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Transarterial chemoembolization plus camrelizumab is an effective and tolerable bridging therapy for patients with intermediate-stage hepatocellular carcinoma: A pilot study

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Abstract. Transarterial chemoembolization (TACE) has been reported to synergize with camrelizumab in the treatment of hepatocellular carcinoma (HCC). The present study aimed to explore the potential of TACE and camrelizumab as a bridging therapy prior to surgery for patients with HCC. For this purpose, 11 patients with HCC with intermediate stage disease [classified by China Liver Cancer (CNLC) staging] who received TACE combined with camrelizumab as a bridging therapy prior to surgery were enrolled in this study. The treatment response was evaluated at 2 weeks following TACE therapy and following camrelizumab treatment. The relapse-free survival (RFS) and overall survival (OS) of the patients were calculated. The objective response and disease control rates were 72.7 and 100.0% following TACE treatment, and were 100.0 and 100.0% following camrelizumab treatment, respectively. The α-fetoprotein levels gradually decreased following TACE, camrelizumab treatment and surgical resection (all P<0.05). Of note, the CNLC stage decreased following treatment (P=0.007) and the downstaging success rate was 63.6%. In terms of survival profiles, the mean RFS (95% CI) was 14.1 (11.7-16.5) months and the 1-year RFS rate was 77.9±14.1%. Furthermore, the mean OS (95% CI) was 15.0 (13.2-16.8) months and the 1-year OS rate was 80.0±17.9%. Successful downstaging was associated with RFS (P=0.041), but not OS (P=0.221). With regard to safety, 6 (54.5%) patients experienced reactive cutaneous capillary endothelial proliferation, 5 (45.5%) patients reported pain and 4 (36.4%) patients had a fever. On the whole, the present study demonstrated that TACE plus camrelizumab may be an effective and safe strategy that has potential for use as a bridging strategy prior to surgery in patients with intermediate-stage HCC.

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Introduction

Liver cancer is the second leading cause of cancer-related mortality worldwide, among which hepatocellular carcinoma (HCC) accounts for ~90% of new cases, featuring a male preponderance and rising mortality rate over the past decade (1-3). The major etiologies of HCC include hepatitis B and/or C virus infections, superfluous alcohol intake and fatty liver disease (4,5). Curative treatment modalities, including liver resection or transplantation, and microwave ablation, provide a survival benefit for patients with early-stage HCC; however, as the majority of patients with HCC are diagnosed at an intermediate or advanced stage, these patients are not considered candidates for these curative treatments (6,7). Currently, diverse interventional treatment approaches, such as bridging therapies, are administered in order make patients eligible for curative resection treatments, thus prolonging the survival profiles of patients with intermediate- to advanced-stage HCC (8,9). However, there is still a lack of consensus on the optimal bridging strategy for these patients. Thus, further investigations are required into bridging strategies.

Transarterial chemoembolization (TACE) is an established first-line palliative treatment for patients with unresectable intermediate-stage HCC. According to recent studies, TACE is effective in promoting a reduction in tumor size and a decrease in tumor burden; it is therefore recognized as a promising bridging therapy for the management of HCC (10-13). For example, a previous study indicated that TACE was an effective bridging strategy for subsequent curative radical treatment

in patients with HCC, with a successful downstaging rate of 59.4% (14).

Immunotherapy with strategies targeting immune checkpoints [especially programmed-death 1 (PD-1) inhibitor] have been developed for antitumor treatment and the combination of these with chemotherapy has been shown to exhibit an enhanced clinical benefit in patients with diverse malignancies (15-17). Camrelizumab is a PD-1 inhibitor developed in China, which has received considerable attention, since it exerts satisfactory antitumor efficacy and it may serve as a promising strategy for the downstaging of HCC followed by liver transplant or surgical resection of the tumor (18-20). Furthermore, there is evidence to indicate that the combination of TACE and programmed cell death protein 1 (PD-1) inhibitor is associated with a prolonged progression-free survival (PFS) compared with TACE monotherapy for patients with intermediate- to advanced-stage HCC (21,22). However, these previous studies do not evaluate the effect of TACE plus camrelizumab as a downstaging strategy for HCC.

Therefore, the present pilot study aimed to explore the potential of TACE plus camrelizumab as a bridging therapy prior to surgery in patients with intermediate-stage HCC.

Patients and methods

Patients. In the present prospective pilot study, 11 patients with HCC with intermediate-stage disease [classified by China Liver Cancer (CNLC) staging] who received TACE plus camrelizumab as bridging therapy prior to surgery were enrolled between June 2019 and July 2020 at Handan Central Hospital (Handan, China). The enrollment criteria included: i) A diagnosis of primary HCC in accordance with the guidelines for liver cancer (23); ii) age ≥18 years; iii) CNLC IIa or IIb stage disease (23); iv) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 1 (24); v) patients had to be ineligible for direct surgery due to one or more of the following reasons: Large and multiple tumors, insufficient residual liver, poor hepatic function, severe complications relating to a high surgical risk, and a potential risk of severe post-excision cirrhosis and post-excision liver failure; and vi) scheduled for TACE combined with camrelizumab as a bridging therapy prior to surgery. Patients were excluded if the following applied: i) Vascular invasion, bile duct invasion or distant metastasis; ii) contraindications to TACE or camrelizumab; iii) an uncontrolled infection or moderate to severe myelosuppression; i) other malignant diseases; or v) pregnant or lactating female patients. The Institutional Review Board of Handan Central Hospital (Handan, China) approved the present study and all patients provided written informed consent.

Assessment prior to treatment. Clinical examinations prior to treatment were performed for all patients and the main clinical data were documented, including age, sex, hepatitis B (HBV) status, liver cirrhosis, ECOG PS score, Child-Pugh stage (25), nodule number, tumor capsule, tumor size, pathological differentiation and CNLC stage. The CNLC stage was evaluated in line with the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2017 Edition) (23).

Treatment process. The total treatment process was as follows: First, all patients received one cycle of TACE; at 2 weeks following TACE, patients began to receive camrelizumab treatment for 2-6 cycles; following camrelizumab treatment, according to the surgical indications, tumor resection was performed. The detailed TACE procedures were conducted as reported in a previous study (26). In brief, following the superselective catheterization of feeding arteries for tumors, a mixture of ethiodized poppyseed oil (Jiangsu Hengrui Pharmaceutical Co., Ltd) and oxaliplatin (200 mg) (Jiangsu Hengrui Pharmaceutical Co., Ltd) was infused into the feeding arteries of the tumor and polyvinyl alcohol particles (Jiangsu Hengrui Pharmaceutical Co., Ltd, China) were then injected as embolization material. The embolization endpoint was that the blood flow reached complete or near stasis in the feeding arteries for the tumor. Camrelizumab was administered intravenously at a dose of 3 mg/kg, with a treatment cycle of every 3 weeks.

Assessments. For the evaluation of the treatment response, an abdominal contrast-enhanced CT examination was performed for the patients at 2 weeks following TACE treatment and following camrelizumab treatment. The clinical response was assessed based on the modified Response Evaluation Criteria in Solid Tumors (27), including the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Furthermore, the objective response rate (ORR) and disease control rate (DCR) were calculated as CR + PR and CR + PR + SD, respectively. When the patients had completed the whole camrelizumab treatment protocol, the CNLC stage of the patients was assessed again. Furthermore, the downstaging success was assessed, which was defined as a change in CNLC stage from stage II to I following TACE combined with camrelizumab bridging therapy (14). To monitor the change in tumor markers, the α-fetoprotein (AFP) level was detected prior to TACE, following TACE, following camrelizumab treatment and following surgical resection. In addition, adverse events were documented for safety assessment.

Follow-up. Following surgery, the patients were followed up every 3 to 6 months, during which the date of disease relapse or patient mortality were recorded in detail for survival evaluation. Relapse-free survival (RFS) and overall survival (OS) were calculated for survival analysis.

Statistical analysis. Variables are presented using numbers with percentages or the mean with standard deviation. Paired comparisons for CNLC stage and AFP at different time-points were performed using McNemar's test or the Wilcoxon signed-rank test, as appropriate. The associations of HBV history and anti-HBV treatment with downstaging success were determined using Fisher's exact test. The RFS and OS were examined using Kaplan-Meier curves and the comparison of the RFS and OS between two groups was performed using the log-rank test. Statistical analysis and graph plotting were completed using SPSS 22.0 software (IBM Corp.) and 7.00 software (GraphPad Software; Dotmatics), respectively. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Characteristics of patients with hepatocellular carcinoma (n=11).

Item	Value
Age, years	60.4±9.6
Sex	
Male	8 (72.7)
Female	3 (27.3)
HBV history	7 (63.6)
Liver cirrhosis	3 (27.3)
ECOG PS score	
0	8 (72.7)
1	3 (27.3)
Child-Pugh stage	
A	8 (72.7)
B	3 (27.3)
Nodule number	3.4±1.0
Tumor size >3 cm	11 (100.0)
Tumor capsular	8 (72.7)
Pathological differentiation	
Well	6 (54.5)
Moderate	3 (27.3)
Poor	2 (18.2)
CNLC stage	
IIa	5 (45.5)
IIb	6 (54.5)

Values are expressed as the mean ± SD or n (%). HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CNLC, China Liver Cancer.

Results

Clinical characteristics of the patients with HCC. In the present study, the 11 patients with HCC had a mean age of 60.4±9.6 years (Table I). The cohort comprised 8 (72.7%) males and 3 (27.3%) females. Regarding the Child-Pugh stage, there were 8 (72.7%) and 3 (27.3%) patients with Child-Pugh stages A and B, respectively. In terms of the CNLC stage, there were 5 (45.5%) and 6 (54.5%) patients with CNLC stage IIa and CNLC stage IIb, respectively. Detailed information on the patients with HCC is provided in Table I.

Treatment response following TACE/camrelizumab treatment in patients with HCC. Following TACE therapy, the CR, PR, SD, PD, ORR and DCR were 9.1, 63.6, 27.3, 0.0, 72.7 and 100.0%, respectively (Fig. 1A). Furthermore, following camrelizumab treatment, the CR, PR, SD, PD, ORR and DCR were 18.2, 81.8, 0.0, 0.0, 100.0 and 100.0%, respectively (Fig. 1B).

Longitudinal change in AFP during the treatment of patients with HCC. The AFP levels were documented at four time-points (including prior to TACE, following TACE, following camrelizumab treatment and following surgical resection). The results revealed that the AFP levels exhibited a marked decrease over these four time-points (all P<0.05; Fig. 2A). Furthermore, the proportion of patients with abnormal AFP levels was 72.7, 63.6, 27.3 and 9.1% at these four time-points, respectively; this proportion significantly decreased following tumor resection when compared with that prior to treatment (P=0.007; Fig. 2B).

Table II. Down-staging success rate in the patients (n=11).

Item	Before treatment	After treatment	P-value
CNLC stage			0.007
Ia	0 (0.0)	1 (9.1)	
Ib	0 (0.0)	6 (54.5)	
IIa	5 (45.5)	4 (36.4)	
IIb	6 (54.5)	0 (0.0)	
Down-staging success		7 (63.6)	

Values are expressed as n (%). CNLC, China Liver Cancer.

Downstaging success in patients with HCC. Prior to treatment, there were 0 (0.0%), 0 (0.0%), 5 (45.5%) and 6 (64.5%) patients with CNLC stages Ia, Ib, IIa and IIb, respectively; following treatment, there were 1 (9.1%), 6 (54.5%), 4 (36.4%) and 0 (0.0%) patients with CNLC stages Ia, Ib, IIa and IIb, respectively (Table II). By comparison, the CNLC stage was decreased following treatment (P=0.007). Furthermore, the downstaging success was 63.6%. In the current study, 2 patients with an HBV history had HBV reactivation and they received anti-HBV treatment, while the other 5 patients with an HBV history did not have any HBV reactivation and thus, they did not receive anti-HBV treatment. Statistically, neither HBV history nor anti-HBV treatment affected the downstaging success (Table SI).

RFS and OS of patients with HCCs. According to the follow-up records following surgery, the mean RFS (95% CI) was 14.1 (11.7-16.5) months and the 1-year RFS rate was 77.9±14.1% (Fig. 3A). Furthermore, the mean OS (95% CI) was 15.0 (13.2-16.8) months and the 1-year OS rate was 80.0±17.9% (Fig. 3B).

Association of downstaging success with the survival profiles of patients with HCC. According to the downstaging success, all patients were divided into the unsuccessful downstaging group (n=4) and the successful downstaging group (n=7). Further comparative analysis revealed that the RFS was increased in the successful downstaging group compared with that in the unsuccessful downstaging group (P=0.041; Fig. 4A); however, the OS was similar between the successful and unsuccessful downstaging groups (P=0.221; Fig. 4B). Detailed information (including clinical features, treatment response, disease relapse, survival status, etc.) of each patient with HCC is presented in Table III.

Common adverse events in patients with HCC. The adverse events that occurred during the treatment period were mild

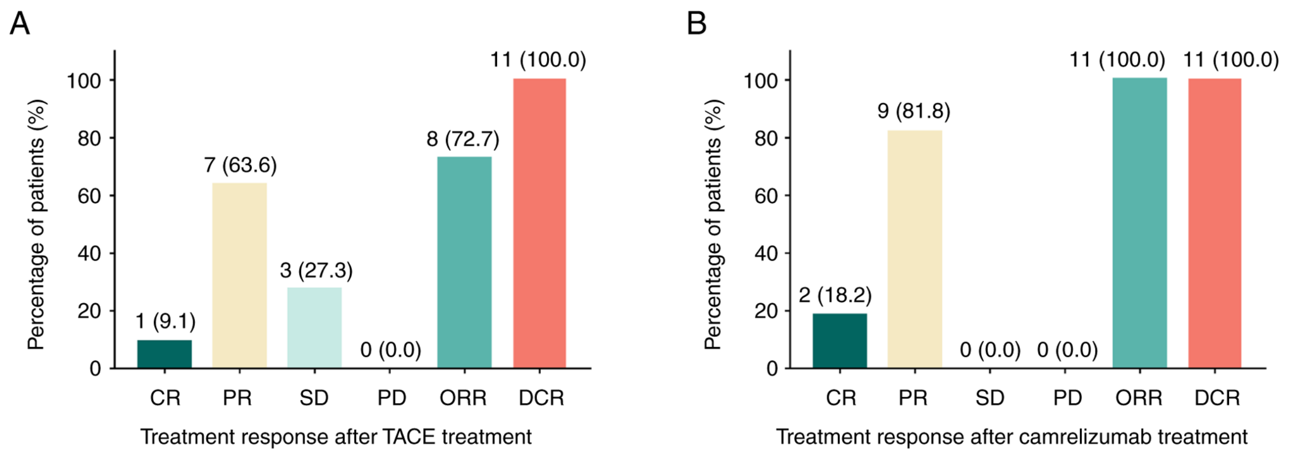

Figure 1. Assessment of the treatment response of patients with HCC. CR, PR, SD, PD, ORR and DCR following (A) TACE and (B) following camrelizumab treatment in patients with intermediate-stage HCC. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

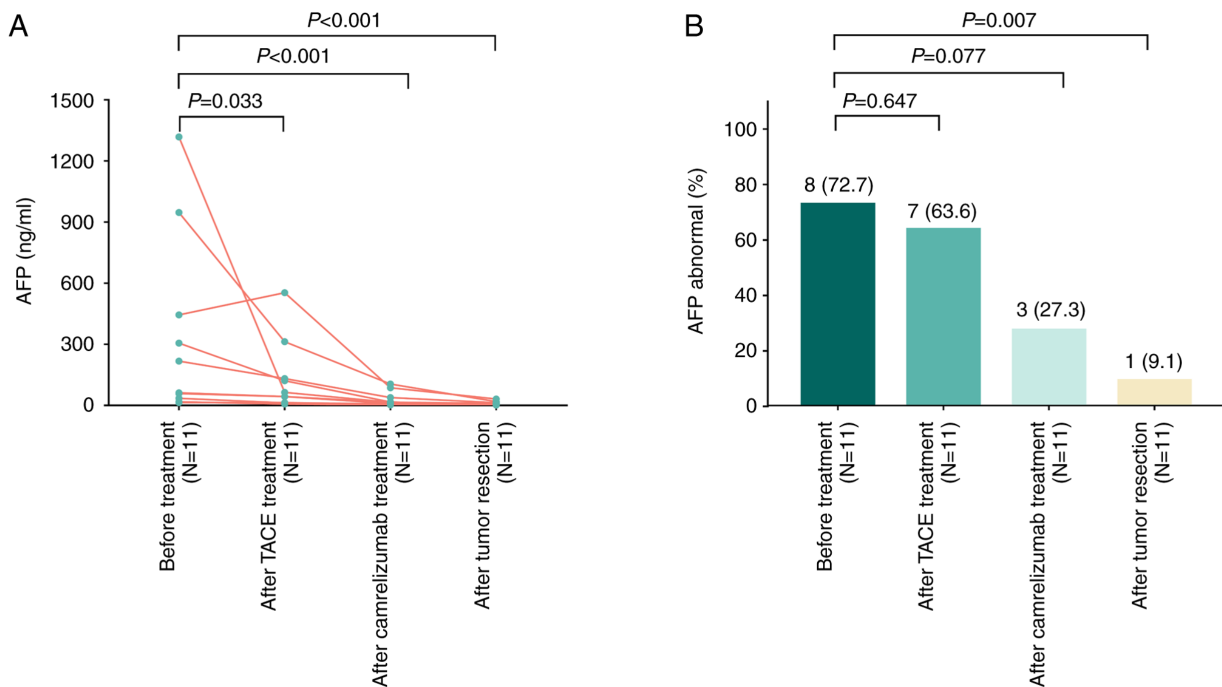

Figure 2. Assessment of AFP levels in patients with hepatocellular carcinoma. (A) Longitudinal change in AFP levels and (B) proportion of patients with abnormal AFP levels during the study period (prior to treatment, following transarterial chemoembolization treatment, following camrelizumab treatment after tumor resection). AFP, α-fetoprotein.

and well-tolerated in the patients with HCC, as indicated in Table IV. In detail, there were 6 (54.5%) patients with reactive cutaneous capillary endothelial proliferation (RCCEP), 5 (45.5%) patients with pain and 4 (36.4%) patients with fever.

Discussion

Camrelizumab is a humanized high-affinity IgG4-κ anti-PD-1 monoclonal antibody that was first administered for the treatment of relapsed/refractory classical Hodgkin's lymphoma (17); recent studies have demonstrated its efficacy in the treatment of multiple malignancies, including HCC (17,22,28). For instance, a previous randomized, open-label, multicenter study indicated that the ORR was 14.7% and the 6-month OS rate was 74.4% in patients with advanced-stage HCC who received camrelizumab treatment (29). Furthermore, a non-randomized, open-label study reported that camrelizumab combined with apatinib led to an ORR of 34.3%, a median PFS rate of 5.7 months and a 12-month OS rate of 74.7% in patients with advanced-stage HCC (28). In addition, other studies have demonstrated that the combination of TACE and PD-1 inhibitors (such as nivolumab, sintilimab or pembrolizumab) has potential for use as an effective treatment strategy for patients with intermediate- and advanced-stage HCC (30,31).

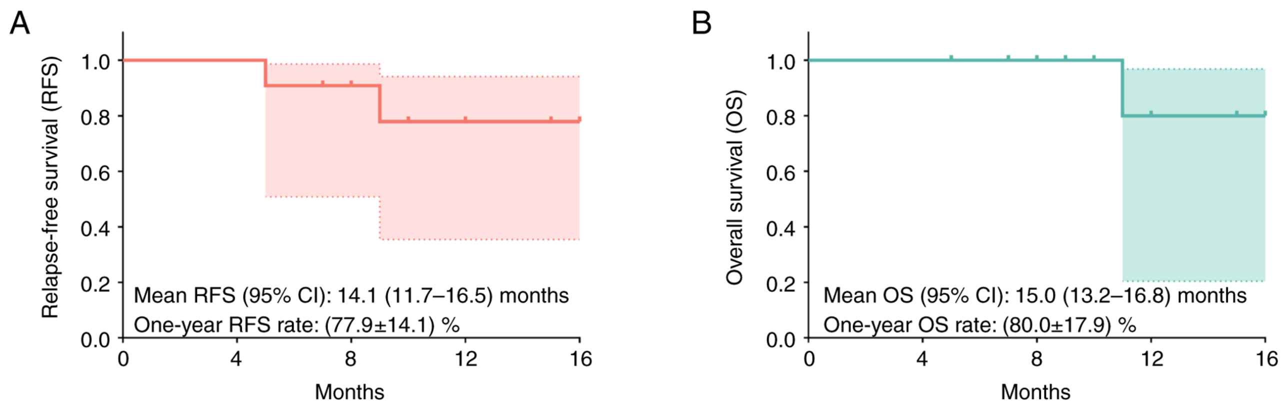

Figure 3. Assessment of the RFS and OS of patients with HCC. (A) Mean RFS and 1-year RFS rate of patients with intermediate-stage HCC. (B) Mean OS and 1-year OS rate of patients with intermediate-stage HCC. The shaded areas indicate 90% confidence intervals. Streaks indicate censored data. RFS, relapse-free survival; OS, overall survival; HCC, hepatocellular carcinoma.

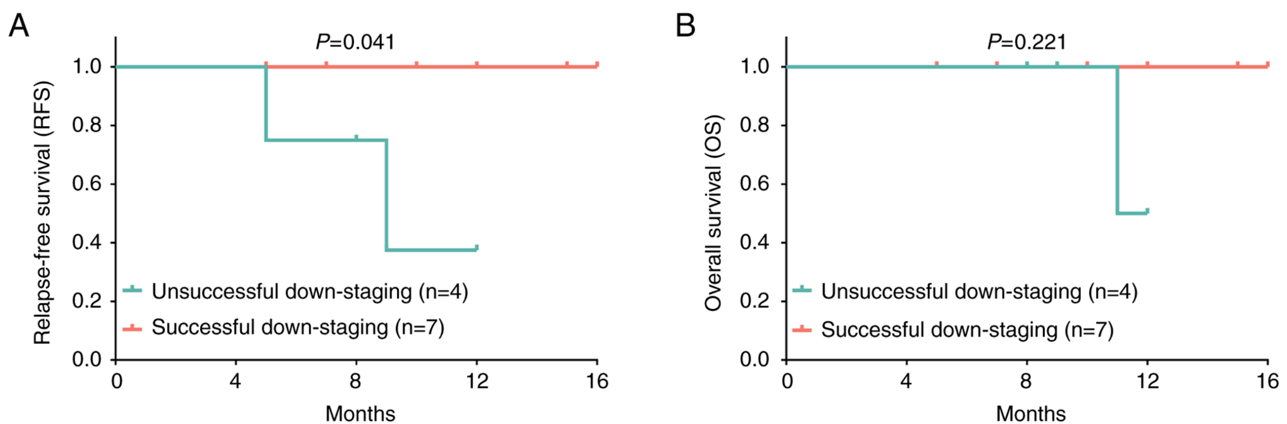

Figure 4. Survival of patients with HCC with unsuccessful/successful downstaging. Association of (A) RFS and (B) OS with successful downstaging in patients with intermediate-stage HCC. RFS, relapse-free survival; OS, overall survival; HCC, hepatocellular carcinoma.

Other studies have also suggested the role of TACE as an effective bridging therapy for patients with initially unresectable HCC (32,33). Hence, according to the aforementioned evidence, it was hypothesized that the combination of TACE and camrelizumab may also have potential value as a novel bridging strategy for patients with intermediate-stage HCC.

In the present study, it was observed that the ORR and DCR were 72.7 and 100.0% following TACE therapy, and 100.0 and 100.0% following camrelizumab treatment, respectively. Of note, the treatment response of TACE plus camrelizumab in the present study was markedly higher than that achieved with camrelizumab alone (ORR, 36.4%; DCR, 81.8%), as previously reported (34), suggesting an elevated treatment response of TACE plus camrelizumab compared with that of camrelizumab alone in patients with intermediate-stage HCC. A possible reason for this may be that TACE therapy has the advantages of minimal trauma and high targeting, thereby effectively suppressing the progression of HCC and leading to a markedly increased treatment efficacy in patients with HCC (30,32). In addition, in the present study, it was found that the AFP level was the highest prior to TACE, followed by after TACE and camrelizumab treatment, and was the lowest following surgical resection. This evidence reflected the good treatment response of TACE plus camrelizumab in the treatment of patients with intermediate-stage HCC. The use of AFP to reflect treatment efficacy in patients with HCC is in accordance with previous studies (35,36). Furthermore, in the present study, the downstaging success rate following TACE plus camrelizumab was 63.6%, which was relatively increased compared with the successful downstaging rate achieved with TACE alone (ranging from 23.7 to 55.0%) in patients with HCC who were not suitable for curative treatments reported in previous studies (37-39). This phenomenon may be attributed to the extra application of camrelizumab, which enhanced the antitumor activities and inhibited HCC growth in patients with HCC (40). In addition, the procedure of TACE may be different in the current study compared with previous studies (37-39). Therefore, the downstaging superiority of TACE plus camrelizumab compared with TACE alone should be further validated in comparative studies.

In addition, in terms of survival profiles, it was observed that successful downstaging was associated with RFS; however, successful downstaging was also associated with OS, although without a statistically significant difference in patients with intermediate-stage HCC. This may have been due to the relatively small sample size in the present study. The

Table III. Detailed data of each patient with hepatocellular carcinoma.

					CNLC stage			Treatment response						
No.	Age, years	Gender	Child-Pugh stage	Pathological differentiation	Before	After	Down-staging	TACE	Camrelizumab	Tumor resection	Disease relapse	RFS, months	Death	OS, months
1	54	Male	A	Well	IIa	Ia	Yes	CR	CR	Yes	No	5	No	5
2	48	Male	A	Well	IIb	Ib	Yes	PR	PR	Yes	No	12	No	12
3	65	Female	B	Poor	IIb	Ib	Yes	SD	PR	Yes	No	10	No	10
4	41	Male	B	Moderate	IIb	IIa	No	PR	PR	Yes	No	12	No	12
5	68	Male	A	Well	IIa	Ib	Yes	PR	CR	Yes	No	7	No	7
6	70	Female	A	Poor	IIb	IIa	No	SD	PR	Yes	Yes	5	No	9
7	56	Male	A	Moderate	IIa	Ib	Yes	PR	PR	Yes	No	10	No	10
8	59	Male	A	Well	IIa	IIa	No	PR	PR	Yes	No	8	No	8
9	69	Female	B	Well	IIa	IIa	No	SD	PR	Yes	Yes	9	Yes	11
10	68	Male	A	Moderate	IIb	Ib	Yes	PR	PR	Yes	No	15	No	15
11	66	Male	A	Well	IIb	Ib	Yes	PR	PR	Yes	No	16	No	16

HCC, hepatocellular carcinoma; CNLC, China Liver Cancer; TACE, transarterial chemoembolization; RFS, relapse-free survival; OS, overall survival.

Table IV. Common adverse events in the patients (n=11).

Adverse event	n (%)
RCCEP	6 (54.5)
Pain	5 (45.5)
Fever	4 (36.4)

RCCEP, reactive cutaneous capillary endothelial proliferation.

aforementioned results were consistent with those of previous studies demonstrating that patients with successful downstaging exhibit improved survival compared to patients with unsuccessful downstaging (10,14,37). A possible reason for this may be that the combination of TACE plus camrelizumab as a bridging therapy helps patients with intermediate-stage HCC achieve downstaging, and the decreased HCC stage was associated with favorable survival.

Regarding the safety profiles, in detail, 6 patients experienced RCCEP, 5 patients reported pain and 4 patients exhibited fever; however, there were no severe adverse events, suggesting mild and manageable safety profiles in patients treated with TACE plus camrelizumab as a bridging therapy. The explanations for these adverse events are as follows: i) According to the existing evidence, RCCEP, as a reflection of the activated immune response, is considered a common skin reaction related to the use of camrelizumab (41). In addition, the presence of RCCEP did not require the discontinuation of treatment or dose reduction, and it often spontaneously regressed (41). ii) Furthermore, based on previous research (19), pain and fever are part of post-embolization syndrome and appear frequently following the application of TACE, which explained the occurrence of fever and pain in the present study.

Of note, there are certain limitations to the present study: i) The sample size of the present study was relatively small; therefore, the results require further validation using a larger sample size; ii) considering the relatively short follow-up period, the efficacy and safety of the combined use of TACE plus camrelizumab as a bridging therapy require to be further assessed in patients with intermediate-stage HCC in studies with longer follow-up times; iii) the present study suggested efficacy of TACE plus camrelizumab as a bridging therapy prior to surgery; however, its superior efficacy over monotherapy requires a control group for further validation; iv) the current study used AFP to reflect the treatment efficacy of TACE plus camrelizumab, while other possible markers, such as AFP-L3, as well as markers of liver function, should be examined to further reflect the efficacy and safety of TACE plus camrelizumab.

In conclusion, the present study demonstrated that TACE plus camrelizumab may be a potential effective and safe strategy as a bridging therapy prior to surgery in patients with intermediate-stage HCC. However, further randomized, controlled trials should be conducted for validation.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PF and SH conceptualized and supervised the study. HH, XW, SX and XN performed analysis and interpretation of data. SX and XN provided resources and performed visualization. LC and ZY conducted the investigation, prepared the original draft and wrote the manuscript. PF and SH confirm the authenticity of all the raw data. All authors contributed critically to the manuscript revision. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of Handan Central Hospital (Handan, China) approved the present study and all patients provided written informed consent to participate.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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