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ORIGINAL RESEARCH

Efficacy of Lenvatinib Combined with PD-1 Inhibitor versus Sorafenib and PD-1 Inhibitor with or Without TACE for Hepatocellular Carcinoma with Extrahepatic Metastasis

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Background: Lenvatinib or Sorafenib combined with programmed cell death protein-1 (PD-1) inhibitor as recommend treatment of advanced hepatocellular carcinoma (HCC) with extrahepatic metastasis (EHM). We aimed to compared the prognosis of Lenvatinib plus PD-1 inhibitor (Len+PD-1) versus Sorafenib plus PD-1 (Sora+PD-1) as an initial therapy for HCC with EHM.

Methods: Incorporating a sum of 229 HCC patients with EHM were encompassed within this study, with 127 in the Sora+PD-1 group and 102 in the Len+PD-1 group. Through propensity score matching (PSM), we compared overall survival (OS), progression-free survival (PFS), and patient safety between these two groups.

Results: The median OS were 13.0 months and 14.2 months in the Sora+PD-1 group and Len+PD-1 group. The 6-, 12-, and 24-month OS rates were 92.9%, 58.9% and 5.6% in Sora+PD-1 group and 93.1%, 61.8% and 22.6% in Len+PD-1 group, respectively. The Len+PD-1 group had obviously better OS than the Sora+PD-1 group ($P = 0.002$). The 3-, 6-, and 12-month PFS rates were 76.4%, 27.6% and 1.6% in Sora+PD-1 group and 86.2%, 50.5% and 12.2% in Len+PD-1 group, respectively. Compared with Sora+PD-1 group, the Len+PD-1 group had obviously better PFS ($P < 0.001$). Analysis within subgroups showed that OS was significant in patients receiving TACE in Len+PD-1 group than Sora+PD-1 group ($p = 0.003$).

Conclusion: Len+PD-1 group had longer OS and PFS than Sora+PD-1 group for patient with EHM. In addition, OS in patients received TACE was improved with Len+PD-1 treatment. For patients without TACE, there was no significance between Sora+PD-1 and Len+PD-1 groups.

Keywords: hepatocellular carcinoma, extrahepatic metastasis, lenvatinib, sorafenib, PD-1 inhibitor

Introduction

Hepatocellular carcinoma (HCC) stands as the sixth most prevalent cancer and the fourth lethal malignancy across the globe.[1] With its insidious onset and rapid progression, HCC often leads to a poor prognosis.[2] Therefore, HCC with extrahepatic metastasis (EHM) is not relatively rare at the time of diagnosis.[3,4] Previous studies reported that HCC with EHM had obviously poorer outcome than those without EHM.[4,5] Data has proven that HCC with EHM, the expected median survival was 6–8 months.[5] The lungs are the most common organ for extrahepatic spread, but most metastases are multifocal and often unsuitable for curable therapy. Thus, the clinical conclusion and prognosis of patients with EHM usually administered with system therapy.[6]

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Since the success of Sorafenib in advanced hepatocellular carcinoma, the Food and Drug Administration (FDA) received authorization to Sorafenib as the primary targeted therapeutic approach for advanced HCC for a duration of ten years.[7,8] It was the first such therapy to demonstrate efficacy and remains the primary treatment option for advanced HCC in China.[9] After numerous failed studies, Lenvatinib emerged as the first drug to demonstrate noninferiority to Sorafenib regarding overall survival (OS), as shown in the Phase 3 trial of Lenvatinib.[10] Lenvatinib and Sorafenib are the two initial multitarget tyrosine kinase inhibitor (TKI) drugs for advanced HCC now in China, especially for the EHM.[9] While single system therapy for this advanced stage tumor was challenging and unsatisfactory.[3,9] Thus, the combination therapy is the tendency for advanced HCC with EHM.[4,9] It is reasonable to anticipate that combining TKI with other treatments would yield benefits over using TKI alone.

Programmed cell death protein 1 (PD-1) inhibitor as one of the immunotherapy methods has obtained much attention and is effective for advanced HCC, enhancing anti-tumor effect of T cells by eliminating immunosuppression.[11] Promising outcomes with PD-1 inhibitors have transformed the therapeutic intervention for advanced HCC.[12] Yet, the objective response rate (ORR) of PD-1 monotherapy was about 16.9–20% for advanced HCC.[13] Numerous studies have demonstrated that combination of PD-1 inhibitor with TKI has presented obvious efficacy in advanced HCC.[11,14] The incorporation of antiangiogenic drugs with PD-1 inhibitor can enhance antitumor responses via many approaches. Firstly, the combination could produce synergistic effect by regulating the vasculature and the immune microenvironment of tumors.[15,16] Secondly, the combination may enhance antigen presentation in dendritic cells.[16] Thirdly, the combined use of these drugs can promote T cell activation in the priming phase, as well as stimulate the mobilization of T cells from the lymph nodes to the tumor microenvironment.[17]

Currently, there were many literatures have reported Lenvatinib plus PD-1 inhibitor for advanced HCC.[18] However, literatures about sorafenib plus PD-1 are rarely documented. Thus, this investigation was undertaken to assess and contrast the efficacy of Lenvatinib plus PD-1 inhibitor versus Sorafenib plus PD-1 inhibitor on the prognosis of HCC with EHM.

Methods

Patients and Study Design

We retrospectively reviewed data on consecutive patients diagnosed HCC with EHM from January 2019 to December 2021 at Nanfang Hospital of Southern Medical University, Hunan Provincial People's Hospital, the First Affiliated Hospital of Sun Yat-Sen University. The study was centrally approved by the ethics committee of Hunan Provincial People's Hospital and was conducted according to the guidelines of the Declaration of Helsinki.[19] In the light of the retrospective design of the study, obtaining informed consent from participants was not deemed necessary.

Patient inclusion was determined according to the following criteria: (1) primary unresectable HCC, either histologically or clinically as per the criteria set by the American Association for the Study of Liver Diseases;[20] (2) Barcelona Clinic Liver Cancer (BCLC) stage C with EHM; (3) Child-Pugh class A or B, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0; (4) no history of other malignancies. Patients were excluded for any of these reasons: (1) recurrent HCC; (2) age under 18 or over 75; (3) advanced HCC involving the atrium or vena cava; (4) incomplete clinical data; (5) loss to follow-up within 3 months post-treatment. Figure 1 displays the flowchart outlining the process of patient selection.

Treatment and Assessment of Response

Tumor staging was determined through systemic imaging modalities, including contrast-enhanced computed tomography (CT) scans of the chest or bone, magnetic resonance imaging (MRI) scans of the abdomen or brain, or positron emission tomography/computer tomography (PET/CT). This examination was conducted within 2 weeks prior to initiating systemic therapy. Patients were classified into two groups (a) The Len+PD-1 group, where Lenvatinib and PD-1 inhibitor were administered together. (b) The Sora+PD-1 group, where Sorafenib and PD-1 inhibitor were used in combination.

Comprehensive data pertaining to treatment initiation, completion, and any encountered adverse events (AEs) were meticulously collected. The recommended dosage of Lenvatinib was administered orally at 12 mg/day for patients weighing of 60 kg or more and 8 mg for individuals with a weight below 60 kg. Sorafenib was originally prescribed at an oral dosage of 400 mg administered twice daily, with dose reductions for both Lenvatinib and Sorafenib implemented in

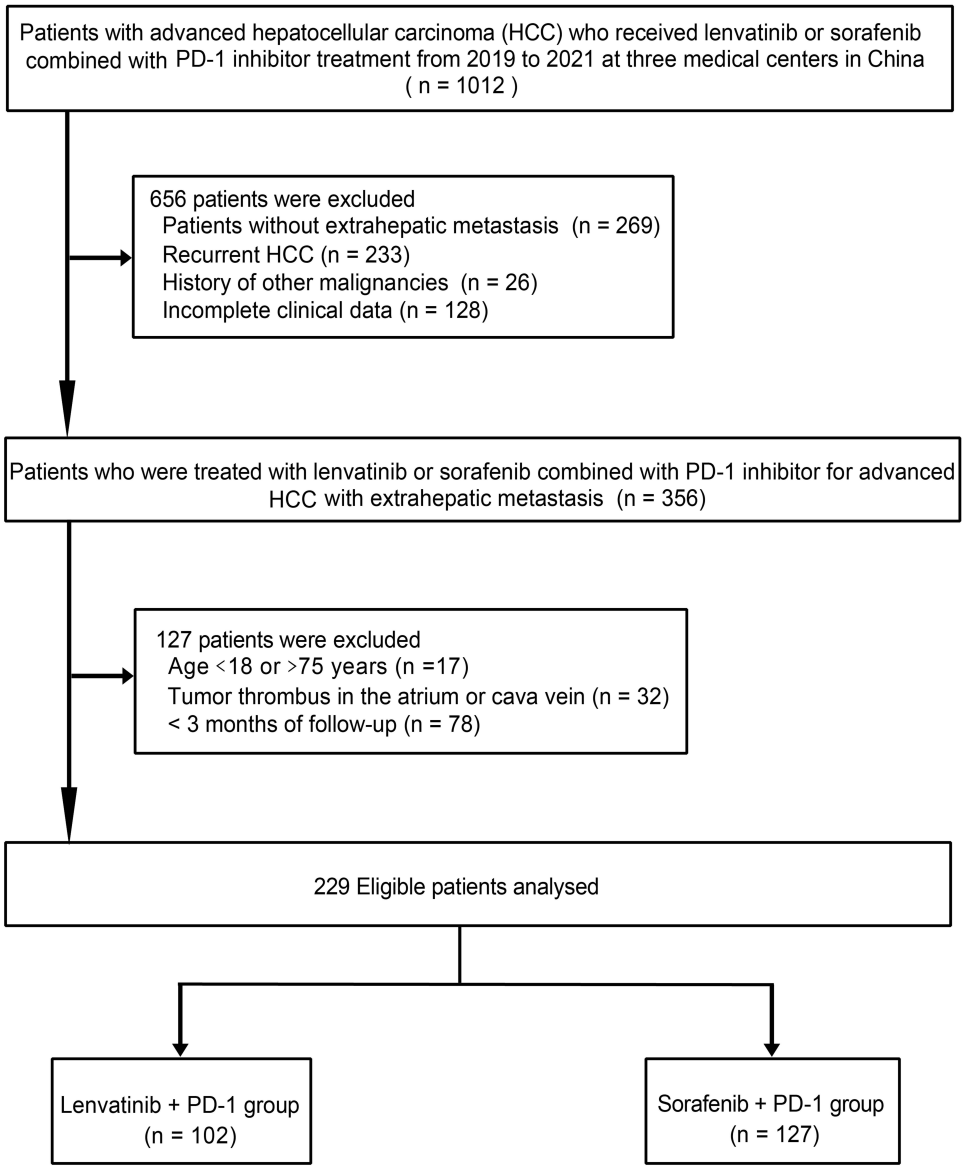

Figure 1 Flow chart of patient selection.

consideration of the occurrence of toxicity. PD-1 inhibitors (including pembrolizumab, nivolumab, sintilimab, toripalimab, camrelizumab) were dosed according to their respective instructions. In cases where adverse events of grade 3 or 4, such as hematologic toxicity, skin-related adverse effects, gastrointestinal complications, hypertension, or hepatic dysfunction (defined by the National Cancer Institute Common Terminology Criteria for Adverse Events), were manifested,[21] dose adjustments were made until the symptoms were alleviated or eliminated. If these adverse effects persisted after adjustment, therapeutic intervention with Lenvatinib and Sorafenib administration was suspended until the effects were alleviated or resolved.

Tumor imaging evaluation was conducted following the guidelines stipulated by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).[22] Complete Response (CR) defined as disappearance of all lesions and pathologic lymph nodes. Partial Response (PR): A decrease of a minimum of 30% in the dimensions of the targeted tumors. Progressive Disease (PD): An increment of no less than 20% in the total dimensions of the specified tumors, or the emergence of a novel lesion. Stable Disease (SD): A condition that met neither the criteria for CR, PR, nor PD. The Objective Response Rate (ORR) was calculated in the aggregate of CR and PR, while the Disease Control Rate (DCR)

encompassed CR, PR, and Stable Disease (SD). Tumor assessments were conducted at regular 6–8 weeks intervals, regardless of dose interruptions or the absence of radiological progression.

Outcomes and Definitions

The main aim of this investigation encompassed overall survival (OS), characterized as the time span between the commencement of systemic therapy and the time of death or the latest follow-up. The secondary endpoints included progression-free survival (PFS) and safety. PFS defined as the time from the date of accepting system therapy to tumor progression or last follow-up. Liver function was assessed using the Albumin-Bilirubin (ALBI) grade.[23] Portal hypertension was defined as the hepatic venous pressure gradient (HVPG) >10 mmHg.[24] Portal vein tumor thrombus (PVTT) type according to Cheng's criteria.[25] The classifications are as follows: I-segmental/sectoral branches of portal vein, II-left and/or right portal vein, III-main portal vein trunk, and IV-superior mesenteric vein.

Follow-Up

Patients underwent evaluation at minimum intervals of 4 weeks following systemic treatment. These evaluations included image examinations, such as contrast-enhanced CT/MRI and laboratory tests encompassing measurements of alfa-fetoprotein (AFP), albumin, bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT). The entire cohort had a median follow-up period of 16.5 months, with the follow-up phase of the study concluding on October 31, 2022.

Statistical Analysis

The employment of propensity score-matching (PSM) study was aimed to mitigate the effects of potential selection bias and plausible confounding may arise among the two cohorts. This was accomplished through the implementation of a multivariate logistic regression model, incorporating various pertinent variables tailored to the study: age, sex, ALT level, AST level, hepatitis, metastasis organs, metastasis sites, tumor size level, tumor number, PVTT type, AFP level, and transarterial chemoembolization (TACE). Patients were paired in a 1:1 ratio employing the nearest neighbor approach maintaining a caliper of 0.2 (Supplementary Figure 1).

Statistical comparisons between the two groups were conducted through the utilization of Pearson $\chi 2$ test and Fisher's exact test, specifically applied to categorical variables. Survival curves for overall survival (OS) and progression-free survival (PFS) were formulated using the Kaplan–Meier method and compared using the Log rank test. Variables identified as significant in univariate analysis were entered into the multivariate Cox proportional hazards regression analysis to identify independent prognostic factors. All statistical investigates were of a two-sided nature, with a statistical significance threshold set at $p< 0.05$. The Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL, USA), and R software for Windows were employed to conduct the statistical computations (Version 4.1.3 http://www.r-project.org).

Results

Baseline Characteristics

A collective sum of 229 patients were included for analysis according to the criteria. Among them, 199 (86.9%) patients were hepatitis B surface antigen (HBsAg) positive, 127 patients received Sorafenib combined with PD-1 inhibitor (Sora +PD-1 group) and 102 patients received Lenvatinib combined with PD-1 inhibitor (Len+PD-1 group). Propensity score–matching analysis created two balanced cohorts of 82 patients each in the Sora+PD-1 and Len+PD-1 groups, using a 1:1 matching ratio. The standardized mean difference for all baseline variables was less than 10%, demonstrating a well-matched comparison (Supplementary Figure 2). Compared to the Sora+PD-1 group, the Len+PD-1 group showed more proportion of patients with tumor size ≤10 cm, metastasis sites ≤5, cirrhosis, ALT > 40 U/L, AST > 40 U/L in the entire cohort. After applying PSM, no statistically meaningful disparities were observed between the two groups. The demographic characteristics, underlying causes of liver disease, and tumor attributes for both the entire and matched cohorts are consolidated in Table 1.

Table 1 Baseline Characteristics of Advanced Hepatocellular Carcinoma (HCC) Patients with Extrahepatic Metastasis (EHM) in Different Treatment Groups

Characteristics	Entire Cohort			Propensity Score-matched Cohort (1:1 ratio)		
	Sora+PD-1 Group (n=127)	Len+PD-1 Group (n=102)	*P* value	Sora+PD-1 Group (n=82)	Len+PD-1 Group (n=82)	*P* value
Age, n (%)			0.116			0.175
≤ 60	81 (63.8)	75 (73.5)		53 (64.6)	61 (74.4)	
>60	46 (36.2)	27 (26.5)		29 (35.4)	21 (25.6)	
Sex, n (%)			0.791			0.678
Male	108 (85.0)	88 (86.3)		67 (81.7)	69 (84.1)	
Female	19 (15.0)	14 (13.7)		15 (18.3)	13 (15.9)	
ALT, U/L, n (%)			0.010			0.876
≤ 40	74 (58.3)	42 (41.2)		41 (50.0)	40 (48.8)	
>40	53 (41.7)	60 (58.8)		41 (50.0)	42 (51.2)	
AST, U/L, n (%)			0.003			0.867
≤ 40	59 (46.5)	28 (27.5)		26 (31.7)	27 (32.9)	
>40	68 (53.5)	74 (72.5)		56 (68.3)	55 (67.1)	
TACE, n (%)			0.757			0.861
No	35 (27.6)	30 (29.4)		23 (28.0)	22 (26.8)	
Yes	92 (72.4)	72 (70.6)		59 (72.0)	60 (73.2)	
Tumor size, cm, n (%)			0.041			0.754
≤ 10	55 (43.3)	58 (56.9)		42 (51.2)	44 (53.7)	
>10	72 (56.7)	44 (43.1)		40 (48.8)	38 (46.3)	
Tumor number, n (%)			0.229			0.724
≤ 3	39 (30.7)	25 (24.5)		23 (28.0)	21 (25.6)	
>3	88 (69.3)	77 (75.5)		59 (72.0)	61 (74.4)	
AFP, ng/mL, n (%)			0.746			0.526
≤ 400	55 (43.3)	42 (41.2)		32 (39.0)	36 (43.9)	
>400	72 (56.7)	60 (58.8)		50 (61.0)	46 (56.1)	
PVTT type, n (%)			0.605			0.700
No	26 (20.5)	22 (21.6)		18 (22.0)	19 (23.2)	
I-II	65 (51.2)	57 (55.9)		46 (56.0)	41 (50.0)	
III-IV	36 (28.3)	23 (22.5)		18 (22.0)	22 (26.8)	
ALBI grade, n (%)			0.591			0.671
Grade 1	16 (12.6)	10 (9.8)		9 (11.0)	9 (11.0)	
Grade 2	95 (74.8)	75 (73.5)		63 (76.8)	59 (72.0)	
Grade 3	16 (12.6)	17 (16.7)		10 (12.2)	14 (17.0)	
Metastasis organs, n (%)			0.224			0.315
Lung	35 (27.6)	38 (37.3)		24 (29.3)	32 (39.0)	
Other organs	60 (47.2)	38 (37.3)		40 (48.8)	31 (37.8)	
Lung + other organs	32 (25.2)	26 (25.4)		18 (21.9)	19 (23.2)	
Metastasis sites, n (%)			0.015			0.737
≤5	32 (25.2)	41 (40.2)		25 (30.5)	27 (30.5)	
>5	95 (74.8)	61 (59.8)		57 (69.5)	55 (69.5)	

(*Continued*)

Table 1 (Continued).

Characteristics	Entire Cohort			Propensity Score-matched Cohort (1:1 ratio)		
	Sora+PD-1 Group (n=127)	Len+PD-1 Group (n=102)	*P* value	Sora+PD-1 Group (n=82)	Len+PD-1 Group (n=82)	*P* value
HBsAg, n (%)			0.152			0.115
Negative	13 (10.2)	17 (16.7)		8 (9.8)	15 (18.3)	
Positive	114 (89.8)	85 (83.3)		74 (90.2)	67 (81.7)	
HBV DNA, n (%)			0.190			1.000
≤ 2000 IU/mL	97 (76.4)	70 (68.6)		58 (70.7)	58 (70.7)	
>2000 IU/mL	30 (23.6)	32 (31.4)		24 (29.3)	24 (29.3)	
Anti-virus, n (%)			0.405			0.182
No	23 (18.1)	23 (22.5)		14 (17.1)	21 (25.6)	
Yes	104 (71.9)	79 (77.5)		68 (82.9)	61 (74.6)	
Cirrhosis, n (%)			0.046			0.531
No	79 (62.2)	50 (49.0)		42 (51.2)	46 (56.1)	
Yes	48 (37.8)	52 (51.0)		40 (48.2)	36 (43.9)	
Portal hypertension, n (%)			0.244			0.700
No	105 (82.7)	78 (76.5)		64 (78.0)	66 (80.5)	
Yes	22 (17.3)	24 (23.5)		18 (22.0)	16 (19.5)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; HBV DNA, hepatitis B virus deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; Len, lenvatinib; PVTT, portal vein tumor thrombus; PD-1, programmed cell death protein-1; Sora, sorafenib; TACE, transarterial chemoembolization.

Overall Survival Analysis Between Sora+PD-1 and Len+PD-1 Groups

In the full group of patients, the median OS were 13.0 ± 0.6 months (95% confidence interval [CI], 11.9–14.2) and 14.2 ± 1.0 months (95% CI, 12.2–16.2) in the Sora+PD-1 group and Len+PD-1 group, respectively. The 6-, 12-, and 24-month OS rates were 92.9%, 58.9% and 5.6% in Sora+PD-1 group and 93.1%, 61.8% and 22.6% in Len+PD-1 group in each case. After PSM, the median OS were 12.3.0±0.7 months (95% confidence interval [CI], 11.0–13.6) and 13.9 ± 1.1 months (95% CI, 11.8–16.0) in the Sora+PD-1 group and Len+PD-1 group, respectively. The 6-, 12-, and 24-month OS rates were 89.0%, 52.8% and 3.3% in Sora+PD-1 group and 95.1%, 57.8% and 25.1% in Len+PD-1 group. The Len+PD-1 group had obviously better OS than the Sora+PD-1 category across the entire study population (hazard ratio [HR], 0.62; 95% CI, 0.46–0.84; $P = 0.002$) (Figure 2A) and in the PSM group (HR, 0.59; 95% CI, 0.41–0.85; $P = 0.004$) (Figure 2B).

The univariate analysis of OS and PFS performed after PSM demonstrated in Supplementary Table 1. The multivariable analyses unveiled that Sora+PD-1 therapy (HR, 1.61; 95% CI, 117–2.41; $P = 0.006$), no TACE (HR, 2.73; 95% CI, 1.82–4.09; $P < 0.001$), PVTT type III–IV (HR, 1.79; 95% CI, 1.04–3.09; $P = 0.035$) and metastasis sites >5 (HR, 1.63; 95% CI, 1.07–2.46; $P = 0.022$) variables correlated with inferior overall survival (Table 2).

Effect of Treatment on Progression-Free Survival

In the full group of patients, the median PFS was 4.6 ± 0.4 months (95% CI, 3.8–5.3) in Sora+PD-1 group, and 6.1 ± 0.5 months (95% CI, 6.1–8.8) in Len+PD-1 group, respectively. The 3-, 6-, and 12-month PFS rates were 76.4%, 27.6% and 1.6% in Sora+PD-1 group and 86.2%, 50.5% and 12.2% in Len+PD-1 group, respectively. After PSM, the 3-, 6-, and 12-month PFS rates were 80.5%, 25.6% and 0% in Sora+PD-1 group, and 84.1%, 49.4% and 12.8% in Len+PD-1 group, respectively. The Len+PD-1 group demonstrated significantly enhanced PFS compared to the Sora+PD-1 category across the complete study population (HR, 0.54; 95% CI, 0.41–0.71; $P < 0.001$) (Figure 2C) and in the PSM cohort (HR, 0.55; 95% CI, 0.40–0.76; $P < 0.001$) (Figure 2D).

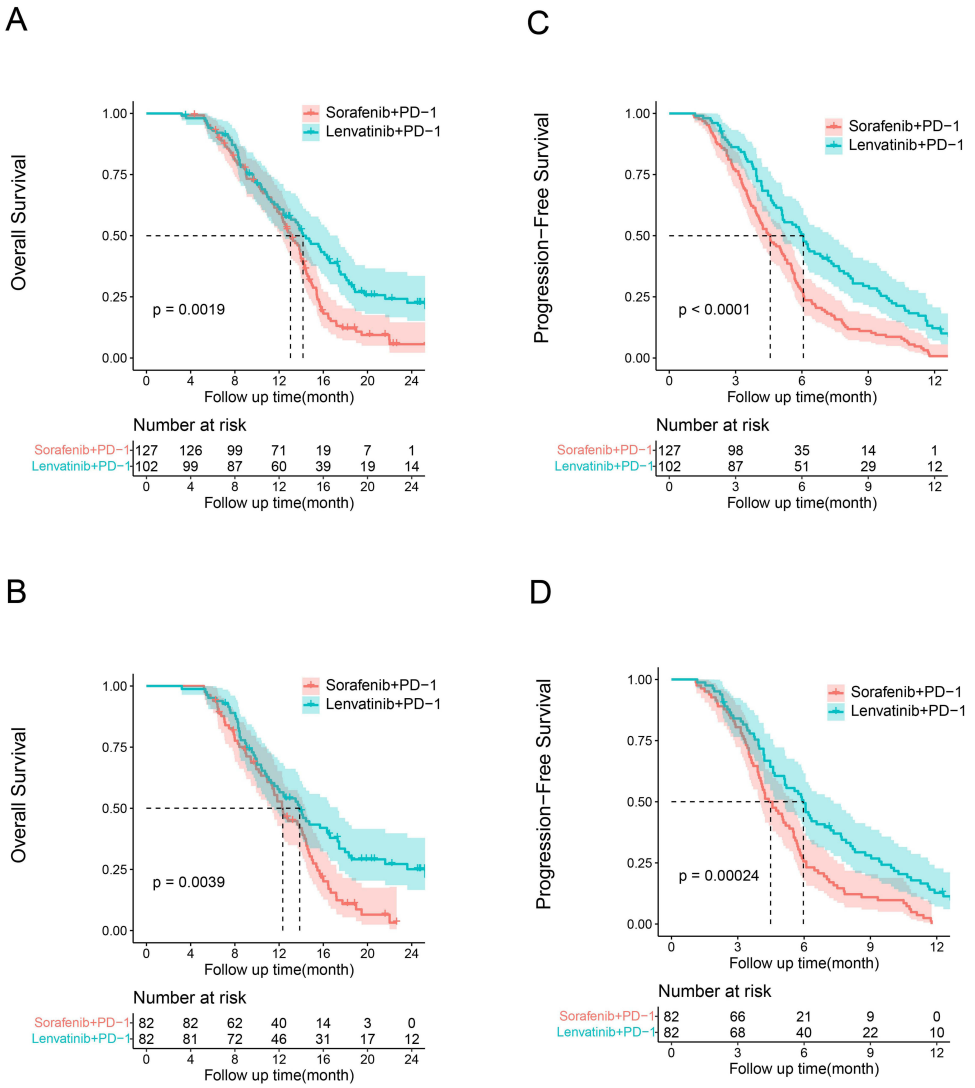

Figure 2 Kaplan–Meier curves of overall survival in the entire cohort (**A**) and in the propensity score-matched cohort (**B**), and progression-free survival in the entire cohort (**C**) and in the propensity score-matched cohort (**D**) of advanced hepatocellular carcinoma (HCC) patients with extrahepatic metastasis who received Lenvatinib or Sorafenib combined with programmed cell death protein-1 (PD-1) inhibitor.

Multivariate Cox regression investigation was conducted in PSM cohort and the results revealed that Sora+PD-1 therapy (HR, 1.95; 95% CI, 1.39–2.74; $P < 0.001$), PVTT type III–IV (HR, 1.72; 95% CI, 1.04–2.84; $P = 0.036$), metastasis sites >5 (HR, 2.89; 95% CI, 2.00–4.18; $P < 0.001$) were factors associated with reduced progression-free survival (Table 2).

Efficacy Evaluation

Tumor treatment response was assessed in accordance with RECIST 1.1 criteria, and the results after PSM were presented in Table 3. During the 3-month evaluation, ORR was 7.3%, 20.7% and the DCR was 61.0%, 69.5% in Sora +PD-1 group, Len+PD-1 group in each case. The proportion of PR, SD, and PD in two groups was obvious difference ($P = 0.021$) (Table 3). At the 6-month evaluation, ORR was 6.1%, 18.3% and the DCR was 19.5%, 36.6% in Sora+PD-1 group, Len+PD-1 group, respectively. Similarly, the proportions of CR, PR, SD, and PD revealed noticeable differences between the groups ($p = 0.038$) (Table 3).

Table 2 Multivariable Analyses of Prognostic Factors for Overall Survival (OS) and Progression-Free Survival (PFS) in Hepatocellular Carcinoma (HCC) with Extrahepatic Metastasis (EHM) After Propensity Score Matching (PSM)

Variable	Overall Survival		Progression-Free Survival	
	HR (95% CI)	*P value*	HR (95% CI)	*P value*
Treatment type		0.006		<0.001
Sora+PD-1 vs Len+PD-1	1.61 (117–2.41)		1.95 (1.39–2.74)	
TACE		<0.001		
Yes vs no	2.73 (1.82–4.09)			
PVTT type				
No	Reference		Reference	
I-II	0.98 (0.62–1.55)	0.928	0.90 (0.61–1.33)	0.589
III-IV	1.79 (1.04–3.09)	0.035	1.72 (1.04–2.84)	0.036
Metastasis sites		0.022		<0.001
≤5 vs >5	1.63 (1.07–2.46)		2.89 (2.00–4.18)	

Abbreviations: CI, confidence interval; HR, hazard ratio. Len, lenvatinib; PVTT, portal vein tumor thrombus; PD-1, programmed cell death protein-1; Sora, sorafenib; TACE, transarterial chemoembolization.

Table 3 Efficacy Outcomes in Patients with Infiltrative Hepatocellular Carcinoma (HCC) in Different Treatment Groups with RECIST1.1 Evaluation

Variables	Evaluation	Sora+PD-1 Group (n=82)	Len+PD-1 Group (n=82)	*P value*
3-month evaluation	CR	0	0	0.021
	PR	6 (7.3)	17 (20.7)	
	SD	44 (53.7)	40 (48.8)	
	PD	32 (39.0)	25 (30.5)	
6-month evaluation	CR	0	0	0.038
	PR	5 (6.1)	15 (18.3)	
	SD	11 (13.4)	15 (18.3)	
	PD	66 (80.5)	52 (63.4)	

Abbreviations: CR, complete response; Len, lenvatinib; PR, partial response; PD, progressive disease; PD-1, programmed cell death protein-1; SD, stable disease. Sora, sorafenib.

Subgroup Analysis on Prognosis of TACE Treatment

We further compared the TACE treatment on the prognosis of HCC with EHM in the PSM cohort. As shown in Table 1, there were 119 patients (59 in Sora+PD-1 group, 60 in Len+PD-1 group) received TACE treatment. The median OS of patients received TACE in Sora+PD-1 group and Len+PD-1 group were 14.1 ± 1.1 months and 15.7 ± 1.4 months, respectively. For Patient without TACE in Sora+PD-1 group and Len+PD-1 group were 8.3 ± 0.8 months and 8.9 ± 0.6 months. Intra-group analysis revealed that there was obvious difference of OS in Sora+PD-1 group ($P < 0.001$) (Figure 3A) and in Len+PD-1 group ($P < 0.001$) (Figure 3B) between patients with or without TACE. While the OS was significant difference for patients with TACE between Sora+PD-1 group and Len+PD-1 group ($P = 0.003$) (Figure 3C). No discernible distinction was noted in OS for patients without TACE between the two groups ($P = 0.373$) (Figure 3D). The OS in patients received TACE was longer in Len+PD-1 group than in Sora+PD-1 group, while for patients without TACE, no statistically significant disparities were observed between the two groups.

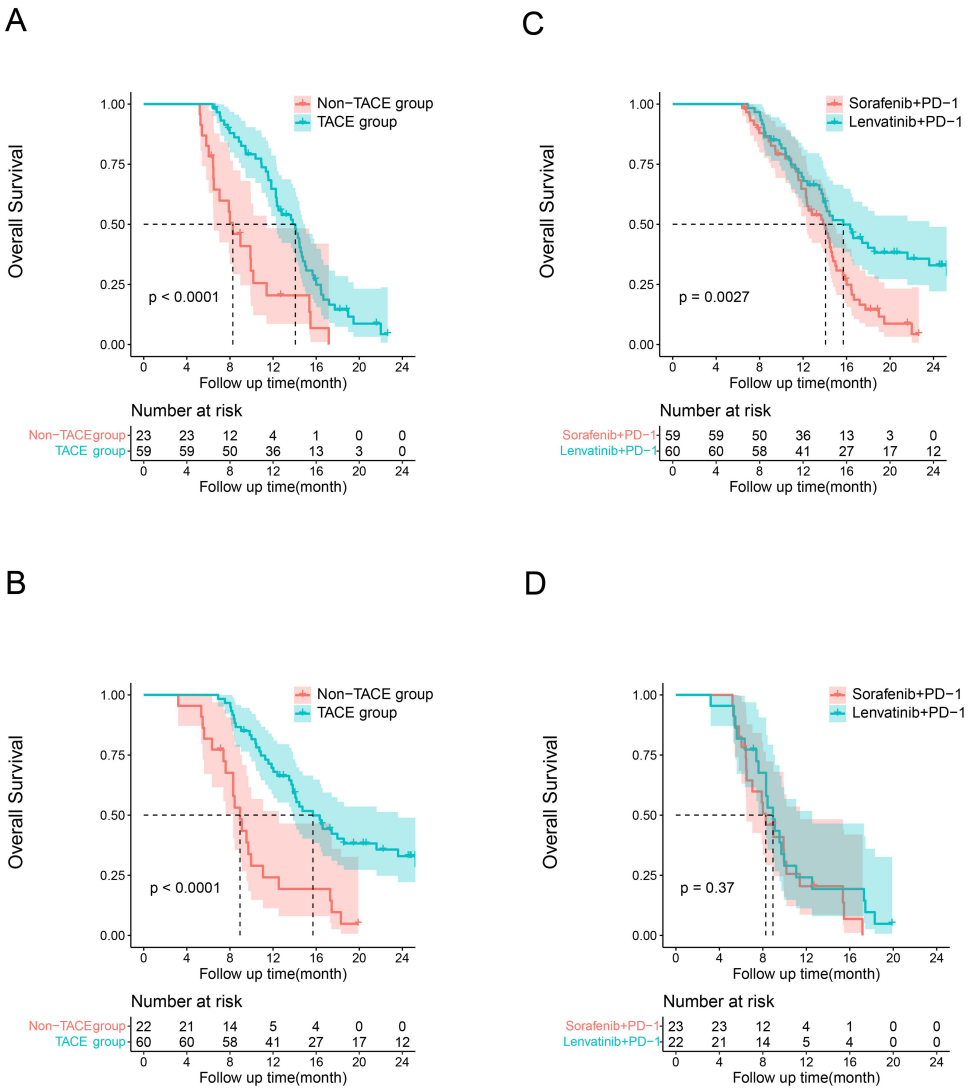

Figure 3 Kaplan–Meier curves for overall survival (OS) in advanced hepatocellular carcinoma (HCC) patients with extrahepatic metastasis who received Lenvatinib (Len) or Sorafenib (Sora) coupled with programmed cell death protein-1 (PD-1) inhibitor with or without transarterial chemoembolization (TACE) in propensity score–matching (PSM) cohort. The OS rate of patients with and without TACE in Sora+PD-1 group (**A**) and Len+PD-1 group (**B**), respectively; The OS rate of patient with TACE (**C**) and without TACE (**D**) between Sora+PD-1 and Len+PD-1 groups.

Treatment-Related Adverse Events

In the present study, no instances of treatment-related mortality were identified, notwithstanding the occurrence of treatment-associated adverse events in the majority of patients. The main adverse events were recorded in Supplementary Table 2. All 229 patients underwent at least 3 months of treatment with either Lenvatinib or Sorafenib plus a PD-1 inhibitor. Within the Len +PD-1 group, the average period of Lenvatinib treatment was 7.5 months (range, 4.0–20.0 months), compared to 6.2 months (range, 4.0–12.0 months) in the Sora+PD-1 group. For undesirable effects categorized as grade 1–2, symptomatic interventions or dose adjustments typically resulted in the amelioration of symptoms. In cases of grade 3–4 adverse events, administration of Lenvatinib or Sorafenib and the PD-1 inhibitor was temporarily suspended until the adverse effects were ameliorated or resolved. Treatment was then resumed if the patients recovered and it was deemed possible to continue.

Discussion

The efficacy of monotherapy is modest, and promising results from clinical trial of Lenvatinib combining PD-1 inhibitor has reshaped the treatment scheme.[4] Systemic therapy such as Sorafenib or Lenvatinib plus PD-1 immunotherapy

remains the recommended treatment modality for HCC patients with EHM.[14] Nowadays, there are two approved agents (Sorafenib and Lenvatinib) as the first-line options in China.[26] In this study, we analyzed 229 consecutive HCC patients with EHM undergoing treatment with TKI combined PD-1 inhibitor as Sora+PD-1 group (n = 127) and Len+PD-1 group (n = 102). We found that, compared with Sora+PD-1 treatment, Len+PD-1 treatment had significantly better OS and PFS in HCC patient with EHM. Len+PD-1 group yielded better ORR than Sora+PD-1 group (69.5% vs 61.0% at 3-month, 36.6% vs.19.5% at 6-month). The results demonstrated that Len+PD-1 group have better antitumor activity than Sora +PD-1 group.

In our study, the results showed that TACE was a protective factor for prognosis. Most patients in advanced stage would die of the liver failure due to the progression of high tumor burden in liver rather than EHM dissemination.[27] For patients with preferred liver function, addition of TACE would be beneficial. Peng Z et al have proven that addition of TACE improved clinical outcomes significantly for advanced HCC.[28] Even in patients with EHM, TACE as a local approach controlling intrahepatic tumors is still beneficial for improving the survival.[29,30]

Subgroup analysis revealed that OS in patients who received TACE resulted in better OS in Len+PD-1 group than Sora+PD-1 group, while for patients without TACE, there was no discernible distinction between Sora+PD-1 and Len +PD-1 groups. The exact mechanism is still not well illustrated, and the underlying reasons for the results might be attributed to by the following aspects. Firstly, TACE could lead to massive tumor necrosis and tumor antigen release and then could augment tumor-specific T-cell stimulation and recruitment, and immunomodulatory effect of TACE increased sensitivity of tumors to Lenvatinib on PD-1 inhibitor combination therapy.[31,32] Secondly, Lenvatinib has the ability to reduce CD4+ regulatory T cells and myeloid-derived suppressor cells, concurrently exerting an influence on the stimulation and differentiation processes of dendritic cells within the tumor milieu. This action creates a synergistic effect with PD-1 inhibitors, fostering an effective immune environment for CD8+ T cells.[33] Thirdly, Lenvatinib has excellent antiproliferative and anti-angiogenic activity and has the ability to modulate the tumor immune microenvironment following TACE, thus improving the immune reaction of PD-1 inhibitors in HCC.[34] The amalgamation of TACE, Lenvatinib, and PD-1 inhibitor might confer a more pronounced synergistic antitumor effect and enhanced clinical outcomes when juxtaposed with the amalgamation of TACE, Sorafenib, and a PD-1 inhibitor.

In the multivariate analysis, PVTT type III–IV and metastasis sites >5 were considered risk factors in relation to poorer PFS and OS. Many studies have proved that PVTT especially type III–IV usually indicates poor prognosis.[35,36] However, the metastasis sites on prognosis have not fully documented. In this study, we found that patients with more than five metastases have poorer survival than those not. As is known that metastasis ≤5 is defined as oligometastasis.[37] Many studies have proved that survival of patients within oligometastasis was longer than those beyond oligometastasis.[38,39] Patents beyond oligometastasis usually presented with more aggressive tumor behavior than within oligometastasis.[40] It is reasonable that metastasis sites >5 was considered risk factors in relation to poorer survival in our study.

The current research is subject to certain limitations. First, despite employing PSM to mitigate biases, a degree of selection bias persisted in choosing between Sorafenib and Lenvatinib treatments. This bias stems not only from physicians' preferences but also from considerations of patients' tolerance and financial capacity. Second, even with meticulous patient selection based on various clinical characteristics, the outcome may still be affected by both measured and unmeasured confounders. Factors such as the heterogeneity of TACE treatment and patient response to different combinations of TKI or PD-1 inhibitors might substantially influence the results. Lastly, the limited number of patients analyzed may have affected the study's conclusions due to insufficient sample size. To validate these findings, future research should include larger, multicenter, prospective studies.

Conclusion

Our study indicated that Lenvatinib combined with PD-1 inhibitor was correlated with extended OS and PFS than Sorafenib plus PD-1 inhibitor for patient with metastasis. In addition, we found that the OS in patients received TACE was longer in Len+PD-1 group than in Sora+PD-1 group, while for patients without TACE, there was no difference between the two groups.

Data Sharing Statement

It is available by contacting the corresponding author.

Ethics Approval and Informed Consent

The Ethics Committee Board of Hunan Provincial People's Hospital approved this retrospective study and waived the requirement for patient consent for this retrospective review. We solemnly promise that this study will strictly abide by relevant laws and regulations and will not disclose patient personal information and related information to any other personnel and organizations to ensure the security and confidentiality of patient information.

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Disclosure

The authors declare no conflict of interest in this work.

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