Original Article

Transcatheter embolization of hepatocellular carcinoma with epirubicin-loaded DC beads in Chinese patients

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Background: This study evaluated the safety and efficacy of transcatheter chemoembolization with drug eluting beads (DEB-TACE) and compared it to the conventional TACE (cTACE) therapy method for hepatocellular carcinoma (HCC) in Chinese patients.

Methods: Seventy-four patients were treated with DEB-TACE using the DC bead, and 80 patients were treated with cTACE for HCC. The modified response evaluation criteria in solid tumors (mRECIST) criteria were used to evaluate clinical response, with adverse events assessed according to the Common Terminology Criteria for Adverse Events (CTCAE).

Results: Post-TACE, 9 patients (12.2%) achieved complete response (CR) and 44 (59.5%) achieved partial response (PR), with an overall tumor response rate (ORR) of 71.6% in the DEB-TACE group. Twelve patients (15%) achieved CR, and 38 (47.5%) achieved PR, with an ORR of 62.5% in the cTACE group. However, there was no significant difference in ORR between the two groups (P=0.229). Univariate logistic regression analysis determined that more than 3 nodules, higher Barcelona clinic liver cancer (BCLC) stage, portal vein invasion, previous chemotherapy (cTACE), and previous surgery were correlated with a worse ORR. Most common adverse events were not severe.

Conclusions: DEB-TACE by DC bead was efficient and well-tolerated compared to cTACE in Chinese HCC patients. However, the present study showed no significant difference in ORR between the DEB-TACE and cTACE in the patient group with HCC. The BCLC stage, number of nodules, portal vein invasion, cTACE, and surgery history could possibly be a predictive factor for HCC treatment response.

Keywords: Transcatheter chemoembolization with drug eluting beads (DEB-TACE); DC bead; hepatocellular carcinoma (HCC); predictive factors

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Introduction

Hepatocellular carcinoma (HCC) is the most common cancer worldwide, and is ranked as the third leading cause of cancer-related death (1). Current therapeutic options are based on the Barcelona clinic liver cancer (BCLC) staging system, integrating tumor characteristics and performance status with liver function. Surgical resection and liver transplantation are currently the accepted treatment choice in patients who have early-stage HCC with decompensated cirrhosis.

Transcatheter chemoembolization (TACE) is the most commonly used palliative treatment for patients with unresectable HCC (2,3). The principle of conventional TACE (cTACE) is the synergistic effect of cytotoxic chemotherapy and ischemia. Intra-arterial chemotherapeutic agents are mixed with lipiodol, which causes cytotoxic damage to the tumor cells, as well as embolization of the supplying blood vessels by gelatin or Gelfoam particles, resulting in ischemia (4). TACE is already recommended as the standard therapy for intermediate HCC patients according to the current guidelines, allowing for cTACE to combine with embolizing particles for chemotherapy drug delivery. Although cTACE is generally applied in HCC treatment, the systemic toxicity of chemotherapy after cTACE is significant (5,6). For optimal therapeutic effect, higher doses of the intra-arterial chemotherapeutic agent need to be retained within the tumor.

Furthermore, a chemotherapeutic drug that is released can reduce systemic side effects, and drug-eluting beads (DEBs) have been developed with these objectives in mind (5). DC beads (BTG International Ltd., UK) can load and release doxorubicin hydrochloride in a controlled manner (5). A previous study reported that TACE using beads loaded with doxorubicin (DEBDOX) induced significantly fewer drug-related side effects than cTACE (7). Moreover, DEB-TACE is reported to be safer and more effective than cTACE in HCC treatment (8-10). Few studies have been performed to evaluate the safety and efficacy of DEB-TACE when compared to cTACE for HCC.

The purpose of this study was to investigate the safety and efficacy of DEB-TACE treatment by DC bead when compared to cTACE for HCC in Chinese patients, as well as to determine the predicting factors for treatment response.

Methods

Patients and specimen characteristics

Seventy-four HCC patients were treated with TACE with DEBs and 80 HCC patients were treated with cTACE at our institution over a 1 and a half year period. Patients were considered for transarterial therapy if they exhibited unresectable HCC (determined by transplant surgery) and met the following criteria: (I) diagnosed with HCC according to the AASLD criteria (American Association for the Study of the Liver Diseases) (11); (II) aged 20–75 years old; (III) Child-Pugh stage A or B (score of no more than 7); (IV) ECOG score (Eastern Cooperative Oncology Group) of 0–2; and (V) without intrahepatic arterial-portal fistula or intrahepatic arteriovenous fistula. The exclusion criteria for this study were as follows: (I) Child-Pugh stage C or renal failure; (II) known allergy or contraindicated for the chemoembolization reagent used in this study; (III) intrahepatic arterial-portal fistula or intrahepatic arteriovenous fistula; (IV) hepatic encephalopathy; (V) uncontrolled ascites; (VI) life expectancy of less than 3 months; and (VII) pregnant or lactating women.

Ethical approval

The study was performed according to the standards set by the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (No. 2016-324). All participants provided signed informed consent.

Procedure

DC beads (300–500 μm, BTG International Ltd., UK) were loaded with 60 mg of epirubicin. The loading process used for the DEBs with epirubicin was as follows: using a tee joint, one vial of DC bead was used to mix the DEBs and epirubicin, and the mixed solution was shaken for 2 minutes and stored for 30 minutes at room temperature; next, the non-ionic contrast agent was added to the mixed solution.

Before the reagent mixing procedure, enhanced magnetic resonance imaging (MRI) of the liver was performed to detect any arteriovenous fistula, and to identify the arterial supply of the tumor. Additionally, all HCC embolization was conducted under topical anesthesia. Subsequently, the tumor arterial supply was catheterized by 2.8 French microcatheters (Boston Scientific, Watertown, MA, USA). After the microcatheters were inserted, the DC bead loaded with epirubicin was injected at the speed of 1 mL/min, with the injection procedure being discontinued when a stasis flow of contrast agent occurred. After 5 minutes,

a second angiography was conducted, and embolization was continued if the tumor blood supply was still present. Once all tumors stains disappeared, the microcatheters were removed, and the embolization was completed. If one vial of DC beads was used and the embolization was not completed, another vial would be utilized to reach the embolization endpoint.

In the cTACE group, emulsions of lipiodol (5–20 mL) and DOX (20–30 mg) were thoroughly mixed by the pumping method, and were slowly injected into the tumor artery through a microcatheter under fluoroscopic monitoring to avoid reflux of lipiodol emulsion followed by the infusion of a gelatin sponge or embosphere. The TACE procedure was terminated when target blood flow interruption or tumor stain disappearance was observed.

Assessments

Clinical response post-treatment with TACE was assessed by MRI at 1–3 months post-TACE, according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (12). The criteria contain the following 4 categories: complete response (CR), which was described as a disappearance of any intra-tumoral arterial enhancement in all target lesions; partial response (PR), defined as at least a 30% decrease in the sum of the diameters of viable target lesions compared with the baseline diameter of the target lesions; stable disease (SD), including any cases that did not meet the criteria for CR, PR or progressive disease (PD); PD, defined as an increase of at least 20% in the sum of the diameters of viable target lesions. The rate of overall response (OR) was calculated as the rate of CR plus PR.

Adverse events during and after treatment were recorded, in addition to all laboratory indices of the patients pre- and post-treatment. The severity of pain post-treatment with TACE was graded by the pain visual analog scale (VAS) (13), with the vomiting grade being determined by the frequency of vomiting episodes during the 24 h post-treatment. Also, liver injury was evaluated according to the grade of liver function, with the severity of liver toxicity being assessed by the Common Terminology Criteria for Adverse Events (CTCAE), developed by the National Cancer Institute (NCI) (14).

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). For the baseline characteristics analyses, the Chi-square and Fisher's exact tests were used for the comparison of categorical variables, and Student's *t*-test was used for the continuous variables. Data were presented as counts (%), mean ± standard deviation (SD), or median values (with 25th–75th percentiles). Univariate and multivariate logistic regression analyses were used for the assessment of predictors for tumor response. A $P<0.05$ was considered to be statistically significant.

Results

Baseline characteristics of HCC patients

Technical success was 100%. A total of 84 TACE procedures were performed in 74 patients (84 person-time patients) in the DEB-TACE group, and 102 TACE procedures were performed in 80 patients (102 person-time patients) in the cTACE group. Baseline characteristics of the patients are listed in *Table 1*. The mean patient age was 57.3±11.0 years in the DEB-TACE group and 55.6±11.9 years in the cTACE group, with this study consisting of 135 males and 19 females. Also, 62 patients (83.8%) in the DEB-TACE group and 69 (86.3%) in the cTACE group had cirrhosis. The median tumor distribution was 30.0% (10.0–40.0%) *vs.* 24.0% (8.0–37.0%), with the largest nodule being 6.2 (4.5–9.8) *vs.* 5.3 (2.5–8.8) cm. Additionally, the number of patients with ECOG PS of 0 and 1 was 65 (87.8%) and 9 (12.2%) in the DEB-TACE group, and 63 (78.8%), 17 (21.3%) in the cTACE group, respectively. The number of patients with Child-Pugh stage A and B was 62 (83.8%), and 12 (16.2%) in the DEB-TACE group, and 74 (92.5%), 6 (7.5%) in the cTACE group, respectively. In addition, 2 (2.7%), 21 (28.4%), and 51 (68.9%) patients were BCLC stage A, B, and C stage in the DEB-TACE group, respectively. Moreover, there was no significant differences observed in all baseline characteristics except the number of nodules >3 or ≤3 (*Table 1*).

Treatment response after TACE treatment

The ORR was 71.6%, with 9 (12.2%) and 44 (59.5%) patients achieving CR and PR in the DEB-TACE group, respectively (*Table 2*). The ORR of the cTACE group was 62.5%, with 12 (15.0%) achieving CR and 38 (47.5%) achieving PR (*Table 2*). There was no significant difference in the ORR between the two groups (P=0.229) (*Figure 1*).

Table 1 Baseline patient characteristics

Parameters	DEB-TACE	cTACE	P vaule
Patient (n)	74	80	–
Gender (male/female)	67/7	68/12	0.296
Age (mean ± SD, years)	57.3±11.0	55.6±11.9	0.414
Etiology			
No hepatitis (n/%)	2 (2.7)	3 (3.75)	–
HBV (n/%)	72 (97.3)	75 (93.75)	–
HCV (n/%)	0 (0.0)	2 (2.5)	–
HIV (n/%)	1 (1.4)	0 (0.0)	–
Drink (n/%)	35 (47.3)	31 (38.8)	0.284
Cirrhosis (n/%)	62 (83.8)	69 (86.3)	0.668
Tumor distribution* (%)	30.0 (10–40.0)	24.0 (8.0–37.0)	0.339
Number of nodules			
1 (n/%)	15 (20.3)	9 (11.3)	0.123
>1 (n/%)	59 (79.7)	71 (88.7)	–
≤3 (n/%)	32 (43.3	22 (27.5)	0.041
>3 (n/%)	42 (56.7)	58 (72.5)	–
Largest nodule size (range, cm)	6.2 (4.5–9.8)	5.3 (2.5–8.8)	0.312
Portal vein invasion (n/%)	43 (58.1)	36 (45.0)	0.104
Hepatic vein invasion (n/%)	9 (12.2)	8 (10.0)	0.669
ECOG score			0.133
0 (n/%)	65 (87.8)	63 (78.8)	
1 (n/%)	9 (12.2)	17 (21.3)	
Child-Pugh stage			0.093
A (n/%)	62 (83.4)	74 (92.5)	
B (n/%)	12 (16.2)	6 (7.5)	
BCLC stage			0.453
A (n/%)	2 (2.7)	6 (7.5)	
B (n/%)	21 (28.4)	28 (35.0)	
C (n/%)	51 (68.9)	46 (57.5)	
AFP abnormal (n/%)	52 (70.3)	65 (81.3)	0.111
Previous treatment			
cTACE (n/%)	25 (33.8)	39 (48.8)	0.060
Surgery (n/%)	10 (13.5)	16 (20.0)	0.283
Targeted therapy (n/%)	8 (10.8)	4 (5.0)	0.179

*, Data are presented as median (25th–75th), mean ± SD or counts (%). DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE; SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona clinic liver cancer; AFP, alpha fetoprotein.

Table 2 Clinical response of HCC patients post-TACE

Parameters	DEB-TACE (n=74, %)	cTACE (n=80, %)	P value
CR	9 (12.2)	12 (15.0)	0.608
PR	44 (59.5)	38 (47.5)	0.137
ORR	53 (71.6)	50 (62.5)	0.229
SD	11 (14.9)	12 (15.0)	0.981
PD	10 (13.5)	18 (22.5)	0.149

Data are presented as counts (%). HCC, hepatocellular carcinoma; DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE.

Table 3 Clinical response of HCC nodules post-TACE

Parameters	DEB-TACE nodules (n=152, %)	cTACE nodules (n=225, %)	P value
CR	18 (11.8)	23 (10.2)	0.620
PR	87 (57.2)	122 (54.2)	0.563
ORR	105 (69.1)	155 (64.4)	0.969
SD	25 (16.4)	32 (12.5)	0.554
PD	22 (14.5)	38 (16.9)	0.529

Data were presented as counts (%). DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE.

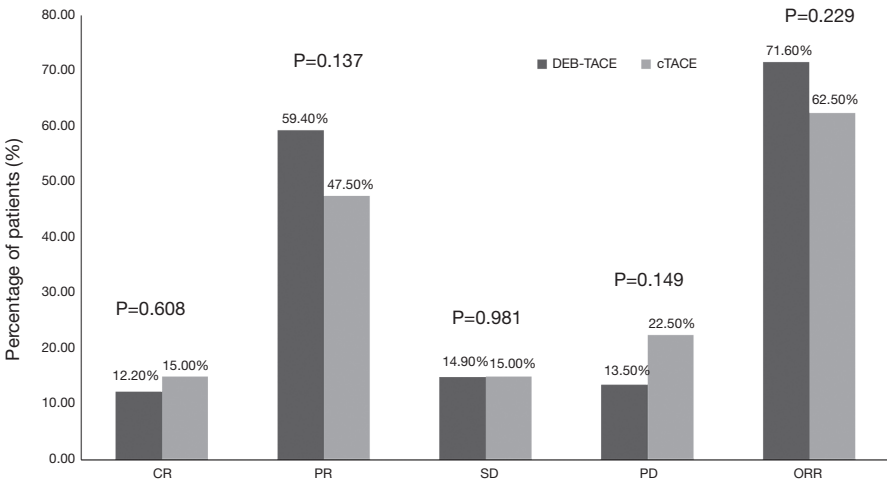

Figure 1 The clinical response of patients between the DEB-TACE group and the cTACE group. The Chi-square test determined comparison among groups. P<0.05 was considered significant. DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE; CR, complete response; PR, partial response; SD, standard deviation; PD, progressive disease; ORR, overall tumor response rate.

In terms of clinical response, the ORR of treated nodules in the DEB-TACE group was 69.1% compared to 64.4% in the cTACE group, in which 18 (11.8%) and 87 (57.2%) patients had nodules that achieved CR and PR compared to 23 (10.2%) and 122 (54.2%) in the cTACE group (*Table 3*), respectively. There were also no significant differences between the two groups (P=0.969). Among the nodules achieving a PR in the DEB-TACE group, 40 (46.0%) had a necrosis rate higher than 80%, 39 (44.8%) had a necrosis rate ranging from 50–80%, and 8 (9.2%) had a necrosis rate less than 50% (*Figure 2*). Also, the mean necrosis rate was (61.28%±22.65%) in the DEB-TACE group and 52.35%±29.75% in the cTACE group (*Table 4*). The PR DEB-TACE group had a higher necrosis rate than the PR cTACE group (P=0.009) (*Figure 2*).

Predictive factors analysis of ORR

Logistic regression analysis was performed to explore the predictive factors for tumor response in patients. As shown in *Table 5*, univariate logistic regression analysis determined that the number of nodules >3 (P=0.001), higher BCLC stage (P=0.047), portal vein invasion (P=0.031), previous cTACE (P=0.028), and previous surgery (P=0.009) were likely to be related with a worse ORR. The multivariate logistic regression analysis was performed with factors with a P<0.1. In the univariate logistic regression analysis, one factor, the number of nodules >3 (P=0.021), could

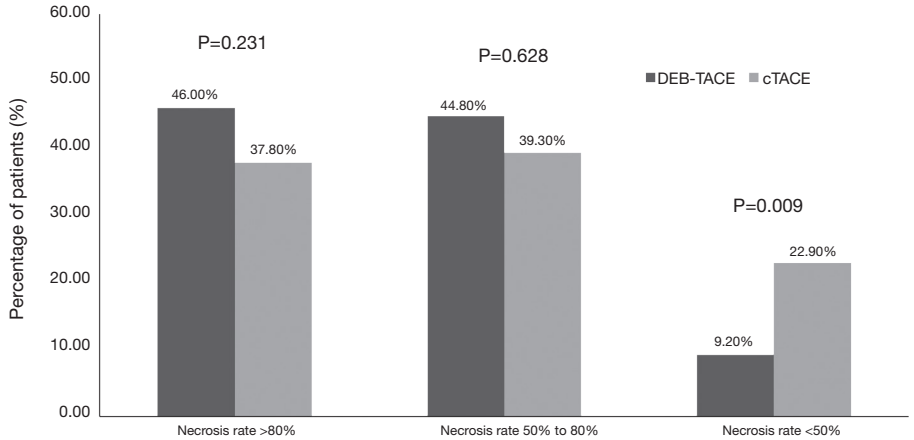

Figure 2 Necrosis rate of nodules achieving partial response. DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE.

Table 4 Necrosis rate of nodules achieving partial response

Parameters	DEB-TACE nodules (n=87, %)	cTACE nodules (n=122, %)	P value
Total necrosis rate (%)	61.28±22.65	52.35±29.75	0.582
Necrosis rate >80%	40 (46.0)	46 (37.8)	0.231
Necrosis rate 50% to 80%	39 (44.8)	48 (39.3)	0.628
Necrosis rate <50%	8 (9.2)	28 (22.9)	0.009

Data are presented as mean ± standard deviation or counts (%). DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE.

independently predict a worse ORR.

Liver function change before and after TACE

Liver function pre- and post-TACE were evaluated. The data showed that the CTCAE grades, based on baseline levels of ALB, TBIL, ALT, and AST, were only grade 0, 1, and 2, with grade 0 being the most prominent (*Tables 6*,*7*). Post-treatment, the liver toxicity grades increased compared to baseline (all P<0.001), with recovery time being within 1–3 months post-treatment (P=0.869, P=0.928, P=0.719, P=0.704 in the DEB-TACE group, and P=0.798, P=0.944, P=0.281, P=0.626 in the cTACE group, respectively).

Common adverse events of the safety profile

As listed in *Table 8*, pain and vomiting were the most common adverse events post-TACE (≤24 h). The number of person-time patients presenting with light, moderate, and severe pain in the DEB-TACE group were 55 (65.5%), 26 (30.9%), and 1 (1.2%) in the cTACE group, respectively. For vomiting in the DEB-TACE group, 73 (86.9%) person-time patients did not vomit, with 11 (13.1%) presenting with grade 1 vomiting, compared to 25 (24.5%) and 77 (75.5%), respectively, in the cTACE group. Vomiting incidence in the cTACE group was higher than that of the DEB-TACE group (P=0.000). Only 7 person-time patients (8.3%) in the DEB-TACE group and 6 (5.88%) in the cTACE group presented with hypertension. In addition, fever was the most common adverse event post-treatment (24–72 h). In the DEB-TACE group, the majority of person-time patients had no fever (n=30, 35.7%), low-grade (n=23, 27.4%), and median-grade (n=23, 27.4%) fever, with only 8 person-time patients (9.5%) having high-grade fever. There were no significant differences in pain incidence, hypertension, and fever between the two groups.

Discussion

HCC is the fifth most common form of cancer and the third

Table 5 Statistical analysis of factors affecting ORR

Parameters	Univariate logistic regression				Multivariate logistic regression			
	P value	OR	95% CI		P value	OR	95% CI	
			Lower	Higher			Lower	Higher
Treatment (DEB-TACE *vs.* cTACE)	0.131	1.683	0.857	3.304	–	–	–	–
Age ≥60 years	0.350	1.380	0.703	2.710	–	–	–	–
Gender (male)	0.430	0.647	0.220	1.907	–	–	–	–
Alcohol use	0.742	1.124	0.559	2.259	–	–	–	–
Cirrhosis	0.200	0.546	0.217	1.378	–	–	–	–
Tumor distribution ≥30%	0.497	0.792	0.405	1.551	–	–	–	–
Number of nodules >1	0.135	0.450	0.158	1.282	–	–	–	–
Number of nodules >3	0.001	0.255	0.112	0.576	0.021	0.355	0.147	0.854
Largest nodule size >5 cm	0.922	1.034	0.528	2.024	–	–	–	–
Portal vein invasion	0.031	0.473	0.241	0.932	0.732	0.799	0.221	2.892
ECOG =0 (*vs.* 1)	0.084	0.540	0.269	1.087	–	–	–	–
Child-Pugh stage A (*vs.* stage B)	0.145	0.478	0.177	1.289	–	–	–	–
Higher BCLC stage (A + B *vs.* stage C)	0.047	1.979	1.008	3.886	0.329	0.528	0.146	1.904
AFP abnormal	0.280	0.637	0.282	1.443	–	–	–	–
Previous cTACE	0.028	0.467	0.237	0.920	0.233	0.630	0.295	1.346
Previous surgery	0.009	0.341	0.152	0.764	0.057	0.419	0.171	1.028
Previous targeted therapy	0.935	1.054	0.302	3.675	–	–	–	–

Data are presented as P value, OR and 95% CI. Factors affecting ORR achievement are determined by univariate logistic regression analysis. OR, odds ratio; CI, confidence interval; ORR, overall tumor response rate; DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona clinic liver cancer.

Table 6 Change of liver function grade pre- and post-DEB-TACE treatment

Parameters	Baseline, TACEs (n=84)					1-week post TACE, TACEs (n=84)					1–3 months post TACE, TACEs (n=84)					P value*	P value#
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4		
ALB (n)	72	10	2	0	0	52	26	6	0	0	69	13	2	0	0	<0.001	0.869
TBIL (n)	59	20	5	0	0	30	37	15	2	0	58	22	4	0	0	<0.001	0.928
ALT (n)	70	11	3	0	0	28	30	19	6	1	68	13	2	0	0	<0.001	0.719
AST (n)	57	25	2	0	0	22	42	12	7	1	61	22	1	0	0	<0.001	0.704

*, baseline *vs.* 1-week post TACE; #, baseline *vs.* 1–3 months post TACE. DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

leading cause of cancer-related death worldwide. Around 50% of worldwide HCC incidence originates in China, with HCC being the second leading cause of cancer-related death in China (1). While resection is the first-line curative treatment for liver cancer, the majority of patients are not candidates for resection, which makes TACE a standard treatment for unresectable, intermediate stage HCC patients. TACE has been clinically shown to prolong survival and can potentially benefit the patient quality of life.

In our study, DEB-TACE treatment for HCC patients showed good efficacy regarding the CR and PR rates, along with the ORR, compared to cTACE. The logistic regression

Table 7 Change of liver function grade pre- and post-cTACE treatment

Parameters	Baseline, TACEs (n=102)					1-week post TACE, TACEs (n=102)					1–3 months post TACE, TACEs (n=102)					P value*	P value#
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4		
ALB (n)	87	12	3	0	0	65	31	6	0	0	85	15	2	0	0	<0.001	0.798
TBIL (n)	71	24	7	0	0	37	45	17	3	0	70	26	6	0	0	<0.001	0.944
ALT (n)	88	12	2	0	0	36	32	26	6	2	80	17	5	0	0	<0.001	0.281
AST (n)	79	21	2	0	0	26	50	13	9	3	73	26	3	0	0	<0.001	0.626

Data are presented as counts. Comparison among subgroups was analyzed by Wilcoxon signed-rank sum test, and P<0.05 was considered significant. *, baseline *vs.* 1-week post TACE; #, baseline *vs.* 1–3 months post TACE. cTACE, conventional transcatheter chemoembolization; cTACE, conventional TACE; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 8 Adverse events from DEB-TACE treatment

Parameters	DEB-TACEs (n=84, %)	cTACEs (n=102, %)	P value
During and post operation (≤24 h)			
Pain#			
No pain#	2 (2.38)	2 (1.96)	0.844
Light pain#	55 (65.5)	65 (63.7)	0.804
Moderate pain#	26 (30.9)	32 (31.4)	0.951
Severe pain#	1 (1.2)	3 (2.94)	0.628
Vomiting*			
No vomiting*	73 (86.9)	25 (24.5)	0.000
Grade 1*	11 (13.1)	77 (75.5)	0.000
Hypertension	7 (8.3)	6 (5.88)	0.514
Post operation (24–72 h)			
Fever			
No fever	30 (35.7)	33 (32.3)	0.630
Low-grade fever	23 (27.4)	28 (27.4)	0.656
Median-grade fever	23 (27.4)	29 (28.4)	0.548
High-grade fever	8 (9.5)	12 (11.8)	0.623

Data are presented as counts (%). #, the severity of pain was calculated by visual analog scale (VAS) of pain: no pain =0; light pain =1–3; moderate pain =4–6; severe pain =7–10; *, Grade 1: times of vomiting =1–2; Grade 2: times of vomiting =3–5. DEB-TACE, transcatheter chemoembolization with drug eluting beads; cTACE, conventional TACE.

analysis elucidated that BCLC stage, number of nodules, portal vein invasion, and cTACE and surgery history could be related to a worse ORR. Liver function of patients recovered within 3 months after a transient deterioration during the first-week post-TACE. DEB-TACE was well tolerable in patients with HCC, with only light to moderate toxicities observed in our study.

Based on previous research, DEB-TACE showed good efficacy in the treatment of HCC patients, with ORRs ranging from 35–84% (15-18). A previous study with DEB-TACE for HCC showed CR and PR rates of 58% and 31%, respectively, which was a higher CR rate than that found in our study (15). Most HCC patients were at BCLC A or B stage, but more than half of the patients in our study were at BCLC C stage, indicating that higher BCLC stage may affect TACE treatment response. While the study of Rahman et al. found that 17% of patients achieved a CR and 22% patients achieved a PR, the ORR was 39%,

which was lower than what was found in our study (16). Moreover, a study performed in Korea found a PR rate of 28.3%, a CR rate of 32.1% and an ORR of 60.4% (18). The difference of tumor response between these studies might be a consequence of the different BCLC stages of hepatocarcinoma. DEB-TACE was used as the first-time treatment choice in some previous studies, which might have resulted in a higher tumor response rate after TACE, while the different sample sizes may also have caused different tumor response rates.

Although some criteria were developed specifically for the prognosis tumor response of HCC treatment, such as BCLC stage for risk classification and the Child-Pugh grade for evaluation of liver function with cirrhosis (19), predictive factors for tumor response of TACE are still not well established (20). Personalized treatment, including DEB-TACE, is becoming increasingly important due to the heterogeneity of liver cancer. Also, according to a prior study, C-arm computed tomography (CT) has been reported to predict the midterm tumor response (21). Another previous study illustrated that tumor enhancement of more than 50% and tumor heterogeneity are associated with CR after DEB-TACE (22). In our study, patients with higher BCLC stage and portal vein invasion had worse ORR, while the BCLC stage C patients had extremely poor tumor response rates. The BCLC stage of this study might be a consequence of the BCLC staging system assessment involving liver function, tumor distribution, and ECOG score, playing a prognostic role in HCC treatment (23). Kao et al. found that from 1,265 treatment-naive HCC patients, those with stages A2–A4 had markedly lower overall survival rates than those in stage 0 and A1. However, they did not compare the overall survival rates in different BCLC stages (24). Regarding predictive values of BCLC stage for tumor response after treatment, a previous study illustrated that the BCLC B and C stage of HCC patients had similar tumor response after chemoembolization (25).

In addition to the BCLC stage, our study found that multiple tumor nodules, along with previous cTACE and surgery, had worse ORR post-TACE. Multifocal tumors have been well accepted as an essential factor for predicting a worse prognosis in HCC patients (26-28). In addition to this, the number of nodules more than three has been reported as a predictive factor for poor survival after resection in patients of HCC (28). Results found from previous studies also indicate that the tumor nodules number may be of bad prognostic value, which is consistent with our findings. As for cTACE patients and surgery history in our study, those with a worse ORR might be this way because these patients, having previous cTACE treatment or HCC resection, were less sensitive to DEB-TACE treatment.

In our study, patient liver function was found to decline in the first week of post-treatment and recover rapidly within 1–3 months after TACE. Another study evaluating liver injury after DEB-TACE using imaging for 114 patients with HCC, found that the occurrence of severe liver injury, biliary injuries, intrahepatic biloma, and portal vein thrombosis to be 36.8%, 32.5%, 16.7%, and 4.4% respectively (29). Injury to the hepatic artery is another severe adverse event associated with DEB-TACE. In a previous study, among 54 HCC patients receiving DEB-TACE treatment, the incidence of grade 1, 2, and 3 hepatic artery injury was 13 (24.1%), 10 (18.5%) and 31 (57.4%) patients, respectively (30). Compared to these two previous studies, the hepatic injury in our study was relatively low, with the difference in this outcome possibly resulting from variation in the baseline global liver function in the previous reports. Moreover, the liver function of most patients recovered within 1–3 months in our study, and we found no significant differences between the DEB-TACE and cTACE group.

DEB-TACE has been found to be at least as tolerable as cTACE in previous related studies, with most toxicities presenting with low grades (16,31). To some extent, doxorubicin-related systemic toxicity has not been observed among patients with DEB-TACE, so DEB-TACE may be better tolerated than cTACE in HCC patients (32). A previous related study reported that for 7 out of 51 patients (13.7%) who presented with complications after DEB-TACE treatment for HCC, including liver abscess, gallbladder necrosis, severe pancreatitis, lung or cerebral embolism, the incidence of complication was relatively low (17). In this study, the most common complication intra and post-TACE were vomiting, fever and pain, among which most symptoms were light to moderate, which is also consistent with previous studies (16,17,31,32). Results from previous studies, as well as our own, demonstrate adequate safety with DEB-TACE treatment, and that DEB-TACE had a lower vomiting incidence than cTACE patients due to no doxorubicin-related systemic toxicity in our study.

Regarding the study's limitations, this was a retrospective study that has a selection bias which could have influenced the results. The overall follow-up was a short, 1 to 3 months period, and thus the overall survival was not analyzed. Most patients had an HCC treatment history, which might have had an impact on the treatment outcome of DEB-TACE and cTACE.

Conclusions

In conclusion, DEB-TACE by DC bead was efficient and well-tolerated compared to cTACE in Chinese HCC patients. However, the present study showed no significant difference in the overall tumor response rate between DEB-TACE and cTACE. The BCLC stage, number of nodules, portal vein invasion, cTACE, and surgery history could possibly be predictive factors for a HCC treatment response.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.01.36). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed according to the standards set by the 1975 Declaration of Helsinki (as revised in 2013) and was approved by the Medical Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (No. 2016-324). All participants provided signed informed consent.

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