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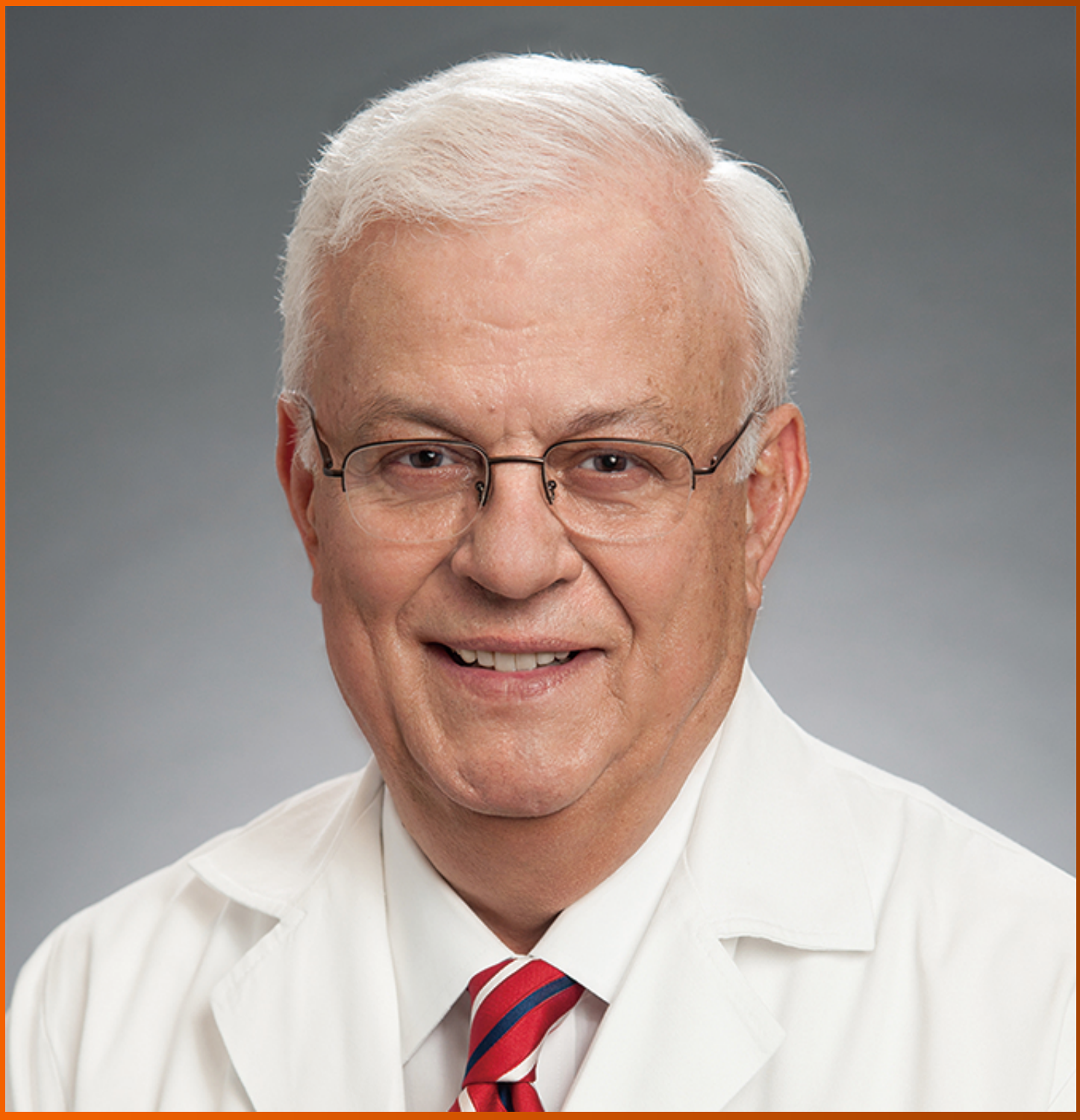

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Contents

Weekly Volume 29 Number 10 March 14, 2023

REVIEW

1539 Precision medicine in inflammatory bowel disease: Individualizing the use of biologics and small molecule therapies

Cheah E, Huang JG

MINIREVIEWS

1551 Systemic treatment for unresectable hepatocellular carcinoma

Leowattana W, Leowattana T, Leowattana P

1569 Systemic treatment for metastatic colorectal cancer

Leowattana W, Leowattana P, Leowattana T

1589 Gastrointestinal microbiome and cholelithiasis: Current status and perspectives

Dan WY, Yang YS, Peng LH, Sun G, Wang ZK

ORIGINAL ARTICLE

Retrospective Study

1602 Quantitative parameters in novel spectral computed tomography: Assessment of Ki-67 expression in patients with gastric adenocarcinoma

Mao LT, Chen WC, Lu JY, Zhang HL, Ye YS, Zhang Y, Liu B, Deng WW, Liu X

1614 Clinical outcomes of lenvatinib plus transarterial chemoembolization with or without programmed death receptor-1 inhibitors in unresectable hepatocellular carcinoma

Wang YY, Yang X, Wang YC, Long JY, Sun HS, Li YR, Xun ZY, Zhang N, Xue JN, Ning C, Zhang JW, Zhu CP, Zhang LH, Yang XB, Zhao HT

1627 Clinical features, diagnosis, and treatment of Peutz-Jeghers syndrome: Experience with 566 Chinese cases

Xu ZX, Jiang LX, Chen YR, Zhang YH, Zhang Z, Yu PF, Dong ZW, Yang HR, Gu GL

Observational Study

1638 Intraprocedural gastric juice analysis as compared to rapid urease test for real-time detection of *Helicobacter pylori*

Vasapolli R, Ailloud F, Suerbaum S, Neumann J, Koch N, Macke L, Schirra J, Mayerle J, Malfertheiner P, Schulz C

LETTER TO THE EDITOR

1648 Reporting the cases of alcohol-associated hepatitis using the National Inpatient Sample data

Marlowe N, Lin WQ, Liangpunsakul S

World Journal of Gastroenterology

Weekly Volume 29 Number 10 March 14, 2023

Contents

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes of lenvatinib plus transarterial chemoembolization with or without programmed death receptor-1 inhibitors in unresectable hepatocellular carcinoma

Yan-Yu Wang, Xu Yang, Yun-Chao Wang, Jun-Yu Long, Hui-Shan Sun, Yi-Ran Li, Zi-Yu Xun, Nan Zhang, Jing-Nan Xue, Cong Ning, Jun-Wei Zhang, Cheng-Pei Zhu, Long-Hao Zhang, Xiao-Bo Yang, Hai-Tao Zhao

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Abstract

BACKGROUND

Programmed death receptor-1 (PD-1) inhibitors have been approved as second-line treatment regimen in hepatocellular carcinoma (HCC), but it is still worth studying whether patients can benefit from PD-1 inhibitors as first-line drugs combined with targeted drugs and locoregional therapy.

AIM

To estimate the clinical outcome of transarterial chemoembolization (TACE) and lenvatinib plus PD-1 inhibitors for patients with unresectable HCC (uHCC).

METHODS

We carried out retrospective research of 65 patients with uHCC who were treated at Peking Union Medical College Hospital from September 2017 to February 2022. 45 patients received the PD-1 inhibitors, lenvatinib, TACE (PD-1-Lenv-T) therapy, and 20 received the lenvatinib, TACE (Lenv-T) therapy. In terms of the dose of lenvatinib, 8 mg was given orally for patients weighing less than 60 kg and 12 mg for those weighing more than 60 kg. Of the patients in the PD-1 inhibitor combination group, 15 received Toripalimab, 14 received Toripalimab, 14 received Camrelizumab, 4 received Pembrolizumab, 9 received Sintilimab, and 2 received Nivolumab, 1 with Tislelizumab. According to the investigators' assessment,

TACE was performed every 4-6 wk when the patient had good hepatic function (Child-Pugh class A or B) until disease progression occurred. We evaluated the efficacy by the modified Response Evaluation Criteria in Solid Tumors (mRECIST criteria). We accessd the safety by the National Cancer Institute Common Terminology Criteria for Adverse Events, v 5.0. The key adverse events (AEs) after the initiation of combination therapy were observed.

RESULTS

Patients with uHCC who received PD-1-Lenv-T therapy (n = 45) had a clearly longer overall survival than those who underwent Lenv-T therapy (n = 20, 26.8 *vs* 14.0 mo; P = 0.027). The median progression-free survival time between the two treatment regimens was also measured {11.7 mo [95% confidence interval (CI): 7.7-15.7] in the PD-1-Lenv-T group *vs* 8.5 mo (95%CI: 3.0-13.9) in the Lenv-T group (P = 0.028)}. The objective response rates of the PD-1-Lenv-T group and Lenv-T group were 44.4% and 20% (P = 0.059) according to the mRECIST criteria, meanwhile the disease control rates were 93.3% and 64.0% (P = 0.003), respectively. The type and frequency of AEs showed little distinction between patients received the two treatment regimens.

CONCLUSION

Our results suggest that the early combination of PD-1 inhibitors has manageable toxicity and hopeful efficacy in patients with uHCC.

Key Words: Lenvatinib; Programmed death receptor-1 inhibitor; Immunotherapy; Hepatocellular carcinoma; Transarterial chemoembolization; Combination therapy

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Core Tip: This retrospective research was designed to evaluate the treatment outcome and safety of transarterial chemoembolization (TACE) and lenvatinib plus programmed death receptor-1 (PD-1) inhibitors in the treatment of patients with unresectable hepatocellular carcinoma (uHCC). Patients with uHCC who underwent PD-1 inhibitors, lenvatinib, TACE therapy (n = 45) had a evidently longer overall survival than those who underrwent lenvatinib, TACE therapy (n = 20, 26.8 *vs* 14.0 mo; P = 0.027). Early combination of PD-1 inhibitors has manageable toxicity and hopeful efficacy in patients with uHCC.

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INTRODUCTION

Primary liver carcinoma is the sixth most common cancer type worldwide and leads to the third most cancer-related deaths[1]. The proportion of hepatocellular carcinoma (HCC) is approximately 80% in primary liver cancers[2]. Due to the powerful compensatory power of the liver, most patients with liver carcinoma are already in the advanced stage when they develop symptoms. Therefore, the systemic therapies of advanced HCC have attracted much attention.

Lenvatinib is an oral small molecule inhibitor of receptor tyrosine kinases [platelet-derived growth factor receptor (PDGFR), KIT, rearranged in transfection, fibroblast growth factor receptor (FGFR) 1-4 and vascular endothelial growth factor receptor (VEGFR) 1-3] that was applied for the first-line therapy of patients with unresectable HCC on the basis of the clinical outcomes from a randomized, multinational, open-label, noninferiority phase III trial[3]. In this clinical trial, lenvatinib demonstrated a better treatment effect than sorafenib. The overall survival (OS) with lenvatinib was 5 mo longer than that with sorafenib and the objective response rate (ORR) was approximately 2 times higher than that of sorafenib in hepatitis B virus (HBV) background subgroup analysis[3].

The main nutrients for liver cancer growth are supplied by the hepatic artery, which can lead to tumor ischemic necrosis by embolization[4]. Therefore, transarterial chemoembolization (TACE) is proposed as the standard therapeutic regimen for stage B HCC as classified by the Barcelona Clinic Liver Cancer (BCLC) staging system[5,6]. However, TACE also aggravates tumor hypoxia, resulting in the accumulation of hypoxia-inducible factor 1α, upregulating the expression of PDGF and VEGF,

which facilitates angiogenesis-induced collateral vessel formation, and contributes to tumor revascularization and locoregional recurrence[7-9]. Therefore, several clinical trials have made an attempt to associate TACE with systemic antiangiogenic treatment[10-12]. A randomized, multicenter prospective trial comparing TACE plus sorafenib and TACE alone in patients with liver cancer confirmed that in patients with unresectable HCC (uHCC), TACE plus sorafenib clearly improved progression-free survival (PFS) compared with TACE alone[12]. As another antiangiogenic drug, lenvatinib has significantly improved clinical efficacy in the remedy of uHCC with TACE plus lenvatinib compared with TACE monotherapy in previous studies[13,14].

Immunotherapy, as a systemic therapy that has attracted much attention in recent years, has also made significant progress in liver cancer[15]. Programmed death receptor-1 (PD-1) expresses on the surface of T cells, and is a key immunosuppressive transmembrane protein[16]. In the tumor microenvironment, cancer cells can express PD ligand 1 (PD-L1), which can bond to PD-1 to inhibit the function of T cells and reduce their killing effect on tumor cells[17]. Studies have shown that lenvatinib has a synergistic effect with immune checkpoint inhibitors (ICIs)[18]. VEGF is a highly expressed angiogenic factor in the tumor microenvironment of HCC that supports tumor growth and promotes immune rejection and is a key mediator in the immunosuppressive microenvironment[19]. Previous researches have suggested that lenvatinib can alleviate immunosuppression in the tumor microenvironment by inhibiting VEGF and can also increase T lymphocyte infiltration in the immunosuppressive microenvironment, providing an effective immunotherapeutic microenvironment for ICIs to function[20].

In conclusion, the combination of systemic and local treatment for liver cancer can synergistically kill tumors and prolong the survival of patients in various ways. Currently, PD-1 inhibitors have been applied as second-line remedy in HCC[21], and it is still worth studying whether patients can obtain clinical benefit from PD-1 inhibitors as first-line drugs combined with targeted drugs and local therapy. This retrospective research was designed to evaluate the clinical outcome and safety of TACE and lenvatinib plus PD-1 inhibitors in the treatment of uHCC and to determine whether the early combination of PD-1 inhibitors could benefit uHCC patients.

MATERIALS AND METHODS

Patients and study design

In this retrospective research, the clinical information and image data of HCC patients were collected from Peking Union Medical College Hospital from September 2017 to February 2022. uHCC was confirmed by more than two clinical experts according to the National Comprehensive Cancer Network guidelines. The main inclusion criteria were as the following: (1) Histologically or clinically confirmed HCC; (2) 1 or more measurable lesion by the modified Response Evaluation Criteria in Solid Tumors (mRECIST criteria); (3) BCLC stage A, B or C HCC; (4) Child-Pugh class scored as A (score 5-6) or B (score 7); (5) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-1; and (6) Prior resection or ablation was allowed. The exclusion criteria were as the following: (1) Secondary malignant tumor of liver; (2) Child-Pugh class C; and (3) Any contraindication to TACE, lenvatinib or PD-1 inhibitors.

Treatment

In this study, patients weighing less than 60 kg received a dose of 8 mg of lenvatinib, and those weighing more than 60 kg received a dose of 12 mg of lenvatinib orally once a day. Of the patients in the PD-1 inhibitor combination group, 15 received Toripalimab, 14 received Toripalimab, 14 received Camrelizumab, 4 received Pembrolizumab, 9 received Sintilimab, and 2 received Nivolumab, 1 with Tislelizumab. Camrelizumab, Sintilimab, Pembrolizumab and Tislelizumab were all given 200 mg every 3 wk. The dose of Toripalimab was 240 mg once every 3 wk. The dose of Nivolumab was 240 mg once every 2 wk.

TACE was performed under local anesthesia. After successful femoral artery puncture, 5-fluorouracil perfusion was performed through the celiac trunk. The tumor-supplying artery was superselected by a microcatheter, and chemoembolization was performed with a mixture of lipiodol and pirarubicin (25-40 mg/m^2). According to the investigators' assessment, TACE was performed every 4-6 wk when the patient had good hepatic function (Child-Pugh class A or B) until disease progression occurred.

According to Common Terminology Criteria for Adverse Events (CTCAE), v5.0, adverse events of patients during treatment were evaluated and graded. For grade 1 to grade 2 adverse events, there was no need to stop medication and symptomatic treatment was performed. If grade 3 or higher adverse reactions occur, medication should be suspended until the adverse reactions improve to grade 0-1 or baseline. For grade 4 or more adverse reactions, medication should be stopped and symptomatic treatment should be carried out actively.

Outcomes and assessments

The primary outcomes were OS and PFS. The definition of OS was the time from the first TACE therapy to death or the last follow-up.Tumor response was evaluated according to contrast-enhanced computed

tomography or magnetic resonance imaging. The definition of PFS was the time between the first TACE therapy and disease recurrence or the last follow-up. The secondary outcome was the frequency of main adverse events (AEs), which were evaluated by the CTCAE, v 5.0. The key AEs after the initiation of combination therapy were observed. We conducted follow-up every 3 wk to assess outcome variables until tumor progression, intolerable AEs, or death.

Statistical analysis

We used *T* tests to compare continuous data conforming to the normal distribution. χ^2 tests were performed to compare categorical variables. We used Mann-Whitney *U* tests to compare the continuous variables that did not conform to the normal distribution. Fisher's exact test was used when the sample size is less than 40 or the theoretical frequency was less than 1. The survival rates were evaluated by the Kaplan-Meier curve. We identified independent prognostic factors related to OS by univariate and multivariate analyses based on the Cox regression model. All statistical analyses were performed by SPSS, v 25.0.

RESULTS

Patient characteristics

We finally enrolled 65 patients with uHCC according to the criteria; 45 received the PD-1 inhibitors, lenvatinib, TACE therapy (PD-1-Lenv-T), and 20 received the lenvatinib, TACE (Lenv-T therapy) (Figure 1). The clinical information and data at baseline of all patients are shown in Table 1. The median age in the PD-1-Lenv-T group was 54 years old and in the Lenv-T group was 62 years old. At baseline, tumors were considered BCLC stage A in 6.67%, stage B in 17.78% and stage C in 75.56% of patients receiving PD-1-Lenv-T and stage A in 10%, stage B in 15% and stage C in 75% of patients receiving Lenv-T (P = 0.88). The ECOG-PSs were 0 in 57.78% and 1 in 42.22% of patients treated with PD-1-Lenv-T and 0 in 35.0% and 1 in 65.0% of patients treated with Lenv-T (P = 0.154). The numbers of TACE treatments were < 3 in 62.22% and ≥ 3 in 37.78% of patients received PD-1-Lenv-T and < 3 in 80.0% and ≥ 3 in 20.0% of patients received Lenv-T therapy (P = 0.26). The tumor numbers were 1 in 37.78% and more than 1 in 62.22% of patients who were treated with PD-1-Lenv-T and 1 in 20.00% and more than 1 in 80.00% of patients who were treated with Lenv-T (P = 0.26). Baseline characteristics of tumor burden score (TBS) group, extrahepatic metastasis rate and portal vein tumor thrombus rate were similar between the two groups. Median administration time of lenvatinib was 5.9 mo (range: 1.0-15.9 mo) and 7.8 mo (range: 1.1-28.2 mo) in the Lenv-T group and the PD-1-Lenv-T group (P = 0.07), respectively. The median injection timesof PD-1 inhibitors in the group that received PD-1 inhibitor therapy was 6 (range: 1-29).

Efficacy

The primary clinical outcomes of this research were OS and PFS. The median follow-up time for all enrolled patients was 25.2 mo [95% confidence interval (CI): 18.8-31.7]. The duration of OS and PFS for all included patients were 17.9 mo (95%CI: 11.8-24.1) and 11.0 mo (95%CI: 7.6-14.4), respectively (Figure 2). The median OS time in the PD-1-Lenv-T group was 26.8 mo (95%CI: 14.4-39.1), while that in the Lenv-T group was 14.0 mo [(95%CI: 10.3-17.8), P = 0.027] (Figures 2A and C). A remarkable median OS improvement of 12.8 mo was observed, suggesting that the PD-1-Lenv-T regimen may have advantage over the Lenv-T regimen. In addition, the median PFS time was different between the two treatment groups [11.7 mo (95%CI: 7.7-15.7) in the PD-1-Lenv-T group *vs* 8.5 mo (95%CI: 3.0-13.9) in the Lenv-T group (P = 0.028)] (Figures 2B and D).

The best tumor responses of all patients with uHCC are shown in Table 2. The ORR in the PD-1-Lenv-T group was 44.4%, which was obviously higher than the ORR of 20% in the Lenv-T group (P = 0.059) according to the mRECIST criteria (Table 2). The disease control rates (DCRs) were 93.3% in the PD-1-Lenv-T group and 64.0% in the Lenv-T group (P = 0.003). When stratified by BCLC stage, the DCR differed between the two groups (patients with BCLC stage A or B *vs* patients with BCLC stage C) (Table 3). A total of nine patients changed medications after disease progression, with two patients switching from lenvatinib to apatinib, two receiving donafenib, one receiving regofenib, and three receiving bevacizumab. Another patient stopped TACE and switched to HAIC (hepatic arterial infusion chemotherapy).

Prognostic factors for OS and PFS in the subgroups

We identified independent prognostic factors related to OS by univariate and multivariate analyses based on the Cox regression model (Figure 3). Basic clinical characteristics (gender, age, *etc.*), tumor characteristics (tumor size, tumor number, *etc.*) and treatment status (number of TACE treatments, *etc.*) were included in the analyses. Univariate analysis suggested that OS was related to the treatment option [P = 0.032, hazard ratio (HR) = 0.44, 95%CI: 0.21-0.93), ECOG-PS score (P = 0.003, HR = 0.34, 95%CI: 0.16-0.69), BCLC stage (P = 0.059, HR = 2.75, 95%CI: 0.96-7.86) and TBS group (P = 0.065, HR = 0.47,

Table 1 The baseline characteristics of included patients (*n*, %)

	Overall	Lenvatinib + TACE + PD-1	Lenvatinib + TACE	*P* value
Patient characteristics				
Number (*n*)	65	45	20	
Age, median (range), yr	57 (18-79)	54 (18-79)	62 (26-75)	0.066[1]
< 65	50 (76.92)	38 (84.44)	12 (60.00)	
≥ 65	15 (23.08)	7 (15.56)	8 (40.00)	
Gender				0.095[1]
Female	8 (12.31)	3 (6.67)	5 (25.00)	
Male	57 (87.69)	42 (93.33)	15 (75.00)	
ECOG-PS				0.154[1]
0	33 (50.77)	26 (57.78)	7 (35.00)	
1	32 (49.23)	19 (42.22)	13 (65.00)	
Etiology				0.002[1]
HBV	54 (83.08)	42 (93.33)	12 (60.00)	
HCV	4 (6.15)	2 (4.44)	2 (10.00)	
Non-HBV, non-HCV	7 (10.77)	1 (2.22)	6 (30.00)	
Hepatic cirrhosis				0.879[1]
Yes	43 (66.15)	29 (64.44)	14 (70.00)	
No	22 (33.85)	16 (35.56)	6 (30.00)	
AFP				0.551[1]
< 400	21 (32.31)	13 (28.89)	8 (40.00)	
≥ 400	44 (67.69)	32 (71.11)	12 (60.00)	
Child-Pugh score				0.095[1]
A5	48 (73.85)	30 (66.67)	18 (90.00)	
A6 or B7	17 (26.15)	15 (33.33)	2 (10.00)	
BCLC stage				1.000[1]
A or B	16 (24.62)	11 (24.44)	5 (25.00)	
C	49 (75.38)	34 (75.56)	15 (75.00)	
Tumor characteristics				
Tumor size				0.035[1]
< 7 cm	25 (38.46)	13 (28.89)	12 (60.00)	
≥ 7 cm	40 (61.54)	32 (71.11)	8 (40.00)	
Tumor number				0.260[1]
Single	21 (32.31)	17 (37.78)	4 (20.00)	
Multiple	44 (67.69)	28 (62.22)	16 (80.00)	
TBS group				0.173[1]
L	23 (35.38)	13 (28.89)	10 (50.00)	
H	42 (64.62)	32 (71.11)	10 (50.00)	
Portal vein tumor thrombus				0.108[1]
Presence	24 (36.92)	20 (44.44)	4 (20.00)	
Absence	41 (63.08)	25 (55.56)	16 (80.00)	
Extrahepatic metastasis				0.376[1]

Yes	23 (35.38)	18 (40.00)	5 (25.00)	
No	42 (64.62)	27 (60.00)	15 (75.00)	
TACE times				0.260[1]
< 3	44 (67.69)	28 (62.22)	16 (80.00)	
≥ 3	21 (32.31)	17 (37.78)	4 (20.00)	

[1]χ^2 test.
AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group performance status; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PD-1: Programmed death receptor-1; TACE: Transarterial chemoembolization; TBS: Tumor burden score.

Table 2 Therapeutic efficacy in all patients, *n* (%)

	Lenvatinib + TACE + PD-1 (*n* = 45)	Lenvatinib + TACE (*n* = 20)	*P* value
CR	0 (0)	0 (0)	
PR	20 (44.4)	4 (20)	
SD	22 (48.9)	9 (45)	
PD	3 (6.7)	7 (35)	
ORR	20 (44.4)	4 (20)	0.059[1]
DCR	42 (93.3)	13 (64)	0.003[1]

[1]χ^2 test.
[2]Fisher's exact test.
BCLC: Barcelona Clinic Liver Cancer; DCR: Disease control rate; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease; PD-1: Programmed death receptor-1; TACE: Transarterial chemoembolization.

Table 3 Therapeutic efficacy in patients with stage A or B and stage C, *n* (%)

	BCLC A or B			BCLC C		
	Lenvatinib + TACE + PD-1 (*n* = 11)	Lenvatinib + TACE (*n* = 5)	*P* value	Lenvatinib + TACE + PD-1 (*n* = 34)	Lenvatinib + TACE (*n* = 15)	*P* value
CR	0 (0)	0 (0)		0 (0)	0 (0)	
PR	8 (72.7)	1 (20)		12 (35.3)	3 (20.0)	
SD	3 (27.3)	2 (40)		19 (55.9)	7 (46.7)	
PD	0 (0)	2 (40)		3 (8.8)	5 (33.3)	
ORR	8 (72.7)	1 (20)	0.077[2]	12 (35.3)	3 (20)	0.235[2]
DCR	11(100)	3 (60)	0.083[2]	31 (91.2)	10 (66.7)	0.047[2]

[1]χ^2 test.
[2]Fisher's exact test.
BCLC: Barcelona Clinic Liver Cancer; DCR: Disease control rate; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease; PD-1: Programmed death receptor-1; TACE: Transarterial chemoembolization.

95%CI: 0.21-1.05). We subsequently included factors with a *P* value < 0.1 in the multivariate analysis and found that only the treatment option was an independent prognostic factor for OS (*P* = 0.031, HR = 0.43, 95%CI: 0.2-0.93). Similarly, univariate analysis revealed that PFS was related to the treatment option (*P* = 0.031, HR = 0.47, 95%CI: 0.23-0.93), ECOG-PS score (*P* = 0.006, HR = 2.42, 95%CI: 1.29-4.55), BCLC stage (*P* = 0.09, HR = 2.02, 95%CI: 0.9-4.56), Child-Pugh score (*P* = 0.071, HR = 1.86, 95%CI: 0.95-3.65) and number of TACE treatments (*P* = 0.017, HR = 0.44, 95%CI: 0.22-0.86). We subsequently included factors with a *P* value < 0.1 in the multivariate analysis and found that only the number of TACE treatments was an independent prognostic factor for PFS (*P* = 0.049, HR = 0.46, 95%CI: 0.21-1).

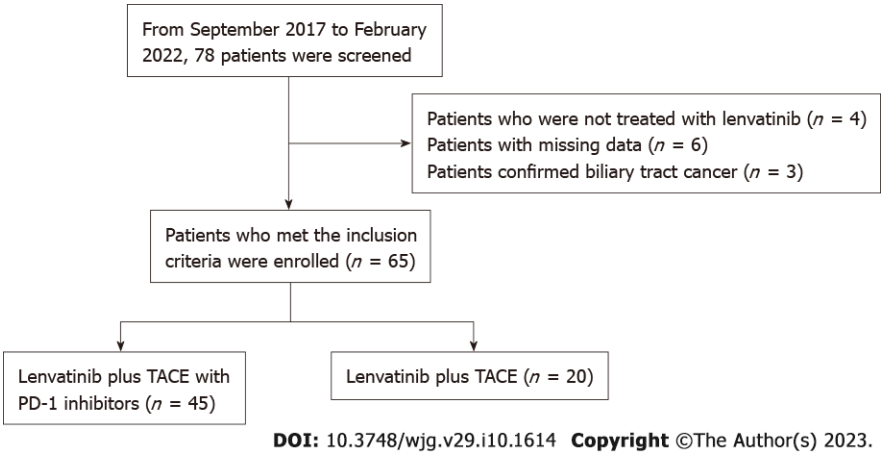

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Figure 1 Workflow of this study. TACE: Transarterial chemoembolization; PD-1: Programmed death receptor-1.

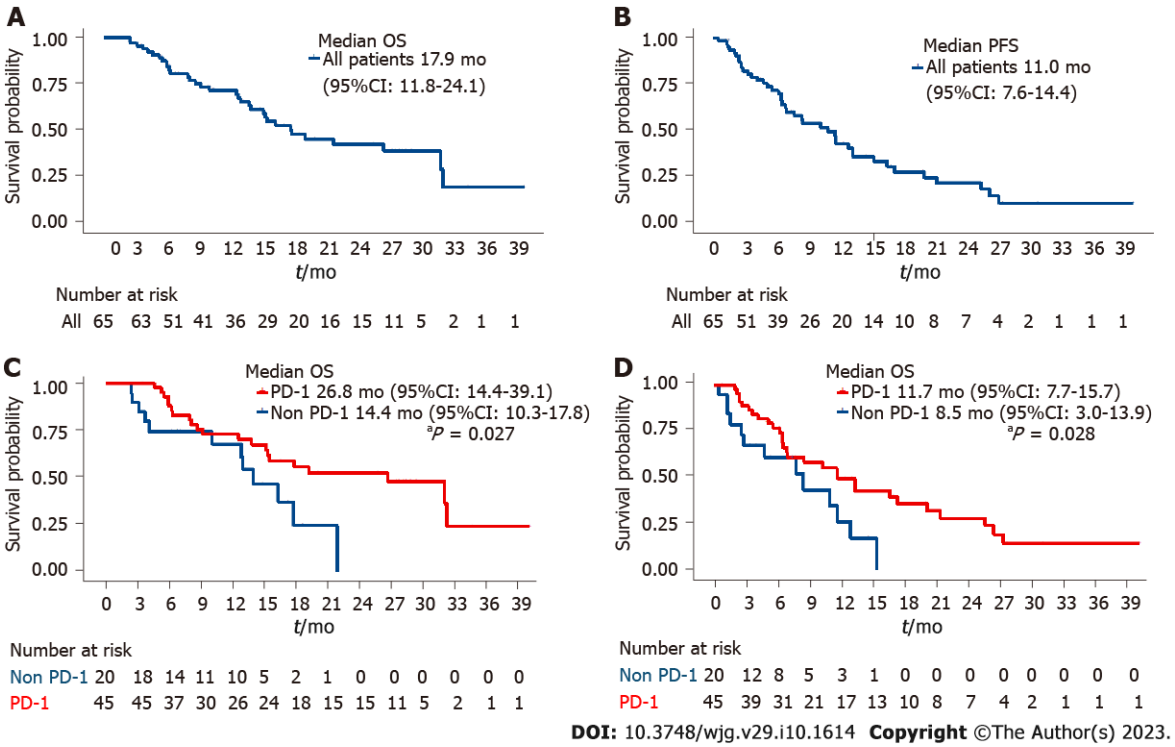

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Figure 2 The overall survival and progression-free survival times of all included patients and programmed death receptor-1-lenvatinib-transarterial chemoembolization group and lenvatinib-transarterial chemoembolization group. A: The overall survival (OS) times of all included patients; B: The progression-free survival (PFS) times of all included patients; C: The OS times of programmed death receptor-1 (PD-1)-lenvatinib-transarterial chemoembolization (TACE) group and lenvatinib-TACE group; D: The PFS times of PD-1-lenvatinib-TACE group and lenvatinib-TACE group. OS: Overall survival; PFS: Progression-free survival; CI: Confidence interval; PD-1: Programmed death receptor-1.

Safety

In total, 61 patients (93.8%) experienced AEs of any grade (Table 4). The top five most frequent treatment-related AEs in the PD-1-Lenv-T group were decreased appetite (42.2%), elevated aspartate aminotransferase (AST) (40.0%), decreased albumin (40.0%), hypertension (28.9%) and diarrhea (28.9%). In the Lenv-T group, fatigue (40.0%), decreased appetite (35.0%), and decreased albumin (30.0%) were the most frequent treatment-related AEs. Diarrhea (11.1%), decreased appetite (6.7%), elevated AST (6.7%), fatigue (6.7%), and hypertension (6.7%) were the most frequent grade 3/4 AEs in the PD-1-Lenv-T group. Decreased appetite (10.0%), decreased albumin (5.0%), diarrhea (5.0%), fatigue (5.0%), decreased platelet count (5.0%) and abdominal pain (5.0%) were the most frequent grade 3/4 AEs in the Lenv-T group. A total of three patients, two in the PD-1-Lenv-T group and one in the Lenv-T group, stopped treatment or changed treatment regimens because of intolerable AEs. Overall, the type and frequency of AEs was relatively similar between the two groups.

Table 4 Adverse events, *n* (%)

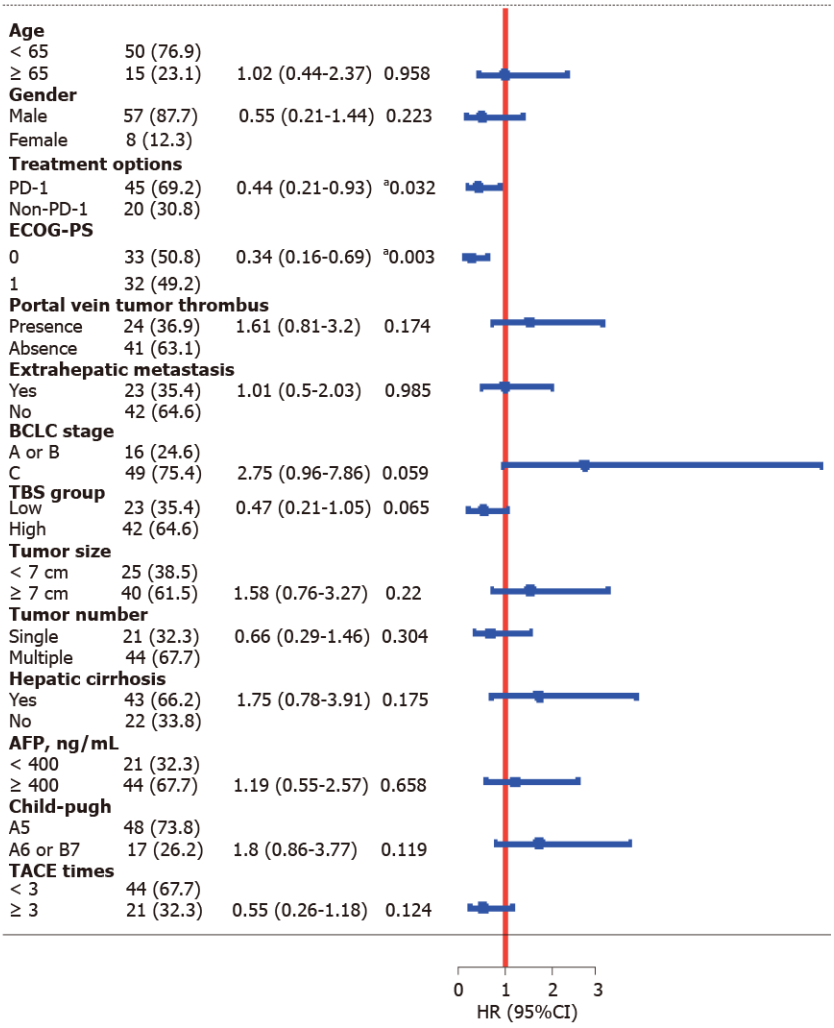
AEs	Lenvatinib + TACE + PD-1		Lenvatinib + TACE	
	All grades	Grade 3/4	All grades	Grade 3/4
Decreased appetite	19 (42.2)	3 (6.7)	7 (35.0)	2 (10.0)
Elevated AST	18 (40)	3 (6.7)	5 (25.0)	0 (0)
Decreased albumin	18 (40)	2 (4.4)	6 (30.0)	1 (5.0)
Fatigue	17 (37.8)	3 (6.7)	8 (40.0)	1 (5.0)
Diarrhoea	13 (28.9)	5 (11.1)	4 (20.0)	1 (5.0)
Hypertension	13 (28.9)	3 (6.7)	3 (15.0)	0 (0)
Elevated blood bilirubin	13 (28.9)	2 (4.4)	5 (25.0)	0 (0)
Decreased platelet count	13 (28.9)	2 (4.4)	5 (25.0)	1 (5.0)
Hypothyroidism	12 (26.7)	2 (4.4)	3 (15.0)	0 (0)
Abdominal pain	11 (24.4)	2 (4.4)	4 (20.0)	1 (5.0)
Elevated ALT	11 (24.4)	2 (4.4)	4 (20.0)	0 (0)
Rash	8 (17.8)	2 (4.4)	2 (10.0)	0 (0)
Decreased WBC	7 (15.6)	0 (0)	4 (20.0)	0 (0)
Vomiting	7 (15.6)	0 (0)	3 (15.0)	0 (0)
Hypocalcemia	6 (13.3)	0 (0)	5 (25.0)	0 (0)
Palmar-plantar erythrodysaesthesia	5 (11.1)	0 (0)	1 (5.0)	0 (0)
Nausea	4 (8.9)	0 (0)	4 (20.0)	0 (0)
Elevated WBC	4 (8.9)	0 (0)	3 (15.0)	0 (0)
Gingival bleeding	4 (8.9)	0 (0)	1 (5.0)	0 (0)
Gastrointestinal hemorrhage	4 (8.9)	1 (2.2)	0 (0)	0 (0)
Decreased weight	3 (6.7)	0 (0)	2 (10.0)	0 (0)
Dysphonia	3 (6.7)	0 (0)	2 (10.0)	0 (0)
Proteinuria	1 (2.2)	1 (2.2)	1 (5.0)	0 (0)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; WBC: White blood cell; AEs: Adverse events; PD-1: Programmed death receptor-1; TACE: Transarterial chemoembolization.

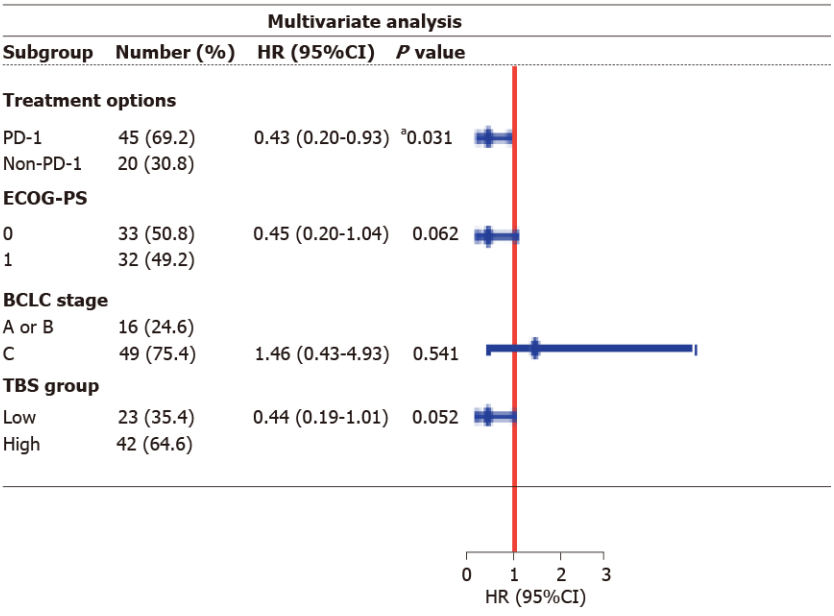
DISCUSSION

With the progress of new tyrosine kinase inhibitors and immunotherapy, individualized strategies for uHCC have improved. A recent randomized phase III trial, LAUNCH, comparing local therapy plus lenvatinib with lenvatinib monotherapy, demonstrated that TACE plus lenvatinib showed better overall survival in patients with uHCC (median OS: 17.8 *vs* 11.5 mo; HR = 0.45, $P < 0.001$)[22]. In our real-world study, patients in the TACE plus lenvatinib group had shorter OS and PFS than those in the LAUNCH trial (median OS: 17.8 *vs* 14.0 mo; median PFS: 10.6 *vs* 8.5 mo). A preclinical study showed that lenvatinib can blocke FGFR4 to reduce tumor PD-L1 expression and Treg differentiation, thus improving anti-PD-1 efficacy[18]. In addition to local therapies such as TACE, systemic therapy with PD-1 inhibitors is also being explored as a first-line therapy for uHCC. At the ESMO congress 2022, LEAP-002, a randomized phase III trial, enrolled 794 patients with advanced HCC who were not systematically treated and received lenvatinib plus pembrolizumab or lenvatinib alone in a 1:1 ratio [23]. Although the survival curve was initially higher in the Len + pembro group than in the monotherapy group approximately 15 mo after treatment, the prespecified statistical end point was not reached (median OS: 21.2 mo *vs* 19.0 mo, HR = 0.840, 95%CI: 0.708-0.997, $P = 0.0227$). However, in the subgroup analysis, HCC patients with HBV background benefited more in the Len + pembro group (HR = 0.75, 95%CI: 0.58-0.97). In our study, HBV-related HCC patients accounted for 93.33% in the PD-1-lenvatinib-TACE group, indicating that in the real world, Chinese HBV-related HCC patients are more likely to benefit from PD-1 inhibitors. This retrospective study estimated the clinical outcomes and safety of TACE in combination with lenvatinib and PD-1 inhibitors *vs* lenvatinib plus TACE in the

A


Univariate analysis
Subgroup Number (%) HR (95%) P value
Age
< 65 50 (76.9)
≥ 65 15 (23.1) 1.02 (0.44-2.37) 0.958
Gender
Male 57 (87.7) 0.55 (0.21-1.44) 0.223
Female 8 (12.3)
Treatment options
PD-1 45 (69.2) 0.44 (0.21-0.93) a0.032
Non-PD-1 20 (30.8)
ECOG-PS
0 33 (50.8) 0.34 (0.16-0.69) a0.003
1 32 (49.2)
Portal vein tumor thrombus
Presence 24 (36.9) 1.61 (0.81-3.2) 0.174
Absence 41 (63.1)
Extrahepatic metastasis
Yes 23 (35.4) 1.01 (0.5-2.03) 0.985
No 42 (64.6)
BCLC stage
A or B 16 (24.6)
C 49 (75.4) 2.75 (0.96-7.86) 0.059
TBS group
Low 23 (35.4) 0.47 (0.21-1.05) 0.065
High 42 (64.6)
Tumor size
< 7 cm 25 (38.5)
≥ 7 cm 40 (61.5) 1.58 (0.76-3.27) 0.22
Tumor number
Single 21 (32.3) 0.66 (0.29-1.46) 0.304
Multiple 44 (67.7)
Hepatic cirrhosis
Yes 43 (66.2) 1.75 (0.78-3.91) 0.175
No 22 (33.8)
AFP, ng/mL
< 400 21 (32.3)
≥ 400 44 (67.7) 1.19 (0.55-2.57) 0.658
Child-pugh
A5 48 (73.8)
A6 or B7 17 (26.2) 1.8 (0.86-3.77) 0.119
TACE times
< 3 44 (67.7)
≥ 3 21 (32.3) 0.55 (0.26-1.18) 0.124
0 1 2 3
HR (95%CI)

B


Multivariate analysis
Subgroup Number (%) HR (95%CI) P value
Treatment options
PD-1 45 (69.2) 0.43 (0.20-0.93) a0.031
Non-PD-1 20 (30.8)
ECOG-PS
0 33 (50.8) 0.45 (0.20-1.04) 0.062
1 32 (49.2)
BCLC stage
A or B 16 (24.6)
C 49 (75.4) 1.46 (0.43-4.93) 0.541
TBS group
Low 23 (35.4) 0.44 (0.19-1.01) 0.052
High 42 (64.6)
0 1 2 3
HR (95%CI)

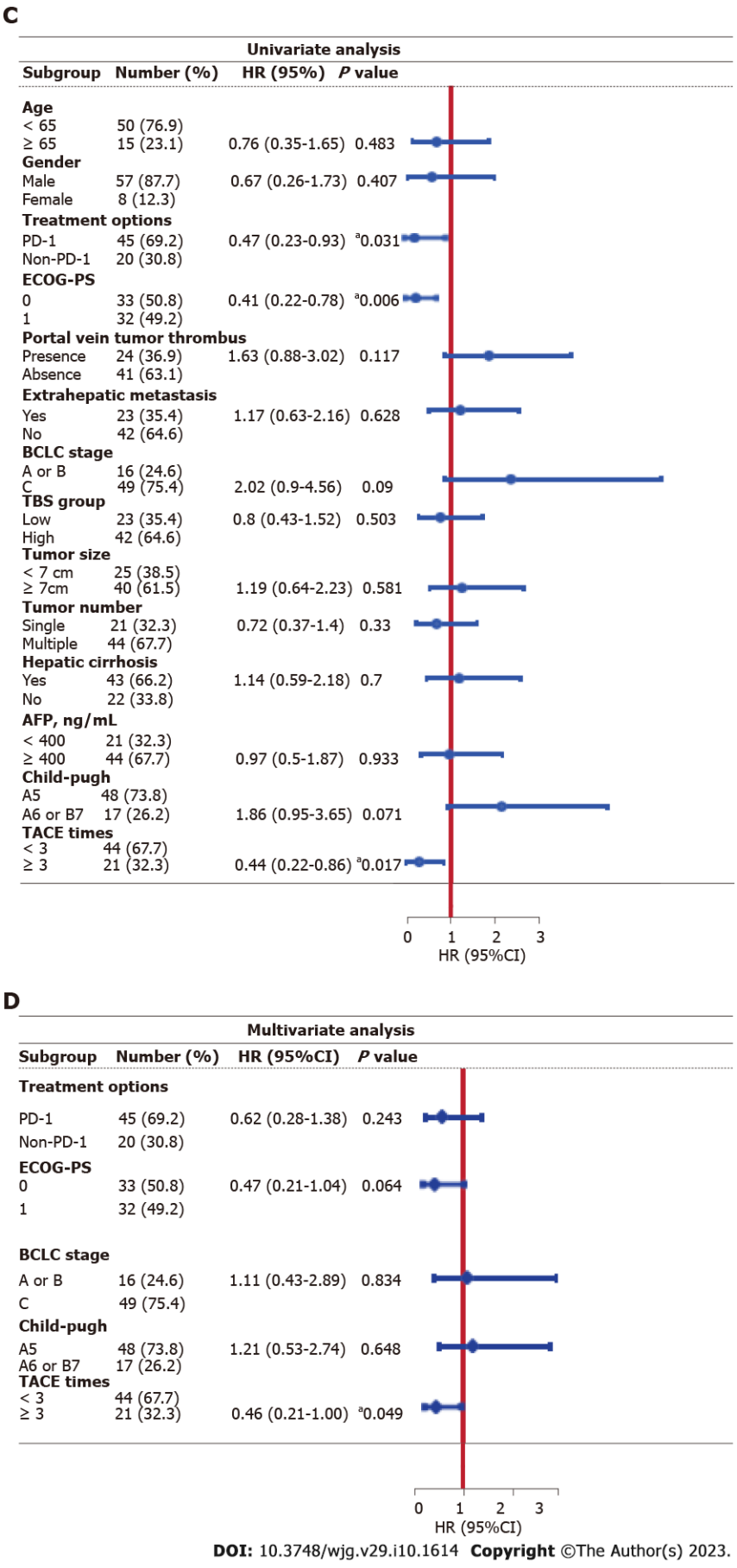


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Figure 3 Univariate and multivariable Cox regression analysis for overall survival and progression-free survival. A: Univariate Cox regression analysis for overall survival (OS); B: Multivariable Cox regression analysis for OS; C: Univariate Cox regression analysis for progression-free survival (PFS); D:

Multivariable Cox regression analysis for PFS. [a]*P* < 0.05. HR: Hazard ratio; CI: Confidence interval; PD-1: Programmed death receptor-1; TACE: Transarterial chemoembolization; ECOG-PS: Eastern Cooperative Oncology Group performance status; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein; TBS: Tumor burden score.

remedy of uHCC. The results suggested that the PD-1-Lenv-T regimen significantly prolonged survival time in patients with uHCC, without unexpected safety-related complications.

After stratification according to BCLC stage, the ORR and DCR were 72.7% and 100%, respectively, in the PD-1-Lenv-T group of uHCC patients with BCLC stage A or B, indicating that combination early treatment with PD-1 inhibitors has a good control effect on lesions. In contrast to proportions in previous studies, 75.4% of patients in this study had BCLC stage C tumors, and 67.7% of patients had multiple tumors, which indicates greater clinical significance for the treatment of patients with advanced HCC. When identifying independent factors associated with OS, similar to previous studies, univariate log-rank analysis indicated that the treatment option (P = 0.032, HR = 0.44, 95%CI: 0.21-0.93) and ECOG-PS score (P = 0.003, HR = 0.34, 95%CI: 0.16-0.69) were associated with OS. This might be accounted for the fact that patients with a good ECOG-PS score have enough physical strength to tolerate treatment. The subsequent multivariate analysis showed that the treatment option was an independent prognostic risk factor for OS. When determining independent prognostic factors associated with PFS, the multivariate analysis suggested that only the number of TACE treatments was an independent prognostic factor for PFS (P = 0.049, 95%CI: 0.21-1); specifically, undergoing TACE ≥ 3 times prolonged the PFS of patients with uHCC. It may be that patients who respond to TACE treatment are more likely to undergo repeated TACE treatments.

According to our data, the PD-1-Lenv-T regimen performed well in terms of safety, and grade 3 or 4 AEs were rare. AEs of any grade occurred more frequently in the PD-1-Lenv-T group than in the pembrolizumab monotherapy group in the KEYNOTE-240 clinical trial, but there was no obvious difference in grade 3/4 AEs. The timely monitoring of and intervention for AEs by the treatment team also played a key role in the remedy of all patients. From the information collected, more symptomatic AEs, such as decreased appetite and fatigue, occurred with this treatment regimen. This study also exists several limitations. For example, this research was a retrospective study based on a single medical center with a limited number of patients.

CONCLUSION

In conclusion, the study results suggest that early combination treatment with PD-1 inhibitors has manageable toxicity and promising efficacy in patients with uHCC.

ARTICLE HIGHLIGHTS

Research background

Programmed death receptor-1 (PD-1) inhibitors have been approved as second-line treatment regimen in hepatocellular carcinoma (HCC), and it is still worth studying whether patients can benefit from PD-1 inhibitors as first-line drugs combined with targeted drugs and local therapy.

Research motivation

To provide more options and references for the therapy of patients with unresectable HCC (uHCC).

Research objectives

Aim to evaluate the clinical outcomes and safety of transarterial chemoembolization (TACE) and lenvatinib plus PD-1 inhibitors for patients with uHCC.

Research methods

We carried out a retrospective investigation of 65 patients with uHCC who were treated at Peking Union Medical College Hospital from September 2017 to February 2022.

Research results

Patients with uHCC who received PD-1 inhibitors, lenvatinib, TACE therapy (n = 45) had a clearly longer overall survival than those who underwent lenvatinib, TACE therapy (n = 20, 26.8 *vs* 14.0 mo; P = 0.027). The type and frequency of adverse events showed little difference between the two treatment groups.

Research conclusions

Our results suggest that the early combination of PD-1 inhibitors has manageable toxicity and promising efficacy in patients with uHCC.

Research perspectives

Patients with uHCC may obtain benefit a lot from the early combination of PD-1 inhibitors with TACE and lenvatinib.

FOOTNOTES

Author contributions: Wang YY participated in the study design and drafting of the manuscript; Yang X, Wang YC, Long JY, Sun HS, Li YR, Xun ZY, Zhang N, Xue JN and Ning C participated in data collection and statistical analysis; Zhang JW, Zhu CP, Yang XB, and Zhao HT participated in study supervision; and all authors have read and approved the final manuscript.

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Institutional review board statement: This study was approved by the Ethical Review Board at Peking Union Medical College Hospital (No.SK-2000).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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