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Comparison of Treatment Response and Survival Profiles Between Drug-Eluting Bead Transarterial Chemoembolization and Conventional Transarterial Chemoembolization in Chinese Hepatocellular Carcinoma Patients: A Prospective Cohort Study

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This study evaluated the difference in treatment response and survival profiles between drug-eluting bead transarterial chemoembolization (DEB-TACE) and conventional transarterial chemoembolization (cTACE) treatments in Chinese hepatocellular carcinoma (HCC) patients. A total of 120 HCC patients were consecutively enrolled in this prospective cohort study, which showed that DEB-TACE achieved higher complete response (CR) (30.8%) compared with cTACE (7.4%) with no difference in overall response rate (ORR) for patients treated with DEB-TACE and cTACE (80.8% vs. 73.5%). In addition, DEB-TACE was associated with a lower rate of progressive disease (PD) compared with cTACE (1.9% vs. 11.8%). With respect to survival, patients in the DEB-TACE group achieved median progression-free survival (PFS) of 15 months (95% CI 12–18 months), which was longer than the cTACE group [median PFS 11 months (95% CI 10–12 months)]. Median overall survival (OS) was also longer with DEB-TACE [25 months (95% CI 22-28 months)] when compared with cTACE [21 months (95% CI 18–24 months)]. Univariate and multivariate logistic regression analysis showed that DEB-TACE was an independent predictive factor for achieving CR. Univariate Cox's regression analysis revealed that DEB-TACE was a predictive factor for prolonged PFS and OS, while multivariate analysis demonstrated that DEB-TACE was not an independent factor for predicting PFS or OS. In conclusion, we found that DEB-TACE achieved higher treatment response and prolonged survival compared with cTACE in Chinese HCC patients.

Key words: Hepatocellular carcinoma (HCC); Overall survival; Response rate; Univariate analysis; Drug-eluting bead-transarterial chemoembolization (DEB-TACE); Treatment response; Conventional transarterial chemoembolization (cTACE); Progression-free survival; Multivariate analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor, and it has become the third leading cause of cancer-related death worldwide. Approximately, 660,000 new cases of HCC are diagnosed every year throughout the world[1,2]. Although several improvements in diagnostic imaging examinations and treatments such as surgical resection, liver transplantation, targeted drugs, and immunotherapy provide various options for HCC patients, a majority of HCC cases are diagnosed at an advanced stage. Unfortunately, when presenting at a more advanced stage, these patients are found to have compromised liver function and are usually not appropriate candidates for many of the common treatments options. Moreover, only less than 20% of patients are deemed to be appropriate candidates for surgery[3–6]. Thus, new treatments are urgently needed.

Transarterial chemoembolization (TACE) is a minimally invasive technique performed widely in recent years. This approach consists of injection of antitumor drugs and embolization in tumor-feeding arteries, results in strong antineoplastic as well as ischemic necrosis of the targeted tumor, and has been considered as the current standard therapy for patients with intermediate HCC[3,7,8]. Conventional TACE (cTACE) involves a mixture of antitumor drug/lipiodol and gelatin sponge, which acts as the embolic agent, and it has been tested in clinical studies and offers favorable survival for HCC patients[9–11].

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Drug-eluting bead TACE (DEB-TACE) is a novel type of TACE that introduces drug-loaded microspheres into TACE and is able to result in a sustained release of antitumor drug and a maximization of ischemic necrosis with less side effects on nontarget tissues. As a result, elevated intratumoral concentrations of cytotoxic agents and a reduced systemic drug-related adverse toxicity would theoretically be realized[12–14]. Some studies have suggested that DEB-TACE provides superior antitumor activity in European and American HCC patients compared with cTACE, while limited studies have attempted to compare the clinical efficacy of DEB-TACE and cTACE in Chinese HCC patients. Moreover, to date, relatively little is known about the various prognostic factors for HCC patients treated by DEB-TACE and cTACE[7,8,15]. With this in mind, we conducted this prospective cohort study to evaluate the difference in treatment response and clinical efficacy profiles between DEB-TACE and cTACE treatments in Chinese HCC patients.

MATERIALS AND METHODS

Patients

A total of 120 HCC patients were consecutively enrolled in this prospective cohort study and were treated with DEB-TACE or cTACE at the Division of Liver Disease in Hubei Provincial Hospital of TCM, between November 1, 2014 and December 31, 2016. The inclusion criteria were as follows: (1) diagnosed as primary HCC according to pathological findings, clinical features, and imaging examination; (2) age above 18 years; (3) patients were to receive DEB-TACE or cTACE treatment based on clinical indication; (4) patients were able to be followed up regularly. Patients with a history of liver transplantation, severe hepatic failure, severe renal failure, severe infection, other tumors, malignant hematological diseases, or women in gestation or lactation period were excluded from this study. The Institutional Review Board of Hubei Provincial Hospital of TCM approved this clinical study: the study protocol was approved in the first ethical meeting, with only minor revision. All patients provided signed informed consents: HCC patients were informed in detail on the risks and benefits of this study, and patients signed informed consent after careful discussion with their physicians of the two treatment approaches.

Study Flow

A total of 120 HCC patients were enrolled in this cohort study. Fifty-two patients were treated with DEB-TACE treatment and 68 patients were treated with cTACE. With respect to the subsequent treatments after DEB-TACE or cTACE, patients who achieved CR or PR and presented high apoptosis rates of HCC cells underwent surgical resection based on their overall clinical condition. For patients who failed to achieve CR or ORR and patients who suffered PD or SD received some subsequent treatments, including DEB-TACE, cTACE, iodine-125 radioactive seed implantation, systematic chemotherapy, radiotherapy, and surgery, which are all exhibited in Table 1.

Data Recording

Baseline characteristics of all HCC patients were collected: (1) demographic characteristics: age and gender; (2) history: hepatitis B (HB) and cirrhosis history; (3) cycles of TACE treatment; (4) previous treatments: cTACE, surgery, systematic chemotherapy, and radiofrequency ablation; (5) clinicopathological characteristics: tumor distribution, tumor size, tumor location, vein invasion, Barcelona Clinic Liver Cancer (BCLC) stage, Child–Pugh stage, and Eastern Cooperative Oncology Group (ECOG) performance status; (6) tumor markers: fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9).

cTACE Procedure and DEB-TACE Procedure

All TACE treatments were performed in the digital subtraction angiography (DSA) suite. cTACE was conducted according to the following procedure: angiography

Table 1. Subsequent Treatments After DEB-TACE or cTACE Treatment

Subsequent Treatments	DEB-TACE Group ($N=52$)	cTACE Group ($N=68$)
DEB-TACE	22 (42.3)	31 (45.6)
cTACE	14 (26.9)	23 (33.8)
Iodine-125 radioactive seed implantation	9 (17.3)	10 (14.7)
Systematic chemotherapy	3 (5.8)	5 (7.4)
Radiotherapy	2 (3.8)	3 (4.4)
Surgery	3 (5.8)	2 (2.9)

Data are presented as count (%). Some patients received multiple therapeutic interventions during the subsequent treatment. DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; CR, complete response.

was applied to detect tumor-feeding vessels. Percutaneous femoral arterial puncture was operated by Seldinger technique under local anesthesia, with the catheter superselectively catheterized into the hepatic artery to locate the tumors and tumor-feeding vessels as well as to detect tumor size and tumor number. Subsequently, adriamycin solution and lipiodol was mixed at a ratio of 1:1, and the mixed solution was injected into tumor-feeding vessels through the microcatheter with the monitoring of X-ray. Embolization was stopped once the sluggish flow appeared. An additional angiography procedure was performed to make sure that the embolization was complete.

For the DEB-TACE procedure, drug loading of Callispheres® beads (diameter 100 μm and 300 μm; Jiangsu Hengrui Medicine Co, Ltd., Jiangsu, P.R. China) or HepaSphere (diameter 50–100 μm; Merit Medical, South Jordan, UT, USA) was first performed: (1) chemoembolization reagent was dissolved in water for injection (WFI) in an injector to prepare a solution (20 mg/ml), which was mixed with beads through a tee joint, and then stored in room temperature (RT); (2) mixture of beads and chemoembolization reagent solution was placed in RT for 30 min and shaken every 5–10 min; (3) nonionic contrast agent was added into the mixed solution (1:1), which was then held in RT for 5 min. Angiography was subsequently conducted using the same method performed with cTACE. Under angiography guidance, the prepared solution of drug-loaded beads was injected into tumor-feeding vessels superselectively using a microcatheter of 2.4 French microcatheters (Merit Maestro, Merit Medical System, Inc.) at a speed of 1 ml/min until the flow of nonionic contrast agent was observed to slow down.

Treatment Response Assessment

The assessment of treatment response of all patients was performed by enhanced magnetic resonance image (MRI) or computed tomography (CT) at 1–3 months on the base of modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria[16]: (1) complete response (CR): disappearance of all intratumoral arterial enhancement in all target tumors; (2) partial response (PR): at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target tumors, taking as reference the baseline sum of the diameters of target tumors; (3) progressive disease (PD): an increase of at least 20% in the sum of the diameters of viable (enhancing) target tumors, taking as reference the smallest sum of the diameters of viable (enhancing) target tumors recorded since treatment started; (4) stable disease (SD): any cases that did not qualify for either PR or PD. Overall response rate (ORR) was defined as the portion of CR plus PR.

PFS and OS Calculation and Univariate/Multivariate Analysis

Patients were followed up every 1–2 months within the first 6 months postprocedure, and every 3–6 months in the following period. The median follow-up duration was 18.5 (quantile 13.0–24.0) months. The last follow-up date was June 30, 2017. Progression-free survival (PFS) was calculated from the time of the procedure to the date of disease progression or death from any cause, and overall survival (OS) was calculated from the time of operation to the date of death from any cause. As to the analysis of factors affecting CR, PFS, and OS, the sample size of our study was relatively small. As a result, not all the factors were included in the multivariate analysis due to lacking events: only the possibly significant factors were included as part multivariate analysis, and we defined the factors with $p < 0.1$ in univariate analysis as the potential significant factors.

Statistics

Statistical analysis was performed by SPSS 21.0 software (IBM, Armonk, NY, USA). Data were mainly presented as count (%), mean ± standard deviation, or median (25th–75th). A comparison between the two groups was determined by *t*-test, Wilcoxon rank sum test, or chi-square test. Kaplan–Meier (K-M) curves and log-rank test were applied to evaluate PFS and OS. Factors affecting CR were determined by univariate logistic regression analysis, and factors affecting PFS and OS were determined by univariate Cox's proportional hazards regression model analysis, and additionally all factors with *p* value below 0.1 in univariate logistic model as well as Cox model were further analyzed by multivariate logistic regression analysis and Cox proportional hazard regression model, respectively. A value of $p < 0.05$ was considered significant.

RESULTS

Baseline Characteristics

Fifty-two HCC patients with a mean age of 59.90 ± 11.25 years in which 44 (84.6%) were males and 8 (15.4%) were females were enrolled in the DEB-TACE group. Sixty-eight HCC patients with a mean age of 58.97 ± 12.11 years in which 55 (80.9%) were males and 13 (19.1%) were females were enrolled in the cTACE group (Table 2). No differences in age ($p = 0.957$) or gender ($p = 0.594$) were observed between the two groups. Meanwhile, no differences in previous treatments including cTACE ($p = 0.372$), surgery ($p = 0.622$), systemic chemotherapy ($p = 0.848$), and radiofrequency ablation (RFA) ($p = 0.828$) were observed between the DEB-TACE and cTACE groups, indicating that no historical

Table 2. Baseline Characteristics of HCC Patients in DEB-TACE and cTACE Groups

Parameters	DEB-TACE Group ($N=52$)	cTACE Group ($N=68$)	p Value
Age (years)	59.90 ± 11.25	58.97 ± 12.11	0.957
Gender			0.594
Male [*n* (%)]	44 (84.6)	55 (80.9)	
Female [*n* (%)]	8 (15.4)	13 (19.1)	
Cycles of treatment			0.854
1 cycle [*n* (%)]	42 (80.8)	54 (79.4)	
2 or more cycles [*n* (%)]	10 (19.2)	14 (20.6)	
History of HB [*n* (%)]	42 (80.8)	56 (82.4)	0.824
History of Cirrhosis [*n* (%)]	30 (57.7)	45 (66.2)	0.341
Previous treatments			
cTACE [*n* (%)]	18 (34.6)	29 (42.6)	0.372
Surgery [*n* (%)]	11 (21.2)	17 (25.0)	0.622
Systemic chemotherapy [*n* (%)]	1 (1.9)	1 (1.5)	0.848
Radiofrequency ablation [*n* (%)]	6 (11.5)	7 (10.3)	0.828
Tumor distribution			0.223
Multifocal [*n* (%)]	32 (61.5)	49 (72.1)	
Unifocal [*n* (%)]	20 (38.5)	19 (27.9)	
Tumor size (cm)	4.2 (3.0–8.1)	6.0 (3.0–10.1)	0.466
Tumor location			0.913
Unilobar [*n* (%)]	37 (71.2)	49 (72.1)	
Bilobar [*n* (%)]	15 (28.8)	19 (27.9)	
Venous invasion [*n* (%)]	12 (19.2)	26 (39.7)	0.078
BCLC stage			0.213
A [*n* (%)]	13 (25.0)	15 (22.1)	
B [*n* (%)]	24 (46.2)	24 (35.3)	
C [*n* (%)]	15 (28.8)	29 (42.6)	
Child–Pugh stage			0.297
A [*n* (%)]	47 (90.4)	57 (83.8)	
B [*n* (%)]	5 (9.6)	11 (16.2)	
ECOG performance status			0.349
0 [*n* (%)]	32 (61.5)	47 (69.1)	
1 [*n* (%)]	18 (34.6)	20 (29.4)	
2 [*n* (%)]	0 (0.0)	1 (1.5)	
3 [*n* (%)]	2 (3.8)	0 (0.0)	
Tumor markers			
AFP (μg/L)	24.5 (4.9–216.0)	138.6 (9.8–1792.6)	0.076
CEA (μg/L)	2.6 (1.8–4.6)	3.2 (1.9–4.7)	0.209
CA19-9 (ku/L)	15.2 (7.0–38.5)	14.4 (6.6–28.7)	0.789

Data are presented as mean ± standard deviation, median (25th–75th), or count (%). Comparison between two groups was determined by *t*-test, Wilcoxon rank sum test, or chi-square test. A value of $p<0.05$ was considered significant. HCC, hepatocellular carcinoma; HB, hepatitis B; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; AFP, fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

bias existed in this study. Patients in the cTACE group presented with a higher percentage of vein invasion ($p=0.078$) and elevated AFP levels ($p=0.076$), but these differences were not statistically significant. A greater number of patients with Child B, BCLC C, and venous invasion were treated with cTACE, while no significant difference in these baseline characteristics was observed between the cTACE group and DEB-TACE group (all p values >0.05). The possible reasons were that the number of patients receiving previous cTACE and the entire group of patients receiving previous treatments were both numerically more than those in the DEB-TACE group, and more previous treatment experiences might be associated with worse disease severity, thus numerically higher percentage of Child B, BCLC C, and venous invasion were found in the cTACE group. No other differences in baseline characteristics were observed between the DEB-TACE and cTACE group as seen in Table 2.

Treatment Response of Patients

As seen in Table 3, DEB-TACE achieved a higher CR ($n=16$, 30.8%) compared with cTACE ($n=5$, 7.4%)

Table 3. Comparison of Treatment Response of Patients Between DEB-TACE and cTACE Groups

Patients	DEB-TACE Group ($N=52$)	cTACE Group ($N=68$)	p Value
Complete response [n (%)]	16 (30.8)	5 (7.4)	**<0.001**
Partial response [n (%)]	26 (50.0)	45 (66.2)	0.074
Overall response rate [n (%)]	42 (80.8)	50 (73.5)	0.353
Stable disease [n (%)]	9 (17.3)	10 (14.7)	0.694
Progressive disease [n (%)]	1 (1.9)	8 (11.8)	**0.043**

Data are presented as count (%). Comparison was determined by chi-square test. A value of $p<0.05$ was considered significant.

($p<0.001$), and the ORR was higher in patients treated with DEB-TACE when compared to cTACE, although this difference did not reach statistical significance [42 (80.8%) vs. 50 (73.5%), $p=0.353$]. In addition, DEB-TACE resulted in a significantly lower rate of PD compared with cTACE [1 (1.9%) vs. 8 (11.8%), $p=0.043$].

Treatment Response of Tumors

Comparison of treatment response of tumors was performed between the DEB-TACE group ($N=86$) and the cTACE group ($N=134$) (Table 4). DEB-TACE therapy achieved a higher CR [31 (36.0%) vs. 21 (15.7%), $p<0.001$] and higher ORR [70 (81.4%) vs. 92 (68.7%), $p=0.036$] of tumors compared with cTACE therapy. Additionally, DEB-TACE achieved lower PD than cTACE [3 (3.5%) vs. 15 (11.2%), $p=0.042$].

Survival Profiles

DEB-TACE treatment resulted in a median PFS of 15 months (95% CI 12–18 months), which was longer than that associated with cTACE [median PFS 11 months (95% CI 10–12 months), $p=0.021$] (Fig. 1A). With respect to OS, DEB-TACE yielded a median OS of 25 months (95% CI 22–28 months), while cTACE resulted in a median OS of 21 months (95% CI 18–24 months). This 4-month improvement in median OS seen with DEB-TACE therapy was highly statistically significant ($p=0.003$) (Fig. 1B).

Analysis of Factors Affecting CR

Univariate logistic regression was conducted to determine the various factors affecting CR (Table 5). DEB-TACE treatment was found to be correlated with the presence of CR ($p<0.001$), while venous invasion ($p=0.017$) and AFP > 38.55 μg/L ($p=0.026$) were confirmed to be associated with the absence of CR. Multivariate logistic regression analysis showed that only DEB-TACE was an independent factor predicting a greater likelihood of achieving CR ($p=0.002$).

Analysis of Factors Affecting PFS

With respect to factors affecting PFS, DEB-TACE was correlated with longer PFS ($p=0.031$). Other factors, such as tumor size >5 cm ($p<0.001$), venous invasion ($p<0.001$), higher BCLC stage ($p<0.001$), and AFP > 38.55 μg/L ($p<0.001$) were all found to be associated with worse PFS (Table 6). Factors with values of $p<0.1$ were subsequently evaluated by multivariate Cox's proportional hazards regression model in which DEB-TACE was assessed to be a nonindependent factor for better PFS ($p=0.163$), and tumor size >5 cm ($p<0.001$), higher BCLC stage ($p=0.001$) as well as AFP > 38.55 μg/L ($p<0.001$) were confirmed to be independent factors predicting shorter PFS.

Analysis of Factors Affecting OS

As listed in Table 7, DEB-TACE treatment was shown to be correlated with prolonged OS by univariate Cox's regression analysis ($p=0.004$). While tumor size > 5 cm ($p<0.001$), venous invasion ($p<0.001$), higher BCLC stage ($p<0.001$), and AFP > 38.55 μg/L ($p<0.001$) were predictive factors for poor OS. Factors with values of $p<0.1$ were further assessed by multivariate Cox's regression, and this analysis showed that DEB-TACE

Table 4. Comparison of Treatment Response of Tumors Between DEB-TACE and cTACE Groups

Tumors	DEB-TACE Group ($N=86$)	cTACE Group ($N=134$)	p Value
Complete response [n (%)]	31 (36.0)	21 (15.7)	<0.001
Partial response [n (%)]	39 (45.3)	71 (53.0)	0.269
Overall response rate [n (%)]	70 (81.4)	92 (68.7)	0.036
Stable disease [n (%)]	13 (15.1)	27 (20.1)	0.345
Progressive disease [n (%)]	3 (3.5)	15 (11.2)	0.042

Data are presented as count (%). Comparison was determined by chi-square test. A value of $p<0.05$ was considered significant.

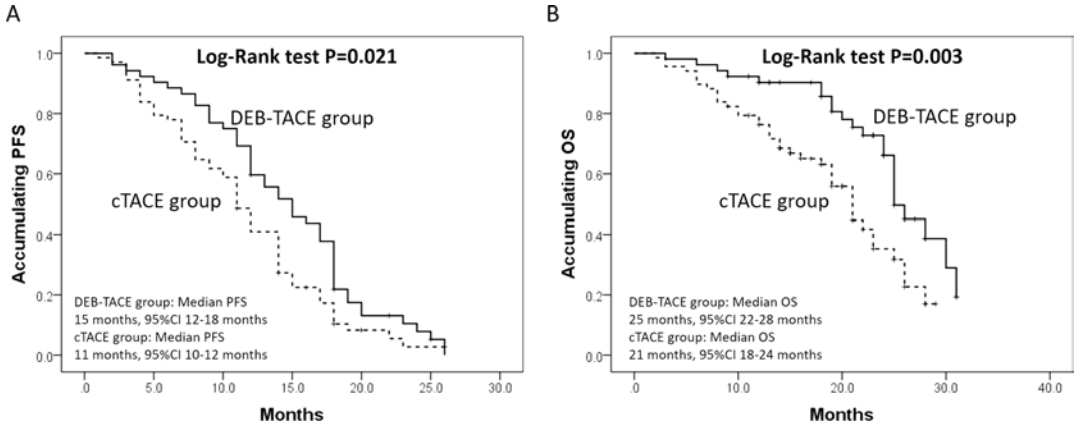

Figure 1. Progression-free survival (PFS) and overall survival (OS) by cTACE and DEB-TACE. (A) Kaplan–Meier curve analysis of PFS. DEB-TACE achieved elevated PFS compared with cTACE (median PFS 15 months, 95% CI 12–18 months vs. median PFS 11 months, 95% CI 10–12 months; $p = 0.021$). (B) K-M curve analysis of OS. DEB-TACE achieved increased OS compared with cTACE (median OS 25 months, 95% CI 22–28 months vs. median OS 21 months, 95% CI 18–24 months; $p = 0.003$). Comparison between groups was determined by log-rank test. A value of $p < 0.05$ was considered significant.

Table 5. Factors Influencing CR Achievement by Logistic Regression Model Analysis

	Univariate Logistic Regression				Multivariate Logistic Regression			
			95% CI				95% CI	
Parameters	*p* Value	OR	Lower	Higher	*p* Value	OR	Lower	Higher
DEB-TACE (vs. cTACE)	<0.001	7.255	2.485	21.179	0.002	5.858	1.949	17.606
Age > 61 years	0.648	0.812	0.331	1.991	–	–	–	–
Male	0.474	1.615	0.434	6.010	–	–	–	–
Two or more cycles of treatment	0.649	0.760	0.233	2.476	–	–	–	–
History of HB	0.413	1.727	0.466	6.400	–	–	–	–
History of cirrhosis	0.349	1.591	0.603	4.199	–	–	–	–
Previous cTACE treatment	0.456	1.410	0.572	3.479	–	–	–	–
Previous surgery	0.200	1.900	0.712	5.069	–	–	–	–
Previous systemic chemotherapy	0.982	+	<0.001	+	–	–	–	–
Previous radiofrequency ablation	0.661	0.703	0.145	3.404	–	–	–	–
Multifocal disease	0.559	0.758	0.298	1.924	–	–	–	–
Tumor size 5 cm	0.205	0.552	0.220	1.383	–	–	–	–
Tumor location-Bilobar	0.686	0.810	0.291	2.253	–	–	–	–
Venous invasion	0.017	0.158	0.035	0.714	0.108	0.271	0.055	1.333
Higher BCLC stage	0.124	0.629	0.348	1.135	–	–	–	–
Child–Pugh B stage (vs. A stage)	0.959	<0.001	<0.001	+	–	–	–	–
Higher ECOG performance status	0.939	0.971	0.454	2.076	–	–	–	–
AFP > 38.55 μg/L	0.026	0.334	0.127	0.879	0.189	0.490	0.169	1.422
CEA > 2.8 μg/L	0.276	0.600	0.240	1.503	–	–	–	–
CA19-9 > 14.35 ku/L	0.411	0.680	0.271	1.704	–	–	–	–

Data are presented as *p* value, OR (odds ratio), and 95% CI (confidence interval). Factors affecting CR achievement were determined by univariate logistic regression analysis, while all factors with *p* 0.1 were further detected by multivariate logistic regression analysis. A value of $p < 0.05$ was considered significant. BCLC stage was scored as 1-Stage A, 2-Stage B, 3-Stage C. CR, complete response.

Table 6. Cox's Proportional Hazards Regression Model Analysis of Factors Predicting PFS

	Univariate Cox's Regression				Multivariate Cox's Regression			
			95% CI				95% CI	
Parameters	*p* Value	HR	Lower	Higher	*p* Value	HR	Lower	Higher
DEB-TACE (vs. cTACE)	0.031	0.656	0.448	0.962	0.163	0.745	0.493	1.126
Age 61 years	0.586	0.901	0.619	1.311	–	–	–	–
Male	0.715	0.907	0.538	1.529	–	–	–	–
Two or more cycles of treatment	0.690	1.101	0.686	1.765	–	–	–	–
History of HB	0.975	0.992	0.610	1.614	–	–	–	–
History of cirrhosis	0.782	0.946	0.641	1.398	–	–	–	–
Previous cTACE treatment	0.910	1.022	0.696	1.502	–	–	–	–
Previous surgery	0.871	1.037	0.670	1.605	–	–	–	–
Previous systemic chemotherapy	0.840	1.155	0.284	4.704	–	–	–	–
Previous radiofrequency ablation	0.113	1.606	0.894	2.884	–	–	–	–
Multifocal disease	0.210	1.293	0.865	1.933	–	–	–	–
Tumor size >5 cm	<0.001	2.814	1.888	4.195	<0.001	2.731	1.754	4.252
Tumor location-bilobar	0.068	1.478	0.972	2.248	0.971	0.991	0.619	1.589
Venous invasion	<0.001	2.158	1.403	3.318	0.753	1.084	0.656	1.792
Higher BCLC stage	<0.001	1.884	1.452	2.445	0.001	1.681	1.246	2.267
Child–Pugh B stage (vs. A stage)	0.076	1.677	0.947	2.968	0.110	1.623	0.896	2.940
Higher ECOG performance status	0.388	1.154	0.834	1.598	–	–	–	–
AFP 38.55 μg/L	<0.001	1.995	1.365	2.917	<0.001	2.103	1.406	3.146
CEA 2.8 μg/L	0.977	1.006	0.689	1.467	–	–	–	–
CA199 14.35 ku/L	0.882	1.029	0.704	1.504	–	–	–	–

Data are presented as *p* value, HR (hazards ratio), and 95% CI (confidence interval). Factors affecting PFS (progression-free survival) were determined by univariate Cox's proportional hazards regression model analysis, while all factors with *p* 0.1 were further detected by multivariate Cox's proportional hazards regression analysis. A value of $p < 0.05$ was considered significant. BCLC stage was scored as 1-Stage A, 2-Stage B, 3-Stage C.

was not an independent factor for improved OS ($p = 0.149$). However, tumor size > 5 cm ($p < 0.001$), higher BCLC stage ($p < 0.001$), as well as AFP > 38.55 μg/L ($p < 0.001$) were shown to be independent factors for shorter OS.

DISCUSSION

In this study, we directly compared the treatment response and efficacy profiles between DEB-TACE and cTACE treatments in Chinese HCC patients and came up with the following conclusions: (1) DEB-TACE achieved a remarkably higher level of CR of HCC patients compared with cTACE, and DEB-TACE was an independent factor for achieving CR; (2) DEB-TACE resulted in prolonged PFS and OS compared with cTACE, although it was not to be an independent predictive factor based on multivariate analysis.

The wide use of cTACE in treating HCC disease depends on the mixture of lipiodol and chemotherapeutic agents, which leads to blocking of the tumor-feeding arteries and cytotoxic effect on cancer cells. Unfortunately, cTACE has limitations in terms of effectively treating patients with HCC, and these include: (1) the liquidity of the lipiodol decreases concentration of the loaded drugs and results in reduced efficacy[17]; (2) the mixture of lipiodol and chemotherapeutic drugs is not able to realize a controlled and sustained release of drugs[18,19]; (3) heterogeneity in the technique and treatment schedules[17]. Given the potential limitations of cTACE, DEB-TACE has been developed to overcome some of the main drawbacks of cTACE[17,20]. Microspheres have become the preferred drug delivery system over the recent years, and a significant advantage of this approach is that it releases a drug in a sustained and controlled manner due to the characteristics of its structure and the degradation of polymers[1]. Thus, DEB-TACE has the ability to ensure more sustained drug release as well as results in more permanent embolization. Finally, it improves treatment efficacy with an increased antitumor activity and is easier to be standardized, while at the same time reducing systemic toxicity[19–21].

A randomized controlled study performed by Golfieri et al. has shown no difference in CR and ORR in HCC patients treated with DEB-TACE and cTACE[20]. In contrast, Song et al. evaluated the treatment response in HCC patients who received cTACE and DEB-TACE, and they reported that DEB-TACE therapy resulted in

Table 7. Cox's Proportional Hazards Regression Model Analysis of Factors Predicting OS

	Univariate Cox's Regression				Multivariate Cox's Regression			
			95% CI				95% CI	
Parameters	*p* Value	HR	Lower	Higher	*p* Value	HR	Lower	Higher
DEB-TACE (vs. cTACE)	0.004	0.447	0.258	0.774	0.149	0.738	0.488	1.115
Age 61 years	0.752	0.921	0.555	1.531	–	–	–	–
Male	0.292	0.710	0.376	1.342	–	–	–	–
Two or more cycles of treatment	0.734	1.117	0.589	2.121	–	–	–	–
History of HB	0.434	0.787	0.431	1.435	–	–	–	–
History of cirrhosis	0.702	0.903	0.537	1.520	–	–	–	–
Previous cTACE treatment	0.209	0.704	0.407	1.217	–	–	–	–
Previous surgery	0.915	0.968	0.530	1.768	–	–	–	–
Previous systemic chemotherapy	0.742	0.717	0.099	5.194	–	–	–	–
Previous radiofrequency ablation	0.630	1.232	0.527	2.884	–	–	–	–
Multifocal disease	0.900	1.035	0.602	1.779	–	–	–	–
Tumor size > 5 cm	<0.001	3.453	1.962	6.077	<0.001	2.688	1.745	4.139
Tumor location-bilobar	0.113	1.603	0.895	2.873	–	–	–	–
Vein invasion	<0.001	3.871	2.102	7.130	0.551	1.157	0.716	1.871
Higher BCLC stage	<0.001	2.227	1.553	3.195	<0.001	1.662	1.261	2.192
Child–Pugh B stage (vs. A stage)	0.175	1.759	0.777	3.981	–	–	–	–
Higher ECOG performance status	0.204	1.338	0.854	2.097	–	–	–	–
AFP > 38.55 μg/L	<0.001	3.761	2.172	6.514	<0.001	2.092	1.401	3.122
CEA > 2.8 μg/L	0.060	1.643	0.978	2.760	0.910	1.022	0.696	1.501
CA199 > 14.35 ku/L	0.718	1.099	0.660	1.830	–	–	–	–

Data are presented as *p* value, HR (hazards ratio), and 95% CI (confidence interval). Factors affecting OS (overall survival) were determined by univariate Cox's proportional hazards regression model analysis, while all factors with *p* 0.1 were further detected by multivariate Cox's proportional hazards regression analysis. A value of $p < 0.05$ was considered significant. BCLC stage was scored as 1-Stage A, 2-Stage B, 3-Stage C.

dramatically increased treatment response compared with cTACE therapy[22]. In this study, we show that DEB-TACE achieved higher CR than cTACE in HCC patients, and further analysis in multivariate Cox's regression revealed that DEB-TACE was an independent predictive factor for higher CR. The improved CR rate achieved by DEB-TACE in our study may result from the following. (1) Unlike the liquid lipiodol in cTACE, DEB-TACE maximizes the antitumor effect of the loaded chemotherapeutic agents in target lesions due to the structure of polymeric microspheres[17–19]. (2) The sustained release of chemotherapeutic drugs in DEB-TACE leads to prolonged contact time with cancer cells[22].

A single-center retrospective study was performed by Massani et al. to evaluate the outcomes of DEB-TACE and cTACE in HCC patients, and it showed no difference in OS between DEB-TACE and cTACE [median OS 29.4 months (CI 20.7–38.1) vs. median OS 22.7 months (CI 11.6-33.8)][23]. Golfieri et al. performed a prospective, multicenter randomized and controlled study to explore the achievability of 2-year survival in 177 HCC patients, and using a regression model analysis, they showed that DEB-TACE was not a factor predicting improved OS[20]. However, in their retrospective case-control study in HCC patients, Cheung and colleagues in Hong Kong showed that DEB-TACE was associated with a trend toward prolonged survival (median 12.53 months) compared with cTACE (median 10.53 months, $p = 0.086$)[24]. Our study has also shown that DEB-TACE was associated with improved PFS and OS when compared to cTACE in Chinese HCC patients. In addition, DEB-TACE was favorable for prolonged PFS and OS according to univariate Cox's regression, although it was not determined to be an independent predictive factor for improved survival profiles. The results of preferable survival in our study might be explained as follows. (1) Since drugs were loaded in microspheres, drug release of DEB-TACE became sustained, and the antitumor effects were enhanced[17–19]. (2) DEB-TACE reduced systematic toxicity, and this might attribute to the better survival profiles[12–14]. (3) Ethnic difference might play a role in the treatment response and tolerance of DEB-TACE therapy, thus we observed different outcomes with the previous studies in Europe[20,23]. (4) In our study, patients in the cTACE group presented with numerically more venous invasion and higher AFP level at baseline compared with the DEB-TACE group, which seemed like a trend of raised severity of HCC in the cTACE group. Thus, in a univariate Cox's analysis, DEB-TACE was a predictive factor for improved

survival profiles, while in multivariate Cox's analysis, it was not an independent predictive factor for prolonged survival.

There were some limitations in our study. (1) Since the sample size of our study was relatively small, not all factors in the univariate analysis were included in the multivariate analysis. (2) Our median follow-up duration of 18.5 (quantile 13.0–24.0) months was relatively short, so differences between DEB-TACE and cTACE in long-term survival was not investigated. (3) This was a prospective cohort study, and we did not directly randomize the treatments or patients' assignment, thus there might be confounding factors affecting the results. For example, there was a higher number of Child B, BCLC C and venous invasion patients with cTACE, although these numbers did not reach statistical significance. In addition, we used univariate and multivariate analysis to eliminate the influence of confounding factors. (4) Subsequent treatments might induce bias in this study.

In conclusion, we found that DEB-TACE achieved higher treatment response and prolonged survival compared with cTACE in Chinese HCC patients. Taken together, these findings provide further evidence for the clinical benefit of DEB-TACE and suggest that DEB-TACE should be the preferred transarterial embolization treatment approach for patients with HCC.

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