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ORIGINAL ARTICLE

Retrospective Study

Efficacy and predictive factors of transarterial chemoembolization combined with lenvatinib plus programmed cell death protein-1 inhibition for unresectable hepatocellular carcinoma

Kun-Peng Ma, Jin-Xin Fu, Feng Duan, Mao-Qiang Wang

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Abstract

BACKGROUND

The efficacy and safety of transarterial chemoembolization (TACE) combined with lenvatinib plus programmed cell death protein-1 (PD-1) for unresectable hepatocellular carcinoma (HCC) have rarely been evaluated and it is unknown which factors are related to efficacy.

AIM

To evaluate the efficacy and independent predictive factors of TACE combined with lenvatinib plus PD-1 inhibitors for unresectable HCC.

METHODS

This study retrospectively enrolled patients with unresectable HCC who received TACE/lenvatinib/PD-1 treatment between March 2019 and April 2022. Overall survival (OS) and progression-free survival (PFS) were determined. The objective response rate (ORR) and disease control rate (DCR) were evaluated in accordance with the modified Response Evaluation Criteria in Solid Tumors. Additionally, the prognostic factors affecting the clinical outcome were assessed.

RESULTS

One hundred and two patients were enrolled with a median follow-up duration of 12.63 months. The median OS was 26.43 months (95%CI: 17.00-35.87), and the median PFS was 10.07 months (95%CI: 8.50-11.65). The ORR and DCR were 61.76% and 81.37%, respectively. The patients with Barcelona Clinic Liver Cancer Classification (BCLC) B stage, early neutrophil-to-lymphocyte ratio (NLR)

response (decrease), or early alpha-fetoprotein (AFP) response (decrease > 20%) had superior OS and PFS than their counterparts.

CONCLUSION

This study showed that TACE/lenvatinib/PD-1 treatment was well tolerated with encouraging efficacy in patients with unresectable HCC. The patients with BCLC B-stage disease with early NLR response (decrease) and early AFP response (decrease > 20%) may achieve better clinical outcomes with this triple therapy.

Key Words: Transarterial chemoembolization; Efficacy; Lenvatinib; Programmed cell death protein-1 inhibitors; Unresectable hepatocellular carcinoma

Core Tip: Transarterial chemoembolization/lenvatinib/programmed cell death protein-1 combined treatment was well tolerated with encouraging efficacy in unresectable hepatocellular carcinoma patients. The patients with Barcelona Clinic Liver Cancer Classification (BCLC) B, with early neutrophil-to-lymphocyte ratio (NLR) response (decrease) and early alpha fetoprotein (AFP) response (decrease > 20%) might achieve better clinical outcomes with this triple therapy. It is advisable that BCLC stage, NLR, and AFP should be considered at clinical decision-making in order to obtain better prognosis.

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INTRODUCTION

Globally, liver cancer is estimated to be the sixth most prevalent cancer and ranks third in terms of mortality[1]. Early-stage hepatocellular carcinoma (HCC) is usually latent in onset, which results in rapid progression without immediate awareness, and makes curative surgical resection non-feasible. In such cases of unresectable HCC, developing methods that provide a prolonged survival benefit to patients is a priority. Transarterial chemoembolization (TACE) is the standard locoregional therapy considered in such cases[2]. TACE induces necrosis and apoptosis of tumor cells, which are deprived of nutrient supply and are locally surrounded by chemotherapeutic agents. However, not every patient can reap the benefits of TACE, and there is also a relatively high post-TACE recurrence[3].

A primary underlying reason is that hypoxia in tumor tissues are aggravated after feeding vessels are eradicated by TACE, which further promotes hypoxia-induced tumor angiogenesis. This leads to tumor regrowth and even residual tumor cell metastasis. In addition, sorafenib and lenvatinib have recently been used as first-line systemic therapy per guideline recommendations[4]. Lenvatinib (Eisai Co., Ltd., Japan) can target the vascular endothelial growth factor receptor, efficiently block neovascularization required for tumor growth, and concurrently target multiple proteins related to tumor growth. The combination of lenvatinib with TACE for HCC treatment has obtained satisfactory efficacy by impeding tumor angiogenesis post-embolization and eliminating residual tumor cells[5,6].

Due to TACE-induced necrosis, tumor cells release large volumes of debris as tumor antigens, which alters the local tumor immune microenvironment. This can cause antigen-presenting cell maturation, promote T lymphocyte infiltration, and eventually activate systemic anti-tumor immunity. Focused on immune regulation, immune checkpoint inhibitors (ICIs) have shown promising results for unresectable HCC[7,8]. In patients with advanced disease with a high intrahepatic tumor burden or extrahepatic metastases, concurrent ICI treatment and TACE could facilitate tumor elimination[9]. Programmed cell death protein-1 (PD-1) inhibitors such as nivolumab and pembrolizumab have been recommended as the first-line systemic therapy for advanced HCC[4]. This has revolutionized the current landscape of systemic therapy. Basic research also showed that tyrosine kinase inhibitors could facilitate current immune therapies, and this combined treatment has synergistic and consolidated effects[10-12]. Clinical trials also consistently showed that 46% of patients with unresectable HCC achieved stable objective radiographic responses after receiving lenvatinib plus pembrolizumab as first-line therapy[13]. However, considering that patients with unresectable HCC usually face severe situations such as vascular invasion or distant metastasis, the sequential therapeutic regimen after TACE remains challenging.

Based on the findings from these studies, we assumed that TACE in combination with lenvatinib plus PD-1 inhibitors may achieve a better prognosis for patients with unresectable HCC. However, the efficacy and safety of this combined therapy have rarely been evaluated, and the factors related to efficacy have yet to be identified. In this study, we first assessed the efficacy and safety of TACE-lenvatinib-PD1 therapy for patients with unresectable HCC to explore the predictive factors of clinical outcomes.

MATERIALS AND METHODS

Study population

This was a single-center retrospective analysis approved by the Institutional Review Board of the Chinese People's Liberation Army General Hospital (Beijing, China). The study complied with the Declaration of Helsinki. Between March 2019 and April 2022, patients with unresectable HCC who were initially treated with TACE combined with at least one dose of anti-PD-1 therapy plus lenvatinib were included for analysis.

The inclusion criteria were as follows: (1) Age more than 18 years; (2) Radiologically or pathologically diagnosed with HCC; (3) Barcelona Clinic Liver Cancer Classification (BCLC) stage B or C; and (4) Eastern Cooperative Oncology Group (ECOG) score 0-1. The exclusion criteria were as follows: (1) Poor patient compliance (such as failure to visit the clinic per schedule, leading to incomplete follow-up data); (2) Presence of medical contraindications, including severe cardiac, pulmonary, renal, or coagulation dysfunction; (3) Presence of central nervous system metastasis or other primary malignancies; (4) Previous treatment with other targeted drugs or PD-1 immunotherapy; and (5) Previous treatment with radiotherapy, chemotherapy or thermal ablation within 3 wk.

Treatment procedure

TACE was initiated before the administration of lenvatinib or PD-1 inhibitors. TACE was performed by two interventional radiologists with 25 (MQ.W) and 15 years (F.D) of vascular and interventional radiology experience, respectively. In the TACE procedure, a 4F catheter was first introduced *via* the femoral artery, and angiography was performed to assess the tumor and the tumor-feeding arteries. Next, chemotherapeutic agents [epirubicin (Pfizer, United States), 40-50 mg; oxaliplatin (Sanofi, United States), 100-150 mg; 5-fluorouracil (Tianjin Jinyao Co., Ltd., China), 500-750 mg; calcium folinate (Jiangsu Hengrui Pharmaceuticals Co., Ltd., China), 200-300 mg] were infused through the hepatic artery at distinct doses. Embolization was conducted using a microcatheter (2.7F, Terumo Medical, Japan; or 2.8F, Boston Scientific, United States; or 2.6F/1.98F, Asahi Intecc, Japan) either selectively or super-selectively using a conventional lipiodol based technique. Following the administration of 4-20 mL of lipiodol (Lipiodol, Laboratoire Guerbet, Roissy, France), a gelatin sponge or polyvinyl alcohol embolic microspheres were injected as supplements if stasis was not achieved. If there were few blood vessels or incomplete tumor staining, the inferior phrenic artery, intercostal artery, internal thoracic artery branches, and omental branches were examined with precision. When these vessels were found to feed the tumor, the collateral arteries were super-selected and embolized.

Based on the restored liver function and the patient's general status, lenvatinib or PD-1 inhibitors were subsequently administered in accordance with the instructions for use. Anti-PD-1 antibodies [sintilimab (Innovent Biologics Co., Ltd., China), 200 mg administered every 3 wk/nivolumab (Bristol-Myers Squibb Company, United States) 3 mg/kg every 2 wk/camrelizumab (Jiangsu Hengrui Pharmaceuticals Co., Ltd., China), 200 mg every 2 wk/pembrolizumab (Merck & Co., Inc., United States), 200 mg every 3 wk/toripalimab (Shanghai Junshi Biosciences Co., Ltd., China), 3 mg/kg every 2 wk] were administered intravenously. The types of PD-1 antibodies depended on the patients' choices based on the offered guideline recommendations and individual financial conditions, among other factors. In addition, lenvatinib (body weight ≥ 60 kg, 12 mg/d; body weight < 60 kg, 8 mg/d) was administered orally. Discontinuation of the therapeutic regimen or changes to the same were considered based on disease progression, unacceptable adverse events (AEs), patient refusal, or clinician decision.

Follow-up and assessments

Before each treatment (TACE and PD-1 inhibition) or contrast-enhanced computed tomography/magnetic resonance imaging at a 4-8-wk interval, we assessed the patients for tumor responses and AEs. The follow-up was routinely performed until death or the end of the study (April 30, 2022). During the imaging follow-up, "on-demand" TACE procedures were repeated based on the presence of viable tumors or intrahepatic recurrences. If these patients had sufficient liver function, repeated TACE was performed. The AFP level was assessed every 4 wk. In addition, lenvatinib/PD-1 inhibitor treatment was discontinued due to disease progression.

Tumor responses were assessed by a physician (MQ.W) with 25 years' experience using the modified Response Evaluation Criteria in Solid Tumors. Tumor responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR and PR. The disease control rate (DCR) was defined as the proportion of patients with CR, PR, and SD. The tumor responses of all patients were confirmed no less than 4 wk after the initial observation. PFS was defined as the time interval between TACE and the time of disease progression owing to any cause. Overall survival (OS) was defined as the period from TACE to the time of death or the last follow-up date.

All AEs during the combination therapy were recorded and evaluated based on the Common Terminology Criteria for Adverse Events Version 5.0 and standard laboratory examinations. TACE-related transient AEs such as fever, nausea, vomiting, abdominal pain, and elevated liver transaminase were not included. The neutrophil-to-lymphocyte ratio (NLR) was calculated using the neutrophil and lymphocyte percentages of whole blood cell counts.

Factors related to clinical outcomes

We evaluated the prognostic factors correlated with survival and disease progression using the variables gender, age, ECOG PS (0 *vs* 1), BCLC stage (B *vs* C), etiology [hepatitis B virus (HBV) *vs* others], maximum tumor diameter (≤ 6.8 cm *vs* > 6.8 cm), number of tumors (≤ 3 *vs* > 3), portal vein invasion, extrahepatic metastasis, Child-Pugh class (A *vs* B), alpha-fetoprotein (AFP), Des-gamma-carboxyprothrombin (DCP), NLR, and lactate dehydrogenase (LDH). Subgroup analysis for each factor was further conducted to evaluate its potential contribution to predicting treatment responses.

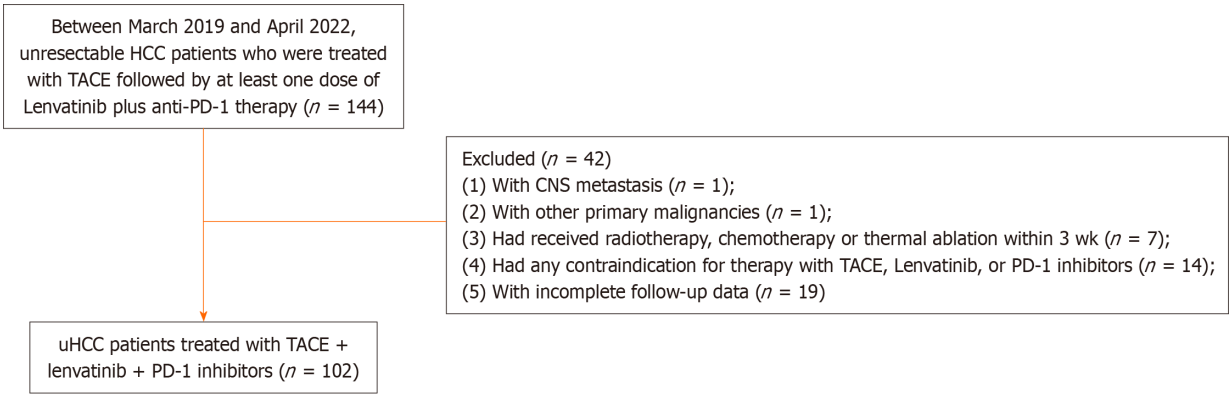

Figure 1 Flowchart of patients. CNS: Central nervous system; uHCC: Unresectable hepatocellular carcinoma; PD-1: Programmed cell death protein-1; TACE: Transarterial chemoembolization.

Statistical analyses

Continuous variables are presented as mean with standard error, and categorical variables are presented as counts with percentages. Survival analysis was conducted using the Kaplan-Meier method, and survival comparison was conducted using the log-rank test. The Cox proportional hazards regression method was used to identify factors associated with the OS and PFS, and multivariate analysis was conducted using variables with $P < 0.05$ obtained in the univariate analysis. Statistical analyses were performed using IBM SPSS software (version 25.0 SPSS Inc., Chicago, IL, United States).

RESULTS

Patient information

Between March 30, 2019, and April 30, 2022, 102 patients with HCC [mean age, 58 years (range, 34-91 years)] who received lenvatinib and PD-1 inhibition following TACE were enrolled (Figure 1). Baseline information, including patient demographics, tumor characteristics, and liver function, are listed in Table 1. Most patients were male (89/102, 87.25%). They had a relatively good performance status, whereas 53 patients (51.59%) had an ECOG score of 0. More than half of the patients were considered to have BLCL stage C (54/102, 52.94%). Chronic HBV infection was the underlying etiology of HCC (80/102, 78.43%). Ninety-three patients (91.18%) were evaluated as Child-Pugh Class A.

Twenty-nine patients (28.43%) showed portal vein tumor thrombosis, and 42 patients (42/102, 41.18%) showed distal metastasis, most commonly in the lung (27/102, 26.47%). Forty-nine patients (48.04%) had an AFP level > 400 ng/mL, and 87.25% patients had a DCP level > 40 mAU/mL at enrollment. The mean baseline NLR and LDH were 2.46 ± 1.59 and 198.52 ± 102.05 U/L, respectively.

Treatment-related toxicity

No patient died due to AEs. Treatment-related AEs for the combination therapy are recorded in Supplementary Table 1. Ninety-five (95/102, 93.13%) patients experienced AEs, with most being grade 1-2 (62/102, 60.78%), which did not warrant medical intervention. The most common clinical toxicity was grade 1-2 asthenia detected in 44 patients (43.14%). Twenty-eight patients (27.45%) reported grade 1-2 hand-foot syndrome. Hypertension (7/102, 6.86%) and rash (6/102, 5.88%) were the most common grade 3-4 AEs.

Therapeutic efficacy

With respect to the cutoff, 77.45% (79/102) of patients were alive. One hundred and two response-evaluable patients were included in the efficacy analysis with a median follow-up of 12.63 months. PD-1 inhibition was performed with a median number of cycles of 6.5 (IQR: 3.75-12.25). Clinical responses are summarized in Table 2. Overall, CR was achieved in ten patients, PR was achieved in 53 patients, and SD and PD were achieved in 20 and 19 patients, respectively. The confirmed ORR was 61.76% (63/102), and the DCR was 81.37% (83/102). The median PFS was 10.07 months (95%CI: 8.50-11.65), and the median OS was 26.43 months (95%CI: 17.00-35.87).

Factors related to OS and PFS

The independent factors that were predictive of clinical outcomes based on the results of univariate and multivariate Cox regression analyses are summarized in Tables 3 and 4. In the univariate analysis, gender, ECOG PS, BCLC stage, NLR, LDH, early NLR response, early AFP response, and early DCP response were found to be significantly associated with OS. In the multivariate analysis, baseline factors of BCLC C [*vs* B; hazard ratio (HR) = 3.10, 95%CI: 1.18-8.13; $P = 0.021$], LDH ≤ 198.52 (*vs* > 198.52; HR = 0.22, 95%CI: 0.08-0.56; $P = 0.002$), post-treatment factor of early NLR decrease (*vs* increase; HR = 0.31, 95%CI: 0.11-0.89; $P = 0.030$), early AFP decrease ≤ 20% (*vs* > 20%; HR = 3.90, 95%CI: 1.42-10.69; $P = 0.008$) were independent factors predictive of OS.

Table 1 Baseline demographic and clinical characteristics of the patients

Variables	Total (*n* = 102)
Age, mean ± SD (range), yr	57.64 ± 10.37 (34-91)
Male, *n* (%)	89 (87.25)
ECOG PS, *n* (%)	
0	53 (51.96)
1	49 (48.04)
Etiology, HBV/others, *n* (%)	80/22 (78.43/21.57)
BCLC stage, B/C, *n* (%)	48/54 (47.06/52.94)
Maximum tumor diameter, mean ± SD, cm	6.80 ± 3.74
Number of tumors > 3, *n* (%)	51 (50.00)
Portal vein invasion, *n* (%)	
Yes	29 (28.43)
Extrahepatic metastasis, *n* (%)	
Yes	42 (41.18)
Extrahepatic metastatic sites, *n* (%)	
Lung	27 (26.47)
Bone	7 (6.86)
Lymph nodes	13 (12.75)
Abdominal cavity	7 (6.86)
PD-1 antibody class, *n* (%)	
Sintilimab	52 (50.98)
Nivolumab	20 (19.61)
Camrelizumab	17 (16.67)
Pembrolizumab	7 (6.86)
Toripalimab	6 (5.88)
Child-Pugh class, *n* (%)	
A	93 (91.18)
B	9 (8.82)
AFP level, *n* (%)	
> 400 ng/mL	49 (48.04)
≤ 400 ng/mL	53 (51.96)
DCP level, *n* (%)	
> 40 mAU/mL	89 (87.25)
≤ 40 mAU/mL	13 (12.75)
NLR, mean ± SD	2.46 ± 1.59
LDH, mean ± SD, U/L	198.52 ± 102.05

AFP: Alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer Classification; DCP: Des-gamma-carboxyprothrombin; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HBV: Hepatitis B virus; LDH: Lactate dehydrogenase; NLR: Neutrophil lymphocyte ratio; PD-1: Programmed cell death protein-1.

Table 2 Clinical outcomes

Variables	Total (*n* = 102)
Best overall response	
CR	10
PR	53
SD	20
PD	19
Objective response rate	61.76%
Disease control rate	81.37%
Median PFS	10.07 months (95%CI: 8.50-11.65)
6-month tumor PFS	70.82% (95%CI: 60.80-78.72)
12-month tumor PFS	36.11% (95%CI: 26.49-45.79)
Median OS	26.43 months (95%CI: 17.00-35.87)
6-month survival	92.63% (95%CI: 85.14-96.42)
12-month survival	84.15% (95%CI: 74.05-90.56)

CR: Complete response; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

In the univariate analysis, BCLC stage, early NLR response, early AFP response, and early DCP response were significantly associated with PFS. In the multivariate analysis, BCLC C (*vs* B; HR = 1.75, 95%CI: 1.12-2.74; $P = 0.014$), early NLR decrease (*vs* increase; HR = 0.56, 95%CI: 0.35-0.90; $P = 0.016$), and early AFP decrease ≤ 20% (*vs* > 20%; HR = 1.73, 95%CI: 1.12-2.66; $P = 0.013$) were independent factors predictive of PFS.

Thus, the BCLC stage, early NLR and early AFP responses were independent predictors of both OS and PFS. We further compared the survival and disease progression stratified by the BCLC stage (C *vs* B), early NLR response (decrease *vs* increase), and early AFP response (decrease ≤ 20% *vs* > 20%). Patients with BCLC B had a superior median OS and PFS (36.60 months, 11.67 months) than patients with BCLC C (26.37 months, $P = 0.0068$; 7.80 months, $P = 0.0036$; Figure 2A). Patients with early NLR decrease had a longer median OS and PFS (36.60, 11.07 months) than patients with NLR increase (19.33 months, $P = 0.0100$; 8.23 months, $P = 0.0025$; Figure 2B). Patients with an early AFP response (decrease ≤ 20%) also exhibited a shorter median OS and PFS (36.60, 11.0 months) than their counterparts (17.47 months, $P = 0.0043$; 7.50 months, $P = 0.0116$; Figure 2C).

DISCUSSION

In this study, TACE-lenvatinib-PD1 therapy showed a favorable efficacy and an acceptable safety profile in patients with unresectable HCC. The ORR was 61.76%, and the DCR was 81.37%, as assessed in 102 response-evaluable patients. The median PFS was 10.7 months, and the median OS was 26.43 months. Most AEs were acceptable with proper medical management. BCLC B, early NLR response (decrease), and early AFP response (decrease > 20%) were identified as independent predictors of clinical outcomes.

Our study investigated the toxicity of combined therapy. The incidences of treatment-related AEs were consistent with those previously reported[14,15]. Most were grade 1-2 AEs and could be managed without life-threatening events. In grade 1-2 AEs, asthenia and hand-foot syndrome were the most frequent AEs and occurred in 43.14% and 27.45% of patients, respectively. Hypertension (6.86%) and rash (5.88%) were the most frequent grade 3-4 AEs. In all, the toxicity profile of this combination therapy was manageable under close monitoring.

In previously reported TACE-sorafenib-PD1 combined therapy, the ORR was 54.6%-60.6%[16-18], which was lower than the ORR in our study (61.76%). Reportedly, as an antiangiogenic agent, lenvatinib showed better efficacy than sorafenib, especially in HBV-positive Chinese patients[19]. Similarly, in a real-world study, lenvatinib-PD1-TACE triple therapy showed encouraging efficacy and manageable safety in patients with unresectable HCC, with a higher ORR of 69.3%[20].

Compared with the previously reported median OS of 12.3 to 23.9 months[16-18,20-25], the median OS of 26.43 months recorded by us was the longest. The excellent survival benefit could be attributed to the use of a more precise microcatheter with a small diameter in TACE for super-selection and the complete embolization of collateral vessels. This could not only eliminate the primary lesion but also prevent potential tumor metastasis originating from the lesions feeding vessels in advance, thus significantly improving patient survival. Ten patients received conversion therapy with positive clinical outcomes (eight for hepatectomy and two for liver transplantation). Another contributing factor is that even though disease progression occurred, many patients underwent various subsequent treatments to improve OS

Table 3 Multivariate Cox regression analysis of overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≤ 58 yr *vs* > 58 yr)	0.65 (0.29-1.48)	0.2900		
Gender (male *vs* female)	0.40 (0.11-1.38)	0.0412		
ECOG PS (0 *vs* 1)	0.44 (0.20-0.98)	0.0392		
Etiology (HBV *vs* others)	0.61 (0.21-1.78)	0.2843		
BCLC stage (C *vs* B)	3.11 (1.36-7.11)	0.0068	3.10 (1.18-8.13)	0.021
Maximum tumor diameter (≤ 6.8 *vs* > 6.8)	0.66 (0.29-1.49)	0.3100		
Number of tumors (≤ 3 *vs* > 3)	0.67 (0.26-1.40)	0.2131		
Portal vein invasion (absent *vs* presence)	0.56 (0.22-1.41)	0.1545		
Extrahepatic metastasis (absent *vs* presence)	0.69 (0.30-1.59)	0.3531		
Child-Pugh class (A *vs* B)	1.29 (0.35-4.78)	0.7266		
Baseline AFP (≤ 400 *vs* > 400)	0.90 (0.39-2.03)	0.7799		
Baseline DCP (≤ 40 *vs* > 40)	1.78 (0.47-6.67)	0.2890		
NLR (≤ 3 *vs* > 3)	0.42 (0.16-1.09)	0.0306		
LDH (≤ 198.52 *vs* > 198.52)	0.43 (0.17-1.06)	0.0347	0.22 (0.08-0.56)	0.002
Early NLR response (decrease *vs* increase)	0.37 (0.16-0.89)	0.0100	0.31 (0.11-0.89)	0.030
Early AFP response (decrease ≤ 20% *vs* > 20%)	3.11 (1.31-7.39)	0.0043	3.90 (1.42-10.69)	0.008
Early DCP response (decrease ≤ 20% *vs* > 20%)	2.42 (0.78-7.51)	0.0407		

AFP: Alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer Classification; DCP: Des-gamma-carboxyprothrombin; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HBV: Hepatitis B virus; HR: Hazard ratio; LDH: Lactate dehydrogenase; NLR: Neutrophil lymphocyte ratio; PD-1: Programmed cell death protein-1.

instead of discontinuing treatment (Supplementary Table 2). For instance, processes for local tumor ablation, such as microwave ablation or radiofrequency ablation, are micro-invasive and help reduce the tumor burden[26]. Owing to subsequent treatment, our patients showed long OS after progression.

We found that TACE combined with lenvatinib treatment plus PD-1 inhibition was a superior treatment option for patients with intermediate- or advanced-stage HCC. This could be explained by the following reasons: (1) TACE can trigger tumor necrosis after feeding vessel embolization and the release of tumor antigens, which can induce the maturation of antigen-presenting cells. Subsequently, tumor-specific immune responses can be initialized, followed by the generation of large amounts of cytokines and the activation of adaptive antitumor immunity. In addition, as the local tumor environment changes substantially, the immunosuppressive cells can also be downregulated, eventually leading to favorable survival prognosis in patients; and (2) Lenvatinib may reduce post-TACE hypoxia-induced angiogenesis[27], modulate VEGF-mediated immunosuppression in the tumor microenvironment, and promote cytotoxic T-cell infiltration. Therefore, TACE, lenvatinib, and PD-1 inhibition exert a synergistic antitumor effect and improve clinical benefits for patients with unresectable HCC.

In the present study, BCLC B, early NLR response (decrease), and early AFP response (decrease > 20%) were identified as independent predictors of OS and PFS. With respect to the BCLC stage, patients with stage C disease had a higher tumor burden at baseline than patients with stage B disease. Early AFP response indicates a reduced tumor burden after combined therapy, indicating a direct and effective tumor-killing capability. Thus, it is not difficult to understand that patients with a low tumor burden either at baseline or in response to treatment effects had better clinical prognoses.

NLR is an indicator of tumor-related inflammation and helps predict tumor prognosis[28,29]. In nivolumab-treated patients with HCC, dynamic changes in the NLR (at week 4) are effective prognostic indicators and may facilitate patient selection and subsequent clinical strategies for immunotherapies[30]. This is consistent with our finding that patients with a decreased NLR had superior median OS and PFS than their counterparts. To be specific, peripheral neutrophils partially reflect the immunosuppressive cell population (tumor-associated neutrophils), indicating immunosuppression and a poor response to immunomodulation therapy. Besides, peripheral lymphocytes indicate the cytotoxic T-cell response. A higher proportion of lymphocytes indicates an enhanced anti-tumor immune response. Therefore, a low NLR is correlated with reduced systemic inflammation and enhanced adaptive anti-tumor immunity.

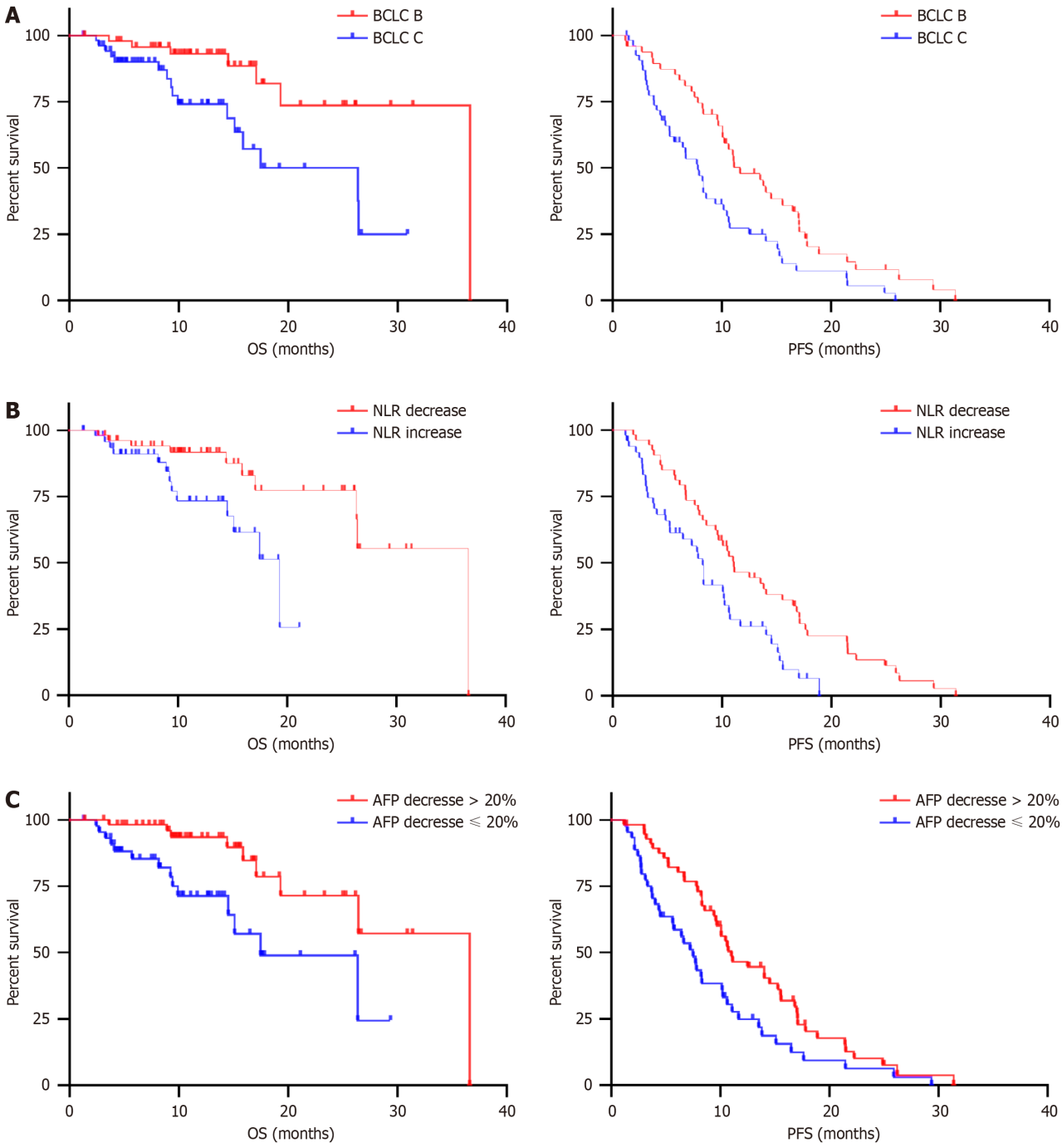

Figure 2 Overall and progression-free survival with different stratifications. A: The overall survival (OS) and progression-free survival (PFS) in Barcelona Clinic Liver Cancer stage (C *vs* B) patients; B: The OS and PFS in early neutrophil lymphocyte ratio response (decrease *vs* increase) patients; C: The OS and PFS in early alpha fetoprotein response (decrease ≤ 20% *vs* > 20%) patients. AFP: Alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer Classification; OS: Overall survival; PFS: Progression-free survival; NLR: Neutrophil lymphocyte ratio.

There were several limitations in this study. First, this was a retrospective single-center study with a small sample size and a short follow-up period. However, our results still indicated high efficacy of the treatment method for patients with unresectable HCC. Further prospective studies with larger sample sizes are necessary. Second, we included more than one type of PD-1 inhibitor, which may have affected the consistency of the results of immunotherapies. Subgroup analyses are necessary to identify further unknown differences attributed to each agent.

CONCLUSION

In summary, our findings demonstrated that TACE-lenvatinib-PD1 therapy is well-tolerated and has promising efficacy in patients with unresectable HCC. Patients with BCLC B-stage disease, early NLR response (decrease), and early AFP response (decrease > 20%) may achieve better clinical outcomes with the proposed triple therapy.

Table 4 Multivariate Cox regression analysis of progression-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≤ 58 *vs* > 58 yr)	0.98 (0.64-1.49)	0.9279		
Gender (male *vs* female)	0.64 (0.31-1.32)	0.1413		
ECOG PS (0 *vs* 1)	0.90 (0.59-1.37)	0.6087		
Etiology (HBV *vs* others)	0.78 (0.45-1.36)	0.3417		
BCLC stage (C *vs* B)	1.82 (1.18-2.80)	0.0036	1.75 (1.12-2.74)	0.014
Maximum tumor diameter (≤ 6.8 *vs* > 6.8)	0.99 (0.65-1.52)	0.9933		
Number of tumors (≤ 3 *vs* > 3)	0.81 (0.53-1.23)	0.3099		
Portal vein invasion (absent *vs* presence)	0.77 (0.47-1.26)	0.2597		
Extrahepatic metastasis (absent *vs* presence)	0.73 (0.47-1.14)	0.1408		
Child-Pugh class (A *vs* B)	1.26 (0.67-2.36)	0.5094		
Baseline AFP (≤ 400 *vs* > 400)	1.00 (0.65-1.53)	0.9992		
Baseline DCP (≤ 40 *vs* > 40)	1.27 (0.64-2.55)	0.4486		
NLR (≤ 3 *vs* > 3)	0.93 (0.56-1.54)	0.7707		
LDH (≤ 198.52 *vs* > 198.52)	0.85 (0.53-1.35)	0.4605		
Early NLR response (decrease *vs* increase)	0.54 (0.34-0.86)	0.0025	0.56 (0.35-0.90)	0.016
Early AFP response (decrease ≤ 20% *vs* > 20%)	1.70 (1.08-2.66)	0.0116	1.73 (1.12-2.66)	0.013
Early DCP response (decrease ≤ 20% *vs* > 20%)	1.73 (0.97-3.09)	0.0250		

AFP: Alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer Classification; DCP: Des-gamma-carboxyprothrombin; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HBV: Hepatitis B virus; HR: Hazard ratio; LDH: Lactate dehydrogenase; NLR: Neutrophil lymphocyte ratio; PD-1: Programmed cell death protein-1.

ARTICLE HIGHLIGHTS

Research background

Transarterial chemoembolization (TACE) is the standard locoregional therapy for unresectable hepatocellular carcinoma (HCC), but not every patient can benefit from TACE, and there is also relatively high post-TACE recurrence. Triple therapy with TACE combined with lenvatinib plus PD-1 inhibitors, may result in a better prognosis for HCC patients.

Research motivation

The efficacy and safety of this triple therapy have been rarely evaluated and it is unknown which factors are related to efficacy. By solving this problem, this will aid clinical decision-making.

Research objectives

In this study, we aimed to first assess the efficacy and safety of TACE-lenvatinib-PD1 therapy for unresectable HCC patients and to explore the predictive factors of clinical outcomes.

Research methods

During follow-up, tumor responses were assessed based on the modified Response Evaluation Criteria in Solid Tumors and categorized as complete response, partial response, stable disease, or progression disease. The objective response rate (ORR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS) were also calculated. The Cox proportional hazards regression method was used to identify the factors associated with OS and PFS.

Research results

The confirmed ORR was 61.76% (63/102), and the DCR was 81.37% (83/102). The median PFS was 10.07 months (95%CI: 8.50-11.65), and the median OS was 26.43 months (95%CI: 17.00-35.87). Barcelona Clinic Liver Cancer Classification (BCLC) B stage, early neutrophil-to-lymphocyte ratio (NLR) response (decrease) and early AFP response (decrease > 20%) were identified as the independent predictors of clinical outcomes.

Research conclusions

This study showed that TACE-lenvatinib-PD-1 treatment was well tolerated with encouraging efficacy in unresectable HCC patients. The patients with BCLC B, with early NLR response (decrease) and early AFP response (decrease > 20%) might achieve better clinical outcomes with this triple therapy.

Research perspectives

Further prospective studies with larger sample sizes are necessary. In addition, subgroup analyses are needed to determine the unknown differences attributing to each agent.

FOOTNOTES

Author contributions: Wang MQ contributed to the conception and design; Ma KP and Fu JX contributed to the analysis and interpretation of data; Ma KP and Duan F contributed to the writing, review, and/or revision of the manuscript; All authors contributed to the acquisition of data (acquired and managed patients) and final approved the manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of the Chinese People's Liberation Army General Hospital.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: The authors have no relevant financial or non-financial interests to disclose.

Data sharing statement: The authors declare that all data and materials supporting the findings of this study are available within the article.

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