).

Subgroup analyses

Across all subgroups analysed, TLS was superior to LS for both PFS and OS (**Figure 3**). Statistically significant improvements in both PFS and OS with TLS vs. LS were observed in patients with hepatitis, BCLC stage C, metastases, and with ≥3 tumors. Significant improvements in PFS with TLS vs. LS were also observed in patients with an ECOG PS of 1 and significant improvements in OS with TLS vs. LS were observed in patients with liver cirrhosis, AFP>400 ng/mL, Child-Pugh class B, aged >65 years, male, with or without vascular invasion, and with tumor size ≤10 cm.

Table 2. Univariate and multivariate analyses of risk factors for PFS

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Treatment group (TLS vs. LS)	0.598 (0.364-0.982)	0.042	0.551 (0.334-0.912)	0.020
Age group (>65 vs. ≤65 years)	0.932 (0.516-1.683)	0.814		
Age	0.998 (0.975-1.022)	0.886		
Sex (male vs. female)	0.081 (0.492-2.372)	0.846		
Hepatitis (presence vs. absence)	0.392 (0.095-1.620)	0.196		
Liver cirrhosis (presence vs. absence)	0.811 (0.485-1.358)	0.426		
AFP group (>400 vs. ≤400 ng/ml)	1.362 (0.835-2.222)	0.216		
AFP	1.000 (1.000-1.000)	0.038	1.000 (1.000-1.000	0.135
Child-Pugh class (B vs. A)	1.977 (1.132-3.452)	0.017	1.741 (0.918-3.299)	0.089
BCLC stage (C vs. B)	1.384 (0.827-2.315)	0.216		
ECOG PS				
1 vs. 0	1.453 (0.860-2.453)	0.163		
2 vs. 0	1.776 (0.633-4.982)	0.275		
Metastasis (presence vs. absence)	1.368 (0.839-2.230)	0.209		
Vascular invasion (presence vs. absence)	0.922 (0.530-1.604)	0.774		
Tumor size (>10 vs. ≤10 cm)	1.543 (0.917-2.596)	0.103		
Tumor number (>3 vs. ≤3 cm)	1.426 (0.875-2.325)	0.154		
History of treatment (yes vs. no)	0.925 (0.566-1.513)	0.757		
CA19-9 level	1.003 (1.000-1.006)	0.055		
ALP level	1.003 (1.000-1.006)	0.049	1.001 (0.998-1.005)	0.410
ALBI grade				
2 vs. 1	1.321 (0.789-2.212)	0.290		
3 vs. 1	1.815 (0.544-6.058)	0.332		

Abbreviations: AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; BCLC, Barcelona Clinic Liver Cancer; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; LS, lenvatinib plus sintilimab; PFS, progression-free survival; TLS, transarterial chemoembolization combined with lenvatinib plus sintilimab.

Tumor response

The tumor response to treatment in the PSM-matched cohorts is summarized in **Table 4**. The TLS group had a significantly higher ORR based on the mRECIST criteria compared with the LS group (44.0% vs. 23.1%; *P*=0.028), while there was no significant difference in DCR (62.7% vs. 43.6%; *P*=0.051). No statistically significant differences between the TLS and LS groups were found for ORR (36.0% vs. 25.7%; *P*=0.262) or DCR (61.3% vs. 43.6%; *P*=0.071) according to RECIST v1.1 criteria.

Safety

In the PSM-matched cohort, the incidence of TRAEs of any grade was 1.90 and 2.24 per patient among the LS and TLS groups, respectively (*P*=0.196, **Table 5**). For TRAEs of grade ≥3, the incidences were 0.23 per patient in the LS group and 0.37 per patient in the TLS group (*P*=0.116). There were no significant differences in the numbers of patients experiencing TRAEs between the two groups (data not shown). The most common TRAEs of any grade were hypertension (0.31 per patient) and decreased appetite (0.26 per patient) in the LS group and hypertension (0.29 per patient) and decreased platelet count (0.29 per patient) in the TLS group. The most common grade ≥3 TRAE was hypertension in both the LS and TLS groups (0.15 and 0.17 per patient, respectively). All TRAEs in this study were consistent with the known safety profile of the treatments used and could be managed by treatment interruption or dose modification. There were no deaths or permanent treatment discontinuations due to a TRAE in either group.

Table 3. Univariate and multivariate analyses of risk factors for OS

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Treatment group (TLS vs. LS)	0.417 (0.224-0.776)	0.006	0.349 (0.176-0.692)	0.003
Age group (>65 vs. ≤65 years)	1.116 (0.547-2.277)	0.763	1.268 (0.411-3.916)	1.268
Age	1.002 (0.971-1.033)	0.903		
Sex (male vs. female)	1.140 (0.405-3.211)	0.805		
Hepatitis (presence vs. absence)	0.444 (0.107-1.847)	0.264		
Liver cirrhosis (presence vs. absence)	0.851 (0.446-1.623)	0.624		
AFP group (>400 vs. ≤400 ng/ml)	0.576 (0.854-2.910)	0.146		
AFP	1.000 (1.000-1.000)	0.562	1.000 (1.000-1.000)	0.524
Child-Pugh class (B vs. A)	1.608 (0.818-3.160)	0.168		
BCLC stage (C vs. B)	2.211 (1.083-4.514)	0.029	1.268 (0.411-3.916)	0.679
ECOG PS				
1 vs. 0	1.476 (0.764-2.848)	0.246	1.285 (0.629-2.627)	0.492
2 vs. 0	3.268 (1.118-9.551)	0.030	0.787 (0.129-4.789)	0.795
Metastasis (presence vs. absence)	2.483 (1.313-4.696)	0.005	1.888 (0.706-5.052)	0.206
Vascular invasion (presence vs. absence)	1.215 (0.604-2.443)	0.585		
Tumor size (>10 vs. ≤10 cm)	1.929 (1.029-3.615)	0.040	1.713 (0.871-3.371)	0.119
Tumor number (>3 vs. ≤3 cm)	1.664 (0.897-3.084)	0.106		
History of treatment (yes vs. no)	0.707 (0.377-1.325)	0.279		
CA19-9 level	1.005 (1.002-1.007)	0.001	1.005 (1.002-1.008)	0.000
ALP level	1.006 (1.003-1.009)	0.000	1.003 (0.999-1.008)	0.172
ALBI grade				
2 vs. 1	1.369 (0.702-2.670)	0.357		
3 vs. 1	1.974 (0.441-8.826)	0.374		

Abbreviations: AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; BCLC, Barcelona Clinic Liver Cancer; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; LS, lenvatinib plus sintilimab; OS, overall survival; TLS, transarterial chemoembolization combined with lenvatinib plus sintilimab.

Discussion

The results of this retrospective study using PSM show that the TLS triple combination regimen led to significantly longer PFS and OS compared with LS, suggesting that the addition of TACE to lenvatinib and sintilimab can prolong survival and improve the prognosis of patients with intermediate or advanced stage HCC. This result was further supported by multivariate Cox regression analyses, which identified treatment with TLS versus LS as an independent predictor of improved PFS and OS.

The improved survival observed with the triple TLS regimen versus LS may be due to a synergistic antitumor effect of the three treatments. In addition to causing tumor ischemia by embolizing tumor-feeding arteries, local TACE interventions introduce higher local concentrations of chemotherapeutic agents to the liver, thereby inducing tumor death [30]. However, transarterial interventions can promote VEGF expression, which is highly expressed in HCC and is a key mediator of the immunosuppressive microenvironment [31]. Lenvatinib acts on the VEGF pathway to inhibit tumor angiogenesis and reduce the high metastatic and invasive nature of tumors that result from VEGF overexpression [32]. Furthermore, lenvatinib increases the infiltration of T lymphocytes in the immunosuppressive microenvironment [33]. Immune checkpoint inhibitors (ICIs) need to function under the conditions of T lymphocyte infiltration [34], therefore, lenvatinib provides an effective immunotherapeutic microenvironment for anti-PD-1 therapy. Meanwhile, ICIs synergistically restore the immune-supportive environment and promote the normalization of blood vessels [35]. Previous preclinical trials have

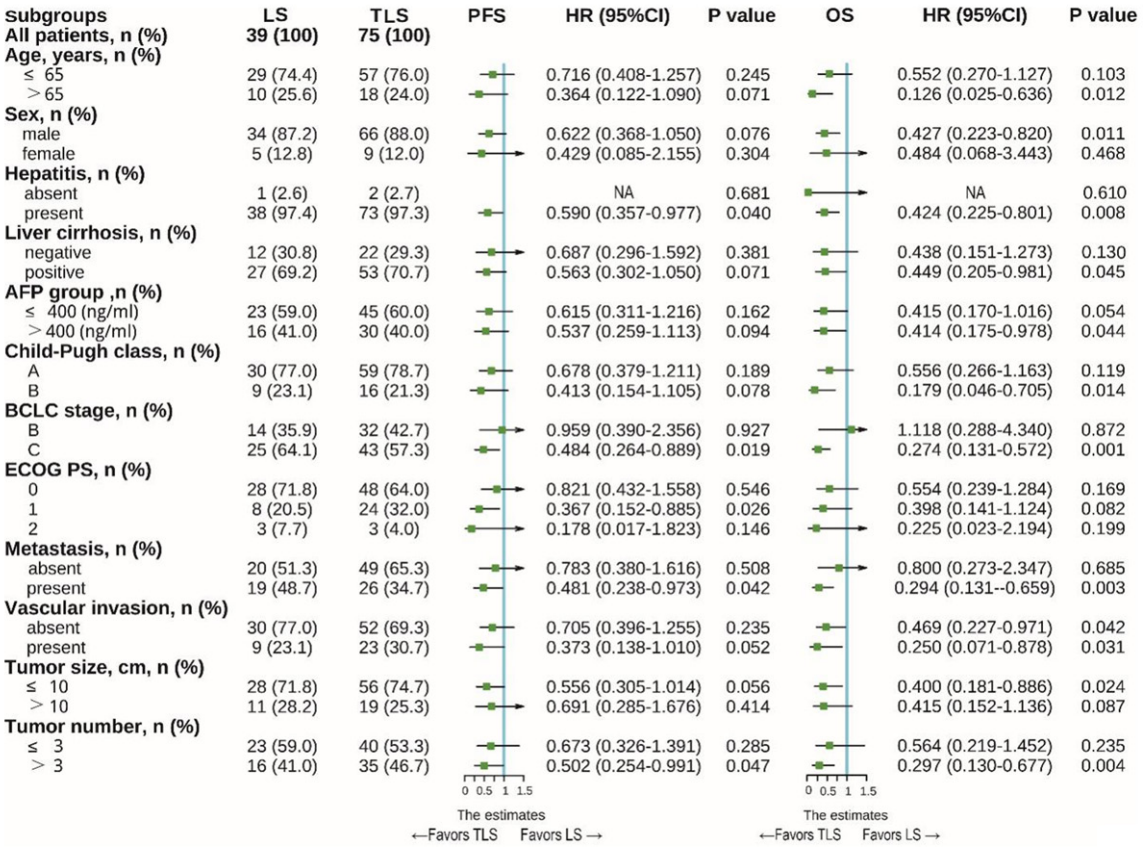

Figure 3. Forest plot of subgroup analysis by baseline characteristics for PFS and OS. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratios; LS, lenvatinib plus sintilimab; OS, overall survival; PFS, progress-free survival; TLS, transarterial chemoembolization combined with lenvatinib plus sintilimab.

Table 4. Tumor response

n (%)	RECIST 1.1			mRECIST		
	LS n=39	TLS n=75	*P*-value	LS n=39	TLS n=75	*P*-value
CR	0	0	-	0	2 (2.7)	0.546
PR	10 (25.7)	27 (36.0)	0.262	9 (23.1)	31 (41.3)	0.053
SD	7 (17.9)	19 (25.3)	0.373	8 (20.5)	14 (18.7)	0.813
PD	22 (56.4)	29 (38.7)	0.071	22 (56.4)	28 (37.3)	0.051
ORR	10 (25.7)	27 (36.0)	0.262	9 (23.1)	33 (44.0)	0.028
DCR	17 (43.6)	46 (61.3)	0.071	17 (43.6)	47 (62.7)	0.051

Abbreviations: CR, complete response; DCR, disease control rate (CR+PR+SD); LS, lenvatinib plus sintilimab; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumors; ORR, overall response (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease; TLS, transarterial chemoembolization combined with lenvatinib plus sintilimab.

demonstrated synergistic antitumor effects when combining sorafenib with chemotherapeutic agents, while combining lenvatinib and PD-1 inhibitors can also increase chemotherapeutic drug delivery by promoting vascular normalization [24, 36]. In line with the results of these previous studies, our study showed that the addition of TACE to lenvatinib and sintilimab may have a stronger antitumor effect compared with lenvatinib and sintilimab alone.

Previous studies have indicated that patients with Child-Pugh class A liver function may have a better response to lenvatinib than those with Child-Pugh class B, potentially due to the difficulty in maintaining a high relative dose intensity and the higher frequency of dose reductions due to adverse events in patients with Child-Pugh class B liver function [37]. Similarly, in our study, Child-Pugh class B was a risk factor for PFS in a univariate analysis, although it

Table 5. Safety summary

Variable	LS (n=39)		TLS (n=75)		*P* value	
	Any grade, n (Incidence*)	Grade ≥3, n (Incidence*)	Any grade, n (Incidence*)	Grade ≥3, n (Incidence*)	Any grade	Grade ≥3
TRAEs	74 (1.90)	9 (0.23)	168 (2.24)	28 (0.37)	0.196	0.116
Decreased appetite	10 (0.26)	0	11 (0.15)	0	0.152	-
Hypertension	12 (0.31)	6 (0.15)	22 (0.29)	13 (0.17)	0.874	0.791
Fatigue	9 (0.23)	0	13 (0.17)	0	0.461	-
Hand-foot skin reaction	5 (0.13)	2 (0.051)	15 (0.20)	2 (0.027)	0.339	0.888
Decreased neutrophil count	2 (0.51)	0	16 (0.21)	3 (0.04)	0.024	0.516
Decreased platelet count	5 (0.13)	0	22 (0.29)	4 (0.053)	0.049	0.351
Abnormal liver function	6 (0.15)	0	13 (0.17)	2 (0.027)	0.791	0.782
Bleeding	7 (0.18)	1 (0.026)	16 (0.21)	1 (0.013)	0.669	1.000
Rash	7 (0.18)	0	10 (0.13)	1 (0.013)	0.512	1.000
Proteinuria	3 (0.08)	0	5 (0.067)	0	1.000	-
Muscle pain	1 (0.026)	0	4 (0.053)	2 (0.027)	0.839	0.782
Dysphonia	0	0	4 (0.053)	0	0.351	-
Vomiting	2 (0.051)	0	12 (0.16)	0	0.168	-
Diarrhea	5 (0.13)	0	5 (0.067)	0	0.451	-

*Number of TRAEs per patient. Abbreviations: LS, lenvatinib plus sintilimab; PSM, propensity score matching; TLS, transarterial chemoembolization combined with lenvatinib plus sintilimab; TRAEs, treatment-related adverse events.

was not an independent prognostic indicator in multivariate analysis. Furthermore, BCLC stage C HCC was a risk factor for OS in a univariate analysis, which may be caused by poor biological behavior of tumors [38], but was not an independent prognostic indicator in multivariate analysis.

Giant HCC is common in China due to hepatitis B virus (HBV) is the main underlying cause of HCC. In contrast, internationally, HCC is mostly related to the hepatitis C virus (HCV) and alcohol-related liver damage, which results in smaller tumors [39]. It has previously been reported that tumors with a diameter >10 cm are associated with a higher frequency of extracapsular tumor invasion into the liver parenchyma, a higher frequency of intrahepatic metastases, and lower survival rates [40-42]. Consistent with this, in our study, the presence of tumors >10 cm was a risk factor for OS in univariate, but not multivariate analysis. Other than the treatment regimen, levels of the tumor marker CA19-9 were the only other independent prognostic indicators of OS in multivariate analysis. CA19-9 is mainly used as a sensitive biomarker for pancreatic malignancies, although previous studies have shown that high levels of CA19-9 are an independent predictor of poor survival in HCC [43-45]. In our study, each unit increase in CA19-9 concentration was associated with a 0.5% increase in the risk of death.

In subgroup analyses, TLS provided a PFS and OS advantage compared with LS across all subgroups evaluated, with statistically significant differences reported for many subgroups. Previous studies have shown that treatment with lenvatinib, PD-1 inhibitors and interventional treatments are more beneficial than treatment with lenvatinib and PD-1 inhibitors alone in patients with tumor diameters ≤10 cm and with >3 tumors [25]. This is consistent with the findings from our study, which demonstrated a 60% lower risk of death with TLS versus LS for patients with a tumor diameter ≤10 cm and 70% lower for patients with >3 tumors. This suggests that triple combination therapy with TACE, lenvatinib and sintilimab may contribute to better disease control in patients with multiple small intrahepatic lesions. Notably, patients with extrahepatic metastases also benefited more from the triple combination regimen, most likely due to the addition of interventional therapy leading to better control of intrahepatic lesions. For patients with metastases, the risk of disease progression and the risk of death was 52% and 71% lower, respectively, with TLS versus LS. This finding is important as the incidence of HCC with extrahepatic metastases is

increasing each year, with autopsies indicating that up to 64% of patients with HCC may have extrahepatic metastases at the time of death [46]. However, it has also been documented that 66-89% of patients with advanced HCC die from intrahepatic tumor progression or liver failure, rather than from the progression of distant metastatic HCC lesions [47]. Therefore, aggressive control of primary intrahepatic lesions is also required to prolong patient survival. By retrospectively analyzing the clinical data of patients with HCC and extrahepatic metastases, Jung et al. and Yoo et al. found that controlling intrahepatic primary tumors using TACE prolonged OS, which is consistent with the findings in the present study [48, 49]. However, further comparative analysis of prospective clinical trials is needed to determine whether primary resection or continued non-surgical treatment should be performed when the primary intrahepatic lesion is resectable.

In a phase Ib clinical trial of lenvatinib combined with pembrolizumab, a high proportion (67%) of patients receiving the standard dose of lenvatinib (12 mg per day for patients ≥60 kg and 8 mg per day for patients <60 kg) experienced a grade ≥3 TRAE [17]. In order to improve the tolerability of treatment and to increase the number of treatment courses received, all patients treated at the Tianjin Medical University Cancer Institute & Hospital received the lower dose of lenvatinib (8 mg per day). No significant differences in adverse reactions were observed between the two treatment groups in this study. Adverse reactions were mainly mild to moderate in both groups and were alleviated by a reduction of drug dose or symptomatic treatment. All treatment regimens were well tolerated in this study.

In this study, we used PSM to balance patient baseline characteristics in the two treatment groups. Although after PSM there were only 39 patients in the LS group, we believe this did not lead to statistical bias for a number of reasons. Firstly, there were no large differences in the baseline characteristics of patients in the LS group before versus after PSM (Supplementary Table 1). Furthermore, PSM is commonly used to deal with imbalances in baseline variables between groups in observational studies and reduce the possibility of confounding and bias. Indeed, despite the relatively small sample size in the LS group in the present study, the differences in treatment outcomes between the two groups were statistically significant, suggesting the results are meaningful and the sample size was sufficient for statistical analysis. Finally, most previous studies comparing triple and double combination therapy in HCC included a similarly small number of patients in the dual therapy group [50, 51].

The present study has several limitations that should be mentioned. Firstly, this trial was a single-center, retrospective study of a small number of patients with a relatively short follow-up period. A randomized, controlled trial with a larger sample size and a longer follow-up period is required for further validation of our findings. Furthermore, the primary cause of HCC in China is HBV infection and it remains to be determined whether the results of this study are applicable to countries where HCV infection is the primary cause of HCC.

Conclusion

The results of this study showed that triple combination therapy with TACE, lenvatinib and sintilimab improved survival with an acceptable safety profile compared to double combination therapy with lenvatinib and sintilimab in patients with intermediate or advanced stage HCC. Large-scale, randomized, controlled trials are needed to confirm these results.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Baseline of patients in the LS group before and after PSM

Variable	Before PSM n = 54	After PSM n = 39	*P* value
Age, n (%)			0.409
≤65 years	44 (81.5)	29 (74.4)	
>65 years	10 (18.5)	10 (25.6)	
Sex, n (%)			0.984
Female	7 (13.0)	5 (12.8)	
Male	47 (87.0)	34 (87.2)	
Hepatitis, n (%)			0.984
None	2 (3.7)	1 (2.6)	
HBV	48 (88.9)	35 (42.2)	
HCV	3 (5.6)	2 (5.1)	
Both HBV and HCV	1 (1.9)	1 (2.6)	
Liver cirrhosis, n (%)			0.656
Positive	35 (64.8)	27 (69.2)	
AFP group, n (%)			0.342
≤400 (ng/ml)	37 (68.5)	23 (59.0)	
>400 (ng/ml)	17 (31.5)	16 (41.0)	
Child-Pugh class, n (%)			0.753
A	40 (74.1)	30 (76.9)	
B	14 (25.9)	9 (23.1)	
BCLC stage, n (%)			0.523
B	16 (29.6)	14 (35.9)	
C	38 (70.4)	25 (64.1)	
ECOG PS, n (%)			0.937
0	37 (68.5)	28 (71.8)	
1	12 (22.2)	8 (20.5)	
2	5 (9.3)	3 (7.7)	
Metastases, n (%)			0.235
Present	33 (61.1)	19 (48.7)	
Vascular invasion, n (%)			0.754
Present	11 (20.4)	9 (23.1)	
Tumor size, cm, n (%)			0.509
≤10	42 (77.8)	28 (71.8)	
>10	12 (22.2)	11 (28.2)	
Tumor number, n (%)			0.566
≤3	35 (64.8)	23 (59.0)	
>3	19 (35.2)	16 (41.0)	
History of local treatment, n (%)			0.472
Yes	29 (53.7)	18 (46.2)	