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research article

Comparison of CalliSpheres® microspheres drug-eluting beads and conventional transarterial chemoembolization in hepatocellular carcinoma patients: a randomized controlled trial

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Background. This trial aimed to compare the outcomes of drug-eluting beads transarterial chemoembolization (DEB-TACE) with CalliSpheres® microspheres (CSM) and conventional transarterial chemoembolization cTACE in the treatment of patients with unresectable hepatocellular carcinoma (HCC).

Patients and methods. A total of 90 patients were divided into DEB-TACE group (n = 45) and cTACE group (n = 45). The treatment response, overall survival (OS), progression-free survival (PFS), and the safety were compared between the two groups.

Results. The objective response rate (ORR) in the DEB-TACE group was significantly higher than that in cTACE group at 1, 3, and 6 months of follow-up ($P = 0.031$, $P = 0.003$, $P = 0.002$). The complete response (CR) in DEB-TACE group was significantly higher than that in cTACE group at 3 months ($P = 0.036$). Survival analysis revealed that, DEB-TACE group had better survival benefits than cTACE group (median OS: 534 days *vs.* 367 days, $P = 0.027$; median PFS: 352 days *vs.* 278 days $P = 0.004$). The degree of liver function injury was more serious in DEB-TACE group at 1 week, but was similar between the two groups at 1 month. DEB-TACE with CSM caused a high incidence of fever and a severe abdominal pain ($P = 0.031$, $P = 0.037$).

Conclusions. DEB-TACE with CSM showed better treatment response and survival benefits than cTACE group. Although a transient more severe liver damage, high incidence of fever and a severe abdominal pain occurred in the DEB-TACE group, it could be resolved through symptomatic treatment.

Key words: cTACE; CalliSpheres® microspheres; DEB-TACE; hepatocellular carcinoma; tumor response

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and has been reported to be the sixth most common cancer and the third most frequent cause of cancer-related deaths worldwide, and the leading cause of cancer-related deaths in men in China.[1] HCC occurs in the setting of chronic liver inflammation, which is closely related to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins, including alcohol or aflatoxin. Despite improvements in the early diagnosis and various treatment methods, most patients with HCC lose the chance of surgical resection, liver transplantation, and radiofrequency ablation.[2,3]

According to Barcelona Clinic Liver Cancer (BCLC) staging system guidelines, transarterial chemoembolization (TACE) is widely applied in HCC patients not suitable for surgical treatment in intermediate and advanced stages.[4] In addition, TACE has been applied as a bridge therapy to liver resection or transplantation in early-stage HCC.[5] The two main protocols for TACE are conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE). cTACE uses lipiodol as a chemotherapy drug carrier to embolize targeting arteries, release antitumor medication, and consequent powerful ischemic and cytotoxic effects. However, the rapid decrease of the local antitumor drug concentration and the high systemic toxicity must be investigated.[6] DEB-TACE uses drug-loaded microspheres, which can not only load chemotherapy drugs and release them slowly in local regions but also have less systemic side effects; it also embolizes the tumor supply vessels permanently.[7]

CalliSpheres® microspheres (CSM) are the first DEBs in China and have been applied clinically for a few years. Previous studies on DEB-TACE with CSM have focused on the survival rate, safety, and prognostic factors[8,9], and most were retrospective studies.[10,11] Limited prospective, randomized studies have compared the treatment response of the two methods. A study in 2020 showed that DEB-TACE using CSM loading with arsenic triox is more effective and equally tolerant compared with cTACE in treating unresectable HCC patients. Although the study was prospective, the patients were not randomized and the sample size was not calculated.[12] Thus, the present study aimed to prospectively and randomized evaluate the efficacy and the safety of DEB-TACE with CSM and cTACE in unresectable HCC patients.

Patients and methods

Study design

This was a prospective, randomized, controlled study designed to compare the efficacy and safety of DEB-TACE with CSM and cTACE. All the subjects who participated in this study were randomized in a 1:1 ratio by a computerized system and enrolled by an investigator physician. The results of allocation were placed in a sealed envelope and delivered to the only assistant aware of DEB-TACE/cTACE progress. All the doctors in charge of surgery and data collection were blinded to the trial design and treatment. All participants were informed about the objective and experimental procedure and allowed to withdraw their consent or discontinue participation without restrictions at any time. Then, those who voluntarily participated in the trial signed the written informed consent. All procedures in the trial were in accordance with the World Medical Association's Helsinki Declaration. The study plan was approved by the Ethics Committee of the Second Hospital Affiliated Harbin Medical University (No. KY2020-267) and has been registered at Chictr.org.cn (No. ChiCTR2100044528).

Patients

From March 2020 to March 2021, 115 HCC patients from the Department of Interventional Radiography of the Second Hospital Affiliated Harbin Medical University were recruited in this study through advertisements or physicians. The inclusion criteria were as follows: (1) Patients diagnosed as primary HCC by pathological findings or clinical features and radiographic examinations according to American Association for the Study of the Liver Diseases (AASLD) guidelines; (2) Tumor location and extent not amenable to elective resection or ablation; (3) Patients undergoing treatment for the first time and were willing to accept CSM DEB-TACE or cTACE; (4) Digital substraction sngiography (DSA) showed that the tumor was abundant in blood supply with no hepatic/portal vein invasion; (5) Patients > 18 years old; (6) Patients met Child-Pugh stage A or B and BCLC stage A or B and with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1; (7) Life expectancy > 6 months. The exclusion criteria were as follows: (1) Patients with a history of liver transplantation or other malignancies; (2) Patients with coagulation dysfunction or massive ascites; (3) Patients complicated with severe liver or renal dysfunction; (4) Patients with iodine allergy; (5) Patients with cognitive impairment or refusals.

Preparation before the procedure

Each patient had fasted for 6 h and water-deprived for 2 h. The patient was placed in a supine position, and a peripheral intravenous line was established before the procedure. The patient was given inhaled oxygen at 3 L/min with a nasal catheter. Vital signs, including ECG, blood pressure, and oxygen saturation, were monitored. Preoperatively, 3 mg granisetron was injected intravenously over 15 s to prevent nausea and vomiting.

TACE procedure

The groin was prepared in a sterile fashion, and after local anesthesia, percutaneous right common femoral artery was punctured using the modified Seldinger method.

Then, a 5F (Terumo, Tokyo, Japan) /4F (Cordis, USA) RH catheter was introduced through a 5F vascular sheath (Merit Medical, USA), and placed into the celiac trunk under DSA guidance to perform celiac angiography to identify the tumor feeding artery. If the blood vessels in a certain area of the liver are sparse or the tumor is not fully displayed during celiac trunk angiography, look for the extrahepatic tumor blood supply artery, such as superior mesenteric artery, inferior phrenic artery, and right adrenal artery, right inferior intercostal artery, internal mammary artery, etc. After confirming the tumor-feeding artery, a superselective (segmental or subsegmental) approach was used whenever possible using a 2.4 F microcatheter (Merit Medical, USA) for embolization. The tip of the catheter was advanced into the hepatic artery and feeding branch if the size, location, and blood supply were optimal.

The cTACE group was injected an emulsified mixture containing 10 mL lipiodol (Jiangsu Hengrui Medicine Co., Ltd, China) and 40 mg pirarubicin (Shenzhen Wanle Pharmaceutical Co., Ltd, China) into the tumor feeding artery through a microcatheter under fluoroscopic monitoring to avoid reflux of the emulsion. The volume of embolization emulsion was based on the size of the focus. Then according to the blood flow velocity of tumor blood vessels, gelatin sponge particles are appropriately selected to strengthen the embolization until the tumor staining was disappeared.

Patients in the DEB-TACE group received CSM (100-300 μm or 300-500 μm in diameter; Jiangsu Hengrui Medicine Co. Ltd, China) loaded with 40 mg pirarubicin.

TACE upon portal vein visualization achieved "near stasis," with a further pause of 5 minutes to allow redistribution of the embolic agents within the lesion and their distal propulsion by the blood inflow. The second time angiography was conducted to detect the presence of the remaining blushed nodules. The endpoint of the treatment was complete satiation of the tumor vessels with drug and the disappearance of the tumor blush on subsequent angiographic imaging.

Postprocedure management

The puncture wound was bandaged with pressure, and all patients were told to rest in bed in the supine position for at least 6 h post-embolization. The blood supply and temperature of the affected leg should be under intensive focus. The patients were given routine treatment after the operation: (1) Reduced glutathione for liver protection; (2) Granisetron for postoperative nausea and vomiting; (3) Ibuprofen for fever; (4) Non-steroidal anti-inflammatory drugs (Flurbiprofen Axetil) or opioids (morphine) for analgesia; (5) Antibiotics to prevent infection.

Assessment of treatment response

All patients underwent blood test (liver function indexes and alpha-fetoprotein) and imaging examination in the first month after TACE. Patients, who showed tumor progression in the first month after TACE, would receive a second TACE according to the previous grouping. Patients with stables disease were followed with imaging every 3 months.

The treatment response was assessed by two experienced radiologists based on enhanced computed tomography (CT) or magnetic resonance imaging (MRI) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria[11] at 1 month, 3 months, 6 months post-treatment: complete response (CR), partial response (PR), stables disease (SD), and progressive disease (PD). In addition, the objective response rate (ORR) was calculated and defined as CR + PR / total × 100%, and the disease control rate (DCR) was calculated and defined as CR + PR + SD / total × 100%.

Although CT response evaluation differentiation between Lipiodol and contrast agent is limited, the tendency to overestimate treatment response was avoided in the cTACE group through comparison of tumor enhancement in the arterial phase and the extent of lipiodol accumulation in the unenhanced phase.

Assessment of overall survival and progression-free survival

The survival status of the two groups was evaluated by overall survival (OS) and progression-free survival (PFS). The OS was defined as the interval between the date of the first TACE treatment and the date of patients'death from any cause or censored at the date of the last follow-up. The PFS was defined as the interval between the start of the first TACE treatment date and the first radiological progression date, patients' death from any cause, or censored at the date of the last follow-up.[12]

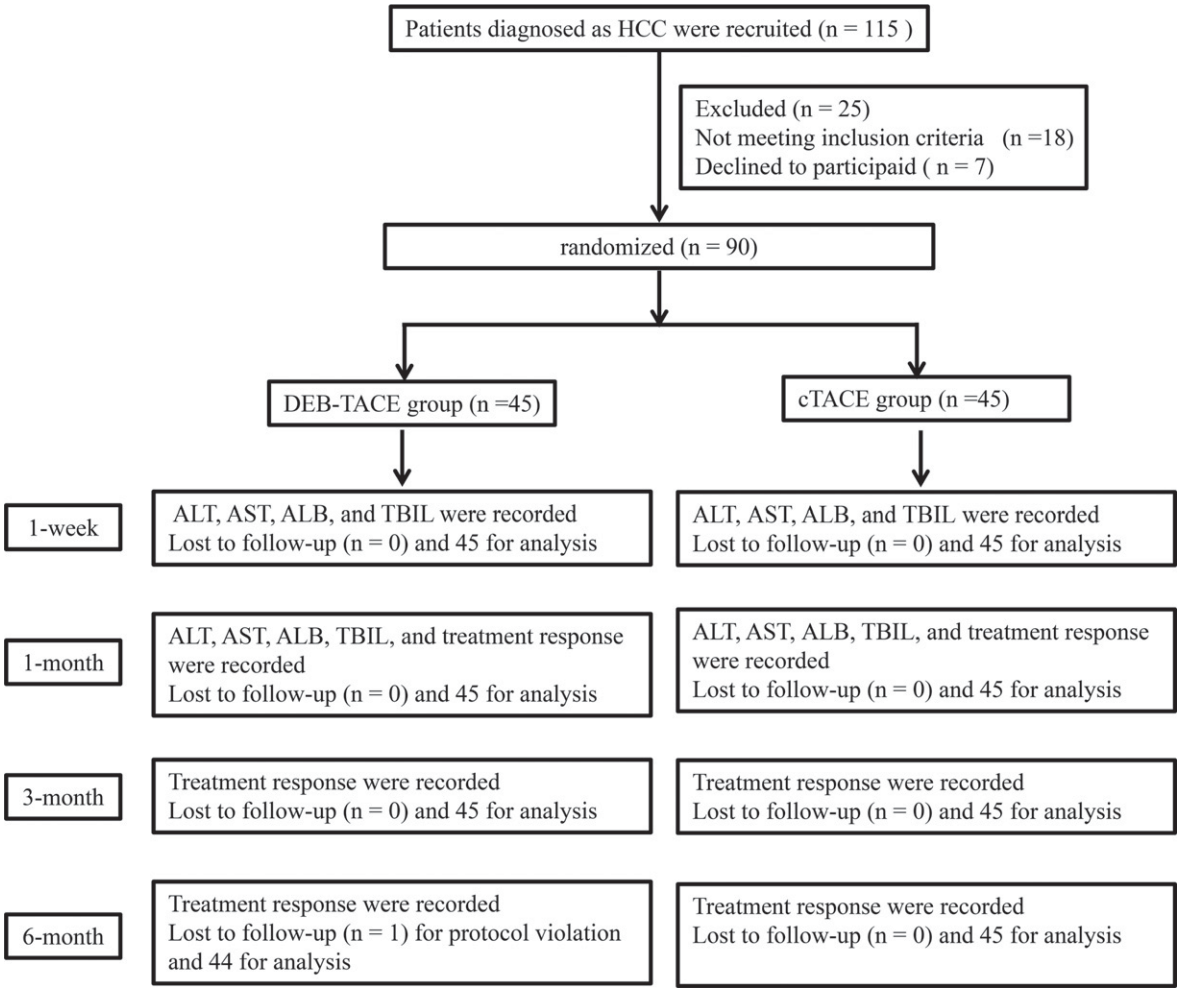

FIGURE 1. Flow diagram of the study.

ALB = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; cTACE = conventional transarterial chemoembolization; DEB-TACE = drug-eluting beads transarterial chemoembolization; HCC = hepatocellular carcinoma; TBIL = total bilirubin

Safety

The safety of the two groups was evaluated by the liver function indexes and post-embolization syndrome. The liver function indexes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), and total bilirubin (TBIL), were assessed before the procedure (baseline), at 1 week, and 1 month post-procedure. The post-embolization symptoms, including fatigue, fever, abdominal distension, abdominal pain, and nausea/emesis, were assessed during the procedure and within 1 month after the procedure. The degree of pain was evaluated by the numeric rating scale (NRS) (0-10), where a score of 0 means no pain and a score of 10 indicates the maximum level of intolerable pain.[11]

Sample size

According to the ORR at 3 months after TACE, as described previously (73.7% in the DEB-TACE group and 42.5% in the cTACE group (P = 0.005))[11], a sample size of at least 39 subjects in each group was required to provide 80% power to detect differences at an α level of 0.05, indicating significance. However, to prevent a 15% attrition rate, we eventually recruited 90 patients with 45 in each group.

Data analysis

GraphPad Prism 8.0.2 software (GraphPad Software Inc., San Diego, CA, USA) was used for statistical analysis and generating graphs. The normally distributed continuous data were presented as the means ± standard deviation, while skewed

TABLE 1. Baseline characteristics of patients

Parameters	DEB-TACE (n = 45)	cTACE (n = 45)	*P* value
Gender (male/female)	40/5	39/6	0.747
Age (years)	58.9 ± 7.1	60.6 ± 6.5	0.229
History of alcohol consumption (n/%)	11 (24.4)	15 (33.3)	0.352
History of viral hepatitis (n/%)	31 (68.9)	27 (60.0)	0.378
Child-Pugh stage (n/%)			
A	33 (73.3)	29 (64.4)	0.326
B	12 (26.7)	16 (35.6)	-
BCLC stage (n/%)			
A	17 (37.8)	14 (31.1)	0.506
B	28 (62.2)	31 (68.9)	-
ECOG performance status (n/%)			
0	17 (37.8)	13 (28.9)	0.371
1	28 (62.2)	32 (71.1)	-
Liver function			
ALT (U/L)	38.0 ± 20.5	35.7 ± 18.7	0.585
AST (U/L)	40.3 ± 16.8	40.1 ± 14.2	0.946
ALB (g/L)	39.9 ± 8.2	40.1 ± 6.2	0.886
TBIL (μmol/L)	19.1 ± 6.1	20.7 ± 7.0	0.246
Tumour location (n/%)			
Unilobar	35 (77.8)	32 (71.1)	0.468
Bilobar	10 (22.2)	13 (28.9)	-
Tumour distribution (n/%)			
Unifocal	36 (80.0)	34 (75.6)	0.612
Multifocal	9 (20.0)	11 (24.4)	
Diameter of the largest tumour (cm)	7.2 ± 2.4	6.8 ± 2.3	0.397

Data were presented as mean ± standard deviation or count (%). Comparisons between two groups were determined by t-test, Wilcoxon rank sum test or Chi-square test. Statistical significance was set at $P < 0.05$.

ALT = alanine aminotransferase; ALB, albumin; AST, aspartate aminotransferase; BCLC = Barcelona Clinic Liver Cancer; cTACE = conventional transarterial chemoembolization; DEB-TACE = drug-eluting beads transarterial chemoembolization; ECOG = Eastern Cooperative Oncology Group; TBIL, total bilirubin

distributed continuous variables were presented as median (25th–75th quantiles) and compared using a t-test. The enumeration data were presented as frequencies and percentages and compared using the chi-squared test. Kaplan–Meier (K–M) method was applied for making the survival curves, and the comparison of OS and PFS between the two groups was estimated by Log-rank test. Statistical significance was set at $P < 0.05$.

Results

Study flow and baseline demographic data

A total of 115 HCC patients were recruited in this trial, 18 did not meet the inclusion criteria, and 7 declined to participate. Finally, 90 patients fulfilled the inclusion criteria and were randomly divided into DEB-TACE or cTACE group (n = 45). The study selection is illustrated in Figure 1. All patients for analysis did not undergo any other treatment previously, including surgery, radiofrequency ablation, TACE, and systematic chemotherapy. At 1 week, 1 month, 3 months, and 6 months all patients in each group were analyzed except 1 patient in the DEB-TACE group died in the 5th month after the procedure.

The mean age of the cohort was 58.9 ± 7.1 years in the DEB-TACE group and 60.6 ± 6.5 years in the cTACE group ($P = 0.229$). In addition, the DEB-TACE group had 40, while the cTACE group consisted of 39 males ($P = 0.747$). The history of alcohol consumption and viral hepatitis, Child–Pugh stage, BCLC stage, ECOG performance status, liver function, tumor location and distribution, and diameter of the largest tumor in the two groups did not differ significantly. The detailed baseline characteristics of patients are listed in Table 1.

Treatment response between the two groups

The treatment response is shown in Table 2. At 1 month after the procedure, the ORR in the DEB-TACE group was significantly higher than that in cTACE group ($P = 0.031$), while there was no significant difference of the CR and DCR between the two groups. At 3 months after the procedure, a significant difference was observed in the treatment response between the two groups. CR, ORR, and DCR in the DEB-TACE group were significantly higher than those in the cTACE group ($P = 0.036$, $P = 0.003$, $P = 0.025$), while PD in the DEB-TACE group was lower than that in the cTACE group ($P = 0.025$). At 6 months after the procedure, CR presented no difference between the two groups, but ORR and DCR were significantly elevated ($P = 0.002$, $P = 0.031$), and PD was significantly reduced in the DEB-TACE group compared to the cTACE group ($P = 0.031$).

Comparison of OS and PFS between the two groups

The final date of survival analysis was March 2022. All patients were followed up until death, or the end of the study and the last follow-up time of the assessment with the median follow-up duration was 365 days (95% CI:150-730 days), which was estimated by reverse Kaplan-Meier method.

Log-rank test revealed that, the median OS of the DEB-TACE group (534 days, 95% CI: 458-634 days) was significantly longer than the cTACE group (367 days, 95% CI: 321-562 days, $P = 0.027$, Figure 2A). The median PFS of the DEB-TACE

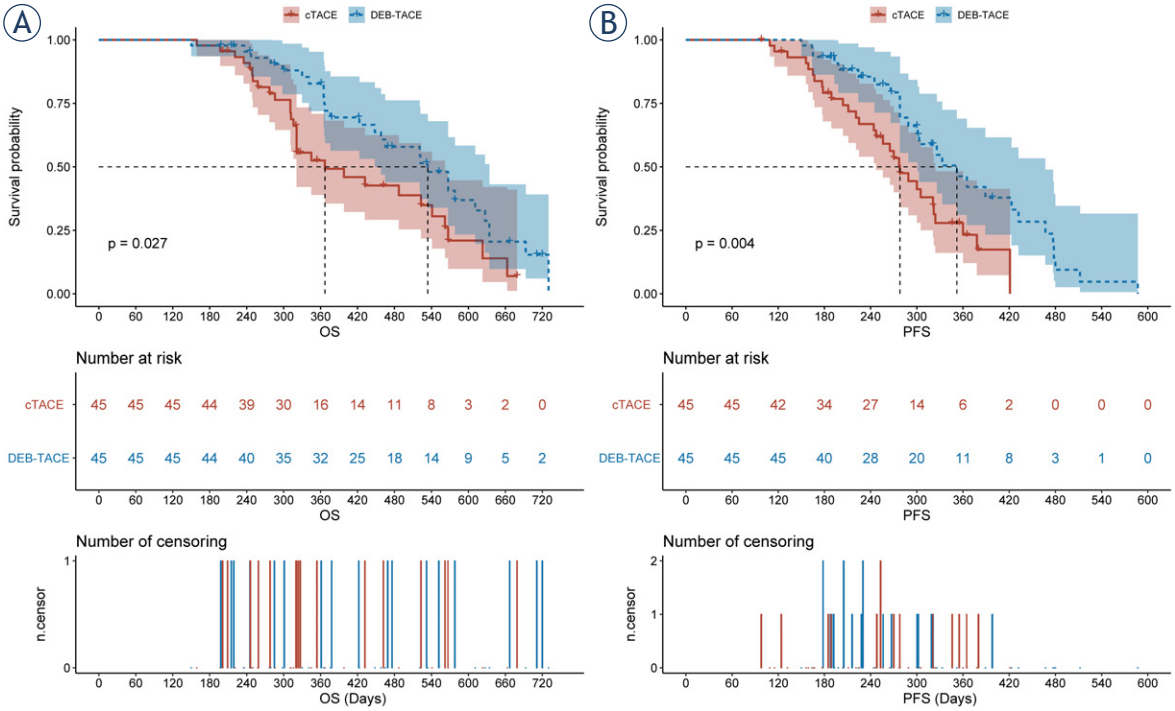

FIGURE 2. The comparison of median overall survival (OS) and progression-free survival (PFS) between the two groups. **(A)** the median OS of the drug-eluting beads transarterial chemoembolization (DEB-TACE) group was significantly longer than the conventional transarterial chemoembolization (cTACE) group (P = 0.027). **(B)** the median PFS of the DEB-TACE group was significantly longer than the cTACE group (P = 0.004).

group (352 days, 95% CI: 301-467 days) was significantly longer than the cTACE group (278 days, 95% CI: 247-324 days, *P* = 0.004, Figure 2B).

Comparison of safety between the two groups

No significant difference was noted in the baseline value of the liver function indexes (AST, ALT, ALB, and TBIL) between the two groups (Figure 3 A–D). At 1 week after the procedure, the AST, ALT, and TBIL indexes were significantly higher in both groups, while the ALB level was lower than the baseline (Table 3). The comparison at 1 week after the procedure between the two groups showed that, the AST, ALT, and TBIL content in the DEB-TACE group was higher than that in cTACE group (Figure 3 A, B, D). However, there was no significant difference of the ALB between the two groups (Figure 3 C). At 1 month after the procedure, all the liver function indexes in the two groups returned to the baseline values (Table 3) and had no difference between the two groups (Figure 3 A–D).

For post-embolization syndrome, the incidence of fatigue, abdominal distension, abdominal pain, and nausea/emesis were similar in the two groups within 1 month after the operation; however, the

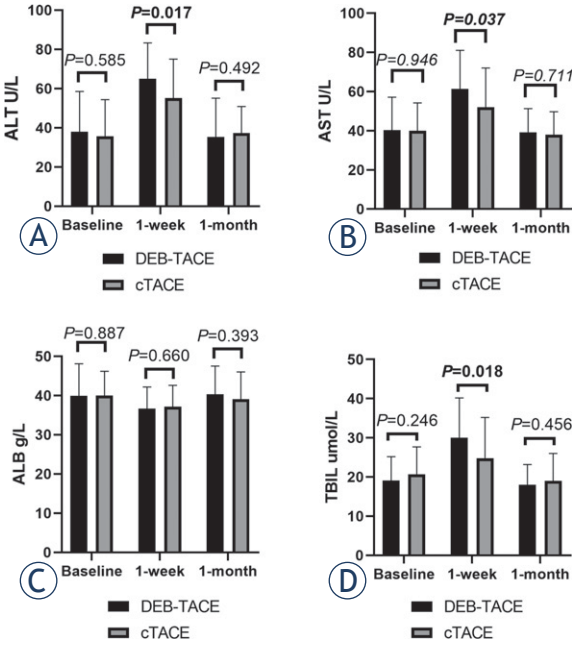

FIGURE 3. Comparison of the liver function between the two groups. The aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL) levels were higher in the drug-eluting beads transarterial chemoembolization (DEB-TACE) group than in the conventional transarterial chemoembolization (cTACE) group at 1 week (*P* < 0.05) after the operation, and all the liver function indexes had no difference between the 2 groups at 1 month after the operation.

TABLE 2. Comparison of treatment response evaluated at 1-month, 3-month, and 6-month after treatment between the two groups

Parameters	1-month			3-month			6-month		
	DEB-TACE group (n = 45)	cTACE group (n = 45)	*P value*	DEB-TACE group (n = 45)	cTACE group (n = 45)	*P value*	DEB-TACE group (n = 44)	cTACE group (n = 45)	*P value*
CR (%)	8 (17.8)	6 (13.3)	0.561	10 (22.2)	3 (6.7)	**0.036**	7 (15.9)	3 (6.7)	0.168
PR (%)	24 (53.3)	16 (35.6)	0.090	23 (51.1)	16 (35.6)	0.137	23 (52.3)	13 (28.9)	**0.025**
ORR (%)	32 (71.1)	22 (48.9)	**0.031**	33 (73.3)	19 (42.2)	**0.003**	30 (68.2)	16 (35.6)	**0.002**
SD (%)	10 (22.2)	18 (40.0)	0.069	6 (13.3)	11 (24.4)	0.178	10 (22.7)	17 (37.8)	0.123
DCR (%)	42 (93.3)	40 (88.9)	0.459	39 (86.7)	30 (66.7)	**0.025**	40 (90.9)	33 (73.3)	**0.031**
PD (%)	3 (6.7)	5 (11.1)	0.459	6 (13.3)	15 (33.3)	**0.025**	4 (9.1)	12 (26.7)	**0.031**

Data were presented as count (%). Comparison between 2 groups was determined by Chi-square test. Statistical significance was set at P < 0.05, and were shown in boldface.

CR = complete response; cTACE = conventional transarterial chemoembolization; DCR = disease control rate; DEB-TACE = drug-eluting beads transarterial chemoembolization; ORR = objective response rate; PR = partial response; SD = stables disease; PD = progression disease

TABLE 3. Compared with the baseline, the changes of liver function at 1-week and 1-month after procedure in the two groups

Parameters	DEB-TACE (n = 45)					cTACE (n = 45)				
	Baseline	1-week	*P value*	1-month	*P value*	Baseline	1-week	*P value*	1-month	*P value*
ALT (U/L)	38.0 ± 20.5	65.0 ± 18.3	**< 0.001**	35.3 ± 19.8	0.431	35.7 ± 18.7	55.2 ± 19.8	**<0.001**	37.4 ± 13.5	0.558
AST (U/L)	40.3 ± 16.8	61.3 ± 19.7	**< 0.001**	39.1 ± 12.2	0.722	40.1 ± 14.2	52.4 ± 20.0	**0.003**	38.2 ± 11.7	0.534
ALB (g/L)	39.9 ± 8.2	36.7 ± 5.5	**0.004**	40.3 ± 7.21	0.758	40.1 ± 6.2	37.2 ± 5.4	**0.027**	39.1 ± 6.9	0.508
TIBL (umol/L)	19.1 ± 6.1	30.0 ± 10.2	**< 0.001**	18.0 ± 5.2	0.399	20.7 ± 7.0	24.8 ± 10.4	**0.003**	19.0 ± 7.0	0.328

Data were presented as mean ± standard deviation and were determined by t-test or Wilcoxon rank sum test. Statistical significance was set at *P* < 0.05, and were shown in boldface

ALT = alanine aminotransferase; ALB = albumin; AST = aspartate aminotransferase; cTACE = conventional transarterial chemoembolization; DEB-TACE = drug-eluting beads transarterial chemoembolization; TBIL = total bilirubin

incidence of fever was higher in the DEB-TACE group than the cTACE group (*P* = 0.031, Table 4). Notably, the NRS of abdominal pain in the DEB-TACE group (4.4 ± 1.9) was higher than that in cTACE group (3.6 ± 1.6, *P* = 0.037, Table 4). Strikingly, the fever alleviated by drinking excess water and taking ibuprofen, and abdominal pain alleviated by intravenous injection of flurbiprofen axetil or by taking in morphine in 2-3 days. In addition, no serious adverse events, such as liver abscess, acute liver function failure, severe infection, gastrointestinal/intratumoral bleeding, and hepatorenal syndrome, occurred in either group.

Discussion

In the present prospective study, we compared the treatment response, the survival, and the safety of unresectable HCC patients treated with DEB-TACE with CSM and cTACE. The results indicated that DEB-TACE was significantly superior to cTACE in the following aspects: (1) The higher ORR at 1 month, 3 months, and 6 months, and the higher DCR at 3 and 6 months in the DEB-TACE group; (2) The higher CR at 3 months in DEB-TACE group; (3) The lower PD at 3 and 6 months in the DEB-TACE group; (4) The longer OS and PFS in the DEB-TACE group. Although, the liver function indexes (ALT, AST, and TBIL) injury were elevated in the DEB-TACE group at 1 week, but the indexes recovered to the preoperative level at 1 month after treatment in both groups. Moreover, DEB-TACE with CSM increases the incidence of fever and causes severe abdominal pain, which could be controlled by drugs. One patient died 5 months after operation in the DEB-TACE group due to disease progression rather than serious complications of DEB-TACE.

In clinical practice, DEB-TACE and cTACE have become the first-line therapeutic selection for in-

termediate and advanced stage HCC according to the BCLC staging system.[13] Although DEBs have the ability to load chemotherapeutic agents and release them in a controlled mode, the evidence to show that DEB-TACE is superior to cTACE is insufficient. Presently, CSM is the first novel DEB product in China that has been applied clinically only in the last several years. Some studies have compared the tumor response of DEB-TACE with CSM and cTACE for HCC; however, most of them are retrospective studies, and the results were inconsistent. For example, Wu *et al*.[10] indicated that CR, ORR, and DCR rates in the DEB-TACE group were significantly higher than those in the cTACE group at 3 and 6 months. Liang *et al*.[14] showed that compared to cTACE, DEB-TACE with CSM treatment had a higher ORR within 6 months and a higher DCR at 3 and 6 months. Different from the above results, Zhang *et al*.[15] demonstrated that ORR was not different between the two groups, while DCR was significantly higher in the cTACE group than in the DEB-TACE group at 1 month and 3 months. Notably, the articles comparing the efficacy and safety of DEB-TACE with CSM and cTACE are mostly retrospective studies. A recent study adopted prospective design to compare the efficacy and safety of cTACE and DEB-TACE with CSM, and the results were similar to ours. But an uncommon cytotoxic drug (arsenic trioxide) was used in DEB-TACE group, so that the significance of clinical guidance is uncertain.[12]

Herein, we prospectively compared the treatment response within 6 months, OS and PFS of cTACE and DEB-TACE using CSM with pirarubicin (a commonly cytotoxic drug). The results exhibited that DEB-TACE with CSM displayed superior CR (at 3 months), ORR (at 1, 3, and 6 months), and DCR (at 3 and 6 months) over cTACE treatment. The improved treatment responses could be attributed to the fact that CSM has the ability to load chemotherapeutic agents and release them in a controlled pattern, thus maintaining a higher concentration of chemotherapeutic drugs and better efficacy on reducing diameters of the tumor tissues than cTACE.[16,17] In addition, calibrated CSM has shown permanent embolization, which improves the tumor responses in the DEB-TACE treatment with CSM group.[18] This might explain the increased CR and decreased PD in the DEB-TACE group at 3 months in this study. Interestingly, with decreased PD in the DEB-TACE group, HCC patients experienced a reduced frequency of operations and thus economic burden. The higher CR at 3 months in patients receiving DEB-TACE treatment with CSM could be ascribed to the fact that CSM achieves a high concentration of chemotherapeutic agents in 3 months.

TABLE 4. Comparison of post-embolization syndrome

Adverse events	DEB-TACE (n = 45)	cTACE (n = 45)	*P* value
Fatigue (n/%)	5 (11.1)	7 (15.6)	0.535
Fever (n/%)	23 (51.1)	13 (28.9)	**0.031**
Abdominal distension (n/%)	9 (20)	7 (15.6)	0.581
Abdominal pain (n/%) Numeric Rating Scale (NRS)	42 (93.3) 4.4 ± 1.9	43 (95.6) 3.6 ± 1.6	0.645 **0.037**
Nausea/emesis (n/%)	10 (22.2)	12 (26.7)	0.624

Data were presented as mean ± standard deviation or count (%). Comparisons between two groups was determined by t-test, Wilcoxon rank sum test or Chi-square test. Statistical significance was set at $P < 0.05$, and were shown in boldface.

cTACE = conventional transarterial chemoembolization; DEB-TACE = drug-eluting beads transarterial chemoembolization

According to the survey, most of the HCC patients are in intermediate and advanced stages at diagnosis.[19] Hence, short-term efficacy and the safety of the treatment are critical for the HCC patients. A recent multi-center, retrospective registry cohort study[8] showed higher CR and ORR, while the DCR was similar in the DEB-TACE group compared to the cTACE group. A meta-analysis reported that DEB-TACE with CSM displays superior treatment response, which was consistent with our results.[20]

As we know, the most important outcomes in oncology trials are OS and PFS. Accumulating evidence showed that DEB-TACE acquired long-term survival profile (such as OS and PFS) than cTACE in HCC patients.[21,22] The patients in DEB-TACE group showed longer OS and PFS in our study, indicating that the patients underwent DEB-TACE with CSM got more survival benefits compared to patients in cTACE group. While a small amount of literature showed no difference in OS or PFS between DEB-TACE and cTACE groups.[11,23] The difference of survival results may be related to the different types of EDBs, heterogeneity of included patients, and the different types of research. It can be seen that our prospective randomized controlled study is very necessary.

After TACE treatment, liver function injury is one of the major safety concerns in HCC patients. Some studies compared the liver function indexes before and after treatment between DEB-TACE and cTACE and revealed that AST, ALT, and TBIL increased substantially 7 days after TACE and re-

turned to baseline in 1 month.[15,24,25] In this study, the liver function was damaged in both DEB-TACE and cTACE groups at 1 week after the treatment, including the increased ALT, AST, and TBIL and the decreased ALB content. Different from other studies, the current results showed that the ALT, AST, and TBIL in the DEB-TACE group was higher than that in the cTACE group at 1 week. Similar to studies, the indexes recovered to the preoperative level at 1 month after treatment. This phenomenon indicated that DEB-TACE with CSM had more serious damage of liver function compared to cTACE in the short term (about 1 week) and could return to baseline in 1 month. The results also showed that DEB-TACE with CSM and cTACE had parallel effects on the liver function at 1 month, and HCC patients can tolerate both procedures satisfactorily. This observation was consistent with previous studies.[13,25]

Postembolization syndrome is the most common adverse event. Partially in line with these studies[15,24,25], adverse events in the current study included fatigue, abdominal distension, abdominal pain, and nausea/emesis, which were similar between the two groups. However, DEB-TACE with CSM resulted in a high incidence of fever. Although no significant difference was observed in the incidence of abdominal pain between the two groups, the NRS of DEB-TACE group was higher. This might be related to the following effects: (1) The tumors in the DEB-TACE group achieved substantial tumor necrosis and results in severe abdominal pain; (2) Patients in the DEB-TACE group had significant tumor necrosis induced by treatment with CSM, and the incidence of inflammation could be enhanced by substances released from the necrotic tumor tissue. Thus, the patients in the DEB-TACE group experienced severe pain and a high risk of fever. However, the fever was alleviated by ibuprofen, and the pain was alleviated by intravenous injection of flurbiprofen axetil or morphine in 2-3 days in both groups. Also, no serious adverse events, such as liver abscess, acute liver function failure, and severe infection, occurred in either of the groups, which could be attributed to the superselective technique, and the selected patients were controlled in BCLC stages A and B.

This is a randomized controlled trial on the efficacy and safety of DEB-TACE with CSM *vs.* cTACE; hence, confounding factors were minimal, providing accurate evidence to the clinicians. Nevertheless, the current study has some limitations: (1) This is a single-center study with small sample size. However, according to the statistical analysis, 39 patients in each group showed varied ORR between the two groups, with 80% power and a 5% significance level; (2) The tumor responses were followed up for only 6 months, and for survival analysis was not based on the death of all patients. At the last follow-up, 64.4% (29/45) of patients in cTACE group and 60.0% (27/45) of patients in DEB-TACE group died. Therefore, a longer follow-up is necessary in the future study; (3) The amount of pirarubicin administered between DEB-TACE group and cTACE group was not compared, which may have an impact on the results, and further study should compare the dose of the pirarubicin between the two groups.

In conclusion, this study demonstrated that DEB-TACE with CMS had a better tumor response in some aspects (higher CR at 3 months, ORR at 1, 3, and 6 months) than the cTACE group. The liver function injury was more serious in DEB-TACE group at 1 week but returned to the baseline at 1 month in the cTACE group. The increased incidence of fever and severe abdominal pain in the DEB-TACE group could be relieved by symptomatic treatment.

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