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Transarterial Chemoembolization plus Apatinib with or without Camrelizumab for the Treatment of Advanced HBV-related Hepatocellular Carcinoma

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ABSTRACT

Aims: To compare the effectiveness and safety of transarterial chemoembolization (TACE) combined with apatinib plus camrelizumab (TACE+AC) versus TACE combined with apatinib alone (TACE+A) for patients with advanced HBV-related hepatocellular carcinoma (HBV–HCC).

Methods: The clinical data of patients with HBV–HCC who received either TACE+AC or TACE+A treatment were retrospectively analyzed. Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) were compared between the two groups. Multivariate Cox proportional hazards model regression analysis was used to identify the independent prognostic factors of OS.

Results: Between March 2019 to January 2022, 76 patients were assigned to the TACE+AC group (n = 37) and the TACE+A group (n=39). The median OS and PFS in the TACE+AC group were significantly longer than those in the TACE+A group (OS, 15.4 vs. 11.3 months; p=0.008; PFS, 7.4 vs. 5.1 months; p=0.001) and the ORR and DCR in the TACE + AC group were significantly greater than those in the TACE+A group (ORR, 43.2% vs. 20.5%; p=0.033; DCR, 67.6% vs. 43.6%; p=0.036). There was no significant difference in the incidence of grade ≥3 AEs between the two groups (p=0.483). Multivariate regression analysis identified the treatment modalities, AFP level, and extrahepatic metastasis as independent prognostic factors (p<0.05).

Conclusion: TACE+AC significantly improved the clinical outcomes of patients with HBV–HCC and elicited relatively controllable AEs.

Key words: transarterial chemoembolization – apatinib – camrelizumab – HBV – hepatocellular carcinoma.

Abbreviations: A: apatinib; AE: adverse event; BCLC: Barcelona Clinic Liver Cancer; C: camrelizumab; CR: complete response; CT: computed tomography; DCR: disease control rate; ECOG-PS: Eastern Cooperative Oncology Group performance status HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MDT: multi-disciplinary treatment; mRECIST: modified response evaluation criteria in solid tumors; MRI: magnetic resonance imaging; ORR: objective response rate; OS: overall survival; PD: progressive disease; PD-1: programmed cell death protein-1; PDL-1: programmed death ligand-1; PFS: progression-free survival; PR: partial response; SD: stable disease; TACE: transarterial chemoembolization; TAM: tumor-associated macrophages; VEGF: vascular endothelial growth factor.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common gastrointestinal tumors [1], especially in East Asia, and accounts for approximately 50% of patients affected by gastrointestinal tumors worldwide [2]. Hepatitis B virus (HBV) infection is a major cause of HCC; in East Asia, approximately 80% of patients with HCC were found to have HBV-related hepatocellular carcinoma (HBV–HCC) [3]. The onset of HCC is insidious; nearly 70% of patients with HCC are in the advanced stage of the disease at the time of diagnosis, thereby rendering the option of radical surgical treatment unsuitable, and such cases can only be treated with palliative care, including transarterial chemoembolization (TACE), targeted therapy, and immunotherapy [4, 5].

Since Yamada et al. [6] first reported the use of TACE for HCC in 1983, it has become the standard treatment for Barcelona Clinic Liver Cancer (BCLC) stage B HCC worldwide [7]. In addition, for BCLC stage C patients with good liver

function and physical performance, the efficacy of TACE is not worse than that of standard targeted therapy [8]. Transarterial chemoembolization blocks the blood supply of the tumor and induces it into a state of ischemia and hypoxia, which can lead to the reduction of the lesion [9]. The short-term effect of this approach is satisfactory, but the long-term effect is poor, because the ischemic and hypoxic state induces the overexpression of vascular endothelial growth factor (VEGF), which eventually leads to tumor angiogenesis [10]. Apatinib (A) is a novel small-molecule-targeted antiangiogenic drug that acts with high selectivity on vascular endothelial growth factor receptor-2 (VEGFR-2) and can effectively inhibit both tumor angiogenesis and tumor proliferation [11]. Therefore, TACE combined with A is beneficial for synergistically enhancing the antitumor effect.

With the development of immunotherapy, the combined application of a variety of therapies based on TACE have been found to achieve good efficacy in HCC [12]. Camrelizumab (C) is the first programmed cell death protein-1 (PD-1) inhibitor approved for the treatment of advanced HCC in China [13]. The results of the RESCUE trial showed that the objective response rate (ORR) of C combined with A in the first-line treatment against advanced HCC was 45.7% and the 12-month overall survival (OS) rate was 74.7% [14]. In this trial, 62.9% of the patients had received previous interventional therapy, including TACE. Transarterial chemoembolization combined with A plus C (TACE+AC) compared with A+C, exhibited better clinical efficacy in the treatment of unresectable HCC [15]. In East Asia, HBV–HCC is the main type of HCC, and some studies have shown a higher response rate to immunotherapy for HBV–HCC compared with non-viral HCC [16-18]. However, there has been no study on the use or effectiveness of TACE+AC in the treatment of HBV–HCC. Thus, this study compared the efficacy, safety, and survival outcomes of TACE+AC and TACE combined with A (TACE+A) in the treatment of advanced HBV-HCC in order to maximize the clinical benefit to patients.

METHODS

Patients

From March 2019 to January 2022, a total of 76 patients with advanced HBV–HCC who received either TACE+AC or TACE+A at the Affiliated Hospital of Xuzhou Medical University were retrospectively analyzed. All patients were assigned to either the TACE+AC group or TACE+A group according to whether they had received C treatment or not.

The inclusion criteria were as follows: (1) the diagnosis of HCC was confirmed pathologically or by imaging ; (2) patients positive for serum hepatitis B surface antigen or positive for serum HBV–DNA; (3) older than 18 years; (4) taking A for more than 4 weeks; (5) there was at least one target lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [19]; (6) Child-Pugh class A or B; (7) BCLC stage B or C; (8) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1.

The exclusion criteria were as follows: (1) the presence of a second malignant tumor; (2) undergoing treatment with hepatic artery infusion chemotherapy; (3) the presence of another hepatitis virus; (4) incomplete clinical data; (5) lost to follow-up.

Transarterial Chemoembolization

For each patient, the location and size of the tumor were determined by digital subtraction angiography, the tumor feeding artery was superselected with the help of micro-guidewire, and 50-100 mg of oxaliplatin was perfused through the catheter. Then, according to the liver function, tumor size, and blood supply status of the patients, certain branches of the tumor-feeding arteries were selected to administer a mixed pirarubicin hydrochloride and iodized oil suspension until the interruption of tumor vessels and the disappearance of abnormal tumor staining were shown during angiography. Patients underwent magnetic resonance imaging (MRI) and/or computed tomography (CT) examination 4 to 6 weeks after TACE. If the arterial blood supply to the tumor was not completely embolized, TACE was performed again.

Apatinib and Camrelizumab

Apatinib and C were started within 3-7 days after the first TACE. Apatinib (250 mg/tablet) was taken orally as one tablet each time, once a day, for 4 weeks, as one cycle. Camrelizumab (200 mg) was administered intravenously, once every 3 weeks, as one cycle. For patients with intolerable adverse events (AEs), the dose of C and A was reduced or discontinued.

Follow-up Assessment

Patients were followed up every 4-6 weeks after the initial treatment, and each follow-up included recording their detailed history, physical examination results, routine laboratory tests, abdominal contrast enhanced CT or MRI, and chest CT. If there were still significant active lesions or new lesions in the liver, TACE therapy was performed again. The deadline for follow-up was April 1, 2022. Overall survival was defined as the time from the start of treatment to death from any cause, and progression-free survival (PFS) was defined as the time from the start of treatment to disease progression or death from any cause. Tumor response was evaluated according to the mRECIST criteria, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as ORR=(CR+PR cases)/total number of cases×100% and the disease control rate (DCR) was defined as DCR=(CR+PR+SD cases)/total number of cases×100%. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Treatment was discontinued when either the radiographic or clinical features indicated tumor recurrence or progression or when the patient had intolerable AEs.

Statistical Analysis

SPSS 23.0 and R 4.2.1. were used for the statistical analysis. Continuous variables conforming to a normal distribution were expressed as the mean ± standard deviation, and the independent sample t-test was used for comparison between the two groups. Categorical data were expressed as frequencies and were compared using the chi-squared test or Fisher's exact test. The Kaplan-Meier method was used to draw survival

curves and the log-rank test was used to compare survival differences. Univariate and multivariate Cox proportional hazards regression analysis was used to identify the independent prognostic factors of OS, and a nomogram model was then established according to these factors. The concordance index (C-index) was calculated for discrimination verification, and a calibration curve was drawn for consistency verification. A p value < 0.05 was considered statistically significant.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (file number XYFY2022-KL320-01).

RESULTS

We initially identified 89 patients with advanced HBV–HCC who were treated with either TACE+AC or TACE+A. Of these patients, 13 were eliminated because they met the excluded criteria (Fig. 1). Ultimately, 76 patients were included in this study (37 in the TACE+AC group and 39 in the TACE+A group). None of the patients had received other treatments than TACE, A, and C. The baseline characteristics of the patients are shown in Table I. The median number of TACE treatments in the TACE+AC group and the TACE+A group was 3 (1-7) and 2 (1-7), respectively. The median number of A treatment cycles in the TACE+AC group and the TACE+A group was 7 (2-15) and 5 (2-16), respectively. In the TACE+AC group, the median number of treatment cycles of C was 4 (2-11). The median follow-up time was 12 months until April 1, 2022.

Patients in the TACE+AC group had a significantly greater ORR compared with the TACE+A group (43.2% vs. 20.5%; p=0.033). The DCR of the TACE+AC group was also significantly greater than that of the TACE+A group (67.6% vs. 43.6%; p=0.036). Of the 37 patients in the TACE+AC group, 2.7% (n=1) had a CR, 40.5% (n=15) achieved a PR, 24.3% (n=9) had SD, and 32.4% (n=12) had PD. In contrast, among the 39 patients in the TACE+A group, no patients had a CR, 20.5% (n=8) achieved a PR, 23.1% (n=9) had SD, and 56.4% (n=22) had PD (Table II).

The median PFS of the TACE+AC group was 7.4 months (95%CI: 5.4-9.4), while that of the TACE+A group was 5.1 months (95%CI: 2.9-7.3) (Fig. 2A). The median PFS was significantly longer for the TACE+AC group than for the TACE+A group (hazard ratio, 0.58; p=0.001). The median OS was 15.4 months (95%CI: 13.7-17.1) in the TACE+AC group and 11.3 months (95%CI: 9.6-13.1) in the TACE+A group (Fig. 2B). The median OS of the TACE+AC group was significantly longer than that of the TACE+A group (hazard ratio, 0.55; p=0.008).

According to the results of univariable and multivariable Cox proportional hazard regression analysis, the independent prognostic factors for OS were identified to be treatment modalities (HR=0.358, 95%CI: 0.210-0.611, p=0.001), the AFP level (HR=0.514, 95%CI: 0.293-0.901, p=0.020), and extrahepatic metastasis (HR=2.997, 95%CI: 1.709-5.256, p=0.001) (Table III).

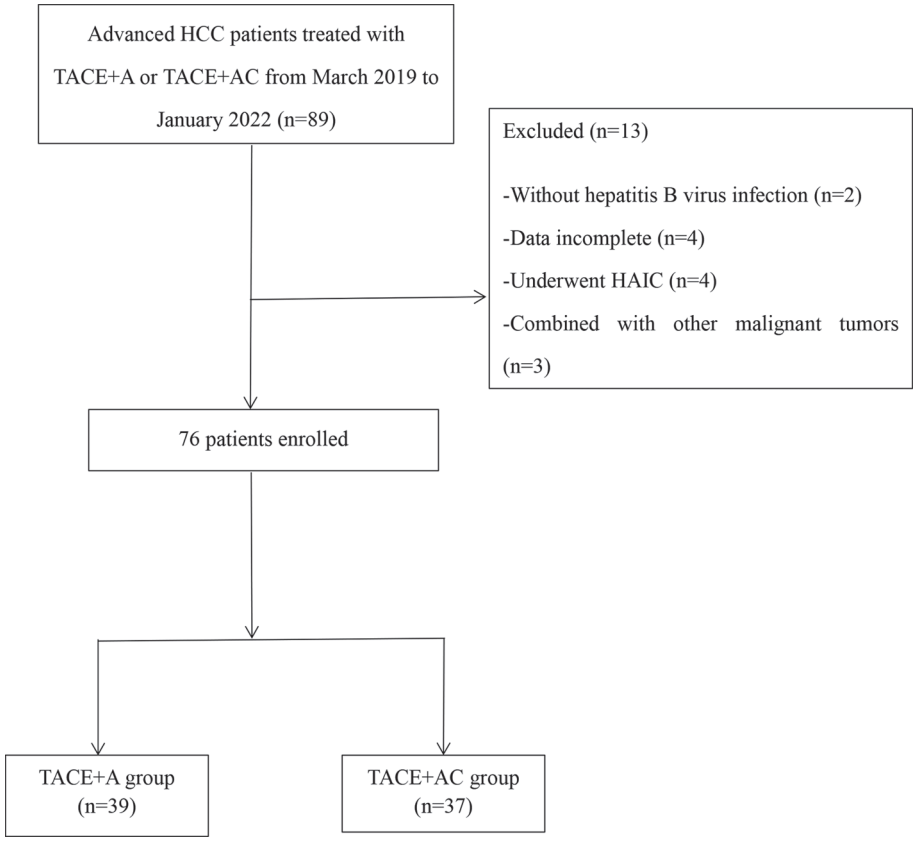

Fig. 1. Flowchart of patient selection. HCC: hepatocellular carcinoma; TACE: transcatheter arterial chemoembolization; TACE+AC: TACE plus apatinib plus camrelizumab; TACE+A: TACE plus apatinib; HAIC: hepatic artery infusion chemotherapy.

Table I. Baseline characteristics of patients

Variable	TACE + AC group (n = 37)	TACE + A group (n = 39)	p
Age (years)			0.060
<60	25 (67.6)	18 (46.2)	
≥60	12 (32.4)	21 (53.8)	
Gender			0.409
Male	32 (86.5)	36 (92.3)	
Female	5 (13.5)	3 (7.7)	
Tumor size			0.246
<5 cm	15 (40.5)	21 (53.8)	
≥5 cm	22 (59.5)	18 (46.2)	
Intrahepatic tumors			0.629
Single	6 (16.2)	8 (20.5)	
Multiple	31 (83.8)	31 (79.5)	
Vascular invasion			0.247
Yes	24 (64.9)	30 (76.9)	
No	13 (35.1)	9 (23.1)	
Extrahepatic metastasis			0.632
Yes	16 (43.2)	19 (48.7)	
No	21 (56.8)	20 (51.3)	
ECGO PS			0.289
0	27 (73.0)	24 (61.5)	
1	10 (27.0)	15 (38.5)	
Child-Pugh class			0.660
A	32 (86.5)	35 (89.7)	
B	5 (13.5)	4 (10.3)	
BCLC stage			0.370
B	19 (51.4)	24 (61.5)	
C	18 (48.6)	15 (38.5)	
Laboratory parameters			
AFP			0.665
<400 ng/ml	20 (54.1)	23 (59.0)	
≥400 ng/ml	17 (45.9)	16 (41.0)	
PIVKA-II			0.597
<100 mAU/ml	13 (35.1)	16 (41.0)	
≥100 mAU/ml	24 (64.9)	23 (59.0)	
AST (U/L)	54.73±50.54	45.82±37.06	0.880
ALT (U/L)	46.76±38.19	39.10±26.55	1.019
ALB (g/L)	41.05±5.13	40.43±5.50	0.510
TBIL (μmol/L)	22.06±26.40	21.03±13.03	0.216
PT (s)	12.20±1.47	12.31±1.51	0.322

Data in brackets represent percentages. TACE: transcatheter arterial chemoembolization; TACE+AC: TACE plus apatinib plus camrelizumab; TACE+A: TACE plus apatinib; ECOG PS: Eastern Cooperative Oncology Group Performance Status; AFP: a-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; ALB: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TBIL: total bilirubin; PT: prothrombin time.

The above three independent prognostic factors (treatment modalities, the AFP level, and extrahepatic metastasis) were included to construct the nomogram models in patients with advanced HBV-HCC (Fig. 3). Each factor corresponds to the upper ruler, and the score of the factor could be obtained. By adding the scores of each factor, the total score was calculated, according to which, the corresponding OS rate of 12 and 15 months was calculated. The higher the score, the worse the prognosis. The C-index of the nomogram model is 0.695, indicating that it has good predictive value and that the calibration curves show that the predicted 12-month and 15-month OS rates are in agreement with the actual observations (Fig. 4).

Table II. Tumor response between the TACE+AC and TACE+A groups

	TACE + AC group (n = 37)	TACE + A group (n = 39)	p
CR	1 (2.7)	0 (0)	
PR	15 (40.5)	8 (20.5)	
SD	9 (24.3)	9 (23.1)	
PD	12 (32.4)	22 (56.4)	
ORR	16 (43.2)	8 (20.5)	0.033
DCR	25 (67.6)	17 (43.6)	0.036

Data in brackets represent percentages. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate. For the rest of abbreviations see Table I.

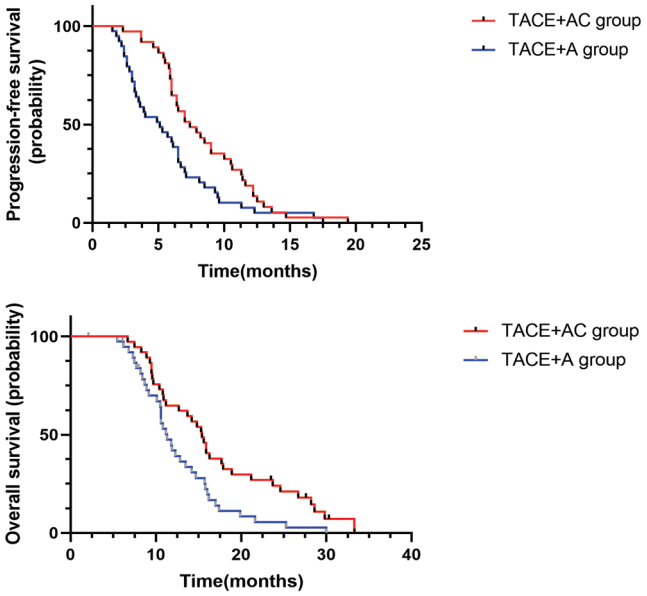

Fig. 2. Kaplan–Meier plot of the TACE+AC and TACE+A groups. (A) Progression-free survival. (B) Overall survival. For abbreviations see Fig.1.

The main adverse reactions in the two groups were of grades 1-2, the most common of these were fever, hand-foot skin reaction, hypertension, and proteinuria (Table IV). Grade ≥3 AEs occurred in 14 patients (8 in the TACE+AC group and 6 in the TACE+A group). There were no noticeable differences in the incidence of grade ≥3 AEs between the two groups (21.6% vs. 15.4%; p=0.483). In the TACE+AC group, one patient discontinued C for one cycle due to experiencing severe AEs (grade 3 myocarditis). In the TACE+A group, the blood pressure of one patient reached 190/100 mmHg, and antihypertensive treatment was not effective. Their blood pressure stabilized after A was reduced to 150 mg/day.

Table III. Univariate and multivariate analyses of the prognostic factors for overall survival

Factors	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (>60 vs. ≤60), year	1.271	0.786–2.054	0.328	-	-	-
Gender (male vs. female)	0.634	0.298–1.348	0.236	-	-	-
Treatment modalities (TACE+AC vs. TACE+A)	0.527	0.325–0.856	0.010	0.358	0.210–0.611	0.001
Tumor size (<5 vs. ≥5), cm	0.765	0.467–1.252	0.286	-	-	-
AFP level (<400 vs. ≥400), ng/mL	0.533	0.325–0.875	0.013	0.514	0.293–0.901	0.020
PIVKA-II level (<100 vs. ≥100), mAU/ml	0.764	0.467–1.252	0.286			
ECOG PS (0 vs. 1)	0.882	0.532–1.462	0.626	-	-	-
Child-Pugh class (A vs. B)	0.760	0.385–1.497	0.427			
BCLC stage (B vs. C)	0.790	0.490–1.274	0.334	-	-	-
Vascular invasion (yes vs. no)	0.747	0.445–1.255	0.271	-	-	-
Extrahepatic metastasis (yes vs. no)	2.543	1.537–4.208	0.001	2.997	1.709–5.256	0.001
Intrahepatic tumors (single vs. multiple)	1.865	1.004–3.466	0.049	1.199	1.436–6.942	0.591

For the abbreviations see Table I.

DISCUSSION

In East Asia, nearly 80% of patients with HCC have chronic hepatitis caused by HBV infection, which in turn develops into cirrhosis and HCC [20]; this is markedly different from the main causes of HCC in other regions (HCV infection, alcoholic liver disease, and nonalcoholic steatohepatitis) [21-23]. This study is the first to compare the efficacy and safety of TACE+AC and TACE+A in patients with advanced HBV–HCC. The results showed that TACE+AC was superior to TACE+A in terms of tumor response and long-term survival, and that the accompanying AEs were controllable. Therefore, TACE+AC may represent an improved treatment option for advanced HBV–HCC patients.

At present, multi-disciplinary treatment (MDT) is the main treatment mode for HCC, and TACE combined with systemic therapy is one of the most important MDT modes. After TACE treatment, liver cancer cells enter a hypoxic state and produce hypoxia-inducible factor-1 (HIF-1) to induce VEGF mRNA synthesis. This, in turn, increases serum VEGF levels, thereby promoting neovascularization and leading to tumor recurrence [24, 25]. Apatinib can inhibit tumor angiogenesis by inhibiting VEGF receptors and regulating downstream ERK-1/2 signaling pathways [26]. Chen et al. [27] reported that TACE+A significantly prolonged median OS compared with TACE alone in patients with BCLC stage C HCC (13.0 months vs. 9.9 months, p=0.041). Lu et al. [28] found that the median PFS of TACE alone and TACE+A for BCLC stage B and C HCC was 6.0 months and 12.5 months, respectively. Anthracycline chemotherapy drugs used for TACE have strong cytotoxicity and can trigger immunogenic cell death, thereby improving the immunogenicity of tumor cells and enhancing the endogenous anti-tumor immune response, while the use of PD-1 inhibitors can further enhance this anti-tumor immune response [29]. The expression of programmed death ligand-1 (PD-L1) is upregulated under hypoxic conditions; that is, the hypoxic environment caused by TACE increases PD-L1 expression [30]. In addition, preclinical studies have

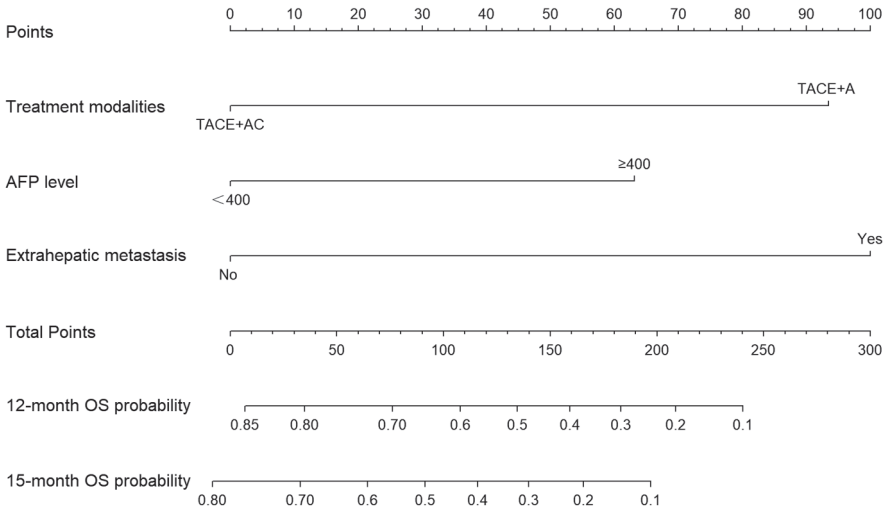

Fig. 3. Graph showing the prognostic model for predicting 12- and 15-month overall survival. AFP: a-fetoprotein. For other abbreviations see Fig.1.

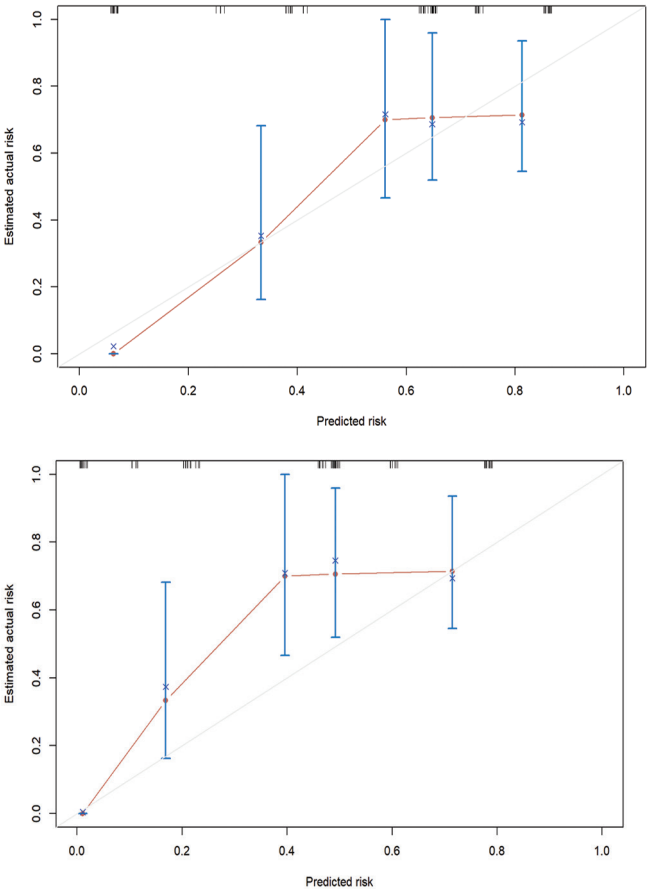

Fig. 4. Calibration plots for overall survival. 12-month overall survival (B) 15-month overall survival.

shown that A can reduce the number of tumor-associated macrophages (TAM). In the tumor microenvironment, TAM is known as an immunomodulator. On this basis, reducing TAM can change the expression levels of cytokines and immune regulatory receptors to promote immune activation [31]. Therefore, TACE, A, and PD-1 inhibitors combination might have synergistic antitumor effects. In this study, C was added to TACE+A, and the results showed that the median OS of the TACE+AC group was significantly longer than that of the TACE+A group (15.4 vs. 11.3 months; p=0.008).

Immunotherapy for HBV–HCC may be more effective than for non-HBV, non-hepatitis C virus (HCV) hepatocellular carcinoma (HCC). On the one hand, the tumor microenvironment that is characteristic of HBV–HCC exhibits a stronger immunosuppressive effect compared with that of non-HBV, non-HCV HCC, and this inhibitory effect can be rapidly reversed after the use of immunotherapy [32]. On the other hand, CD8/PD-1 double-positive T cells have been found to be abnormally activated and gradually increased in non-HBV, non-HCV HCC following the administration of PD-1 inhibitors, but these cells did not play an immune surveillance role and hence were not able to kill tumor cells [17]. Pfister et al. [17] conducted a meta-analysis that showed no significant improvement in survival after immunotherapy in non-HBV, non-HCV HCC patients (HR=0.92; 95%CI: 0.77–1.11). Liu et al. [16] found that the ORR and PFS of C in HBV-HCC were significantly better than those of non-HBV non-HCV HCC in Chinese patients (ORR, 28.6% vs. 7.7%, p=0.048; PFS, 9.2 months vs. 6.7 months, p=0.003). This finding may be an important reason to add C to TACE+A to achieve satisfactory efficacy in HBV–HCC patients.

Table IV. Treatment-related adverse events

Effect	All grades		Grade ≥ 3	
	TACE + AC group (n = 37)	TACE + A group (n = 39)	TACE + AC group (n = 37)	TACE + A group (n = 39)
RCCEP	8 (21.6)	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	12 (32.4)	9 (23.1)	0 (0.0)	1 (2.6)
Thrombocytopenia	5 (13.5)	6 (15.4)	1 (2.7)	0 (0.0)
Neutropenia	7 (18.9)	3 (7.7)	1 (2.7)	0 (0.0)
Anemia	5 (13.5)	4 (10.3)	0 (0.0)	1 (2.6)
Hypothyroidism	5 (13.5)	2 (5.1)	0 (0.0)	0 (0.0)
Hyperthyroidism	2 (5.4)	1 (2.6)	0 (0.0)	0 (0.0)
Hypertension	14 (37.8)	12 (30.8)	1 (2.7)	1 (2.6)
Rash	2 (5.4)	4 (10.3)	0 (0.0)	0 (0.0)
Nausea	4 (10.8)	4 (10.3)	0 (0.0)	0 (0.0)
Diarrhea	6 (16.2)	5 (12.8)	0 (0.0)	1 (2.6)
Fatigue	9 (24.3)	6 (15.4)	0 (0.0)	1 (2.6)
Myocarditis	2 (7.1)	0 (0.0)	1 (2.7)	0 (0.0)
Fever	17 (45.9)	15 (38.5)	1 (2.7)	0 (0.0)
UGIB	1 (2.7)	2 (5.1)	0 (0.0)	0 (0.0)
Mouth ulcers	7 (18.9)	4 (10.3)	0 (0.0)	0 (0.0)
Hand-foot skin reaction	16 (43.2)	13 (33.3)	2 (5.4)	1 (2.6)
ALT increase	7 (18.9)	9 (23.1)	1 (2.7)	0 (0.0)
AST increase	8 (21.6)	7 (17.9)	0 (0.0)	0 (0.0)

RCCEP: Reactive cutaneous capillary endothelial proliferation; UGIB: upper gastrointestinal bleeding; AST: aspartate aminotransferase; ALT: alanine aminotransferase; For other abbreviations see Table I.

Multivariate Cox proportional hazards model regression analysis showed that combining C with TACE+A was an independent prognostic factor for prolonged median OS (HR=0.358, 95%CI: 0.210-0.611, p=0.001). Next, we developed a nomogram prediction model based on the results of the multivariate Cox proportional hazard regression analysis. The nomogram prediction model also showed that treatment modalities (TACE+AC vs. TACE+A) had the largest impact on median OS, thereby further validating our conclusions. To validate the nomogram prediction model, we calculated the C-index and plotted the calibration curve. The C-index of the nomogram model in this study was 0.695, and the calibration curve showed that our model was in good agreement with the actual observations, thereby demonstrating the accuracy and validity of the model.

This study had some limitations. First, this study was a single-center retrospective study with a small sample size comprised of an all-Chinese population, which may therefore have involved some degree of selection bias. Secondly, A and C were started within 3–7 days after the first TACE, while the appropriate timing of their combination in therapy remains to be determined. Thirdly, the follow-up time in this study was relatively short, and it will be necessary to continue to expand the follow-up time in subsequent investigations. Finally, this study only investigated TACE+AC as a triple regimen, and other triple regimens (TACE combined with targeted agents plus PD-1 inhibitors) still need to be explored.

CONCLUSIONS

Transarterial chemoembolization combined with A and C is a promising therapy for the treatment of patients with advanced HBV–HCC, featuring favorable local treatment responses, survival benefits, and a good safety profile compared with TACE+A. In the future, multi-center prospective studies with larger sample sizes must be conducted to confirm our conclusions.

Conflicts of interest: None to declare.

Authors' contribution: Z.H. and H.L. conceived and designed the study. H.L. and Q.Y. analyzed and interpreted the data. T.G. and P.Q. prepared the original draft. X.M. and Z.H. critically revised the paper. All authors read and approved the final version of the manuscript submitted for publication.

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