*Oncology Research*, Vol. 27, pp. 565–573
Printed in the USA. 

0965-0407/19 $90.00 + .00
DOI: https://doi.org/10.3727/096504018X15313896322888
E-ISSN 1555-3906
www.cognizantcommunication.com



# Efficacy and Safety of CalliSpheres® Drug-Eluting Beads Transarterial Chemoembolization in Barcelona Clinic Liver Cancer Stage C Patients

Yaohong Liu, Wensou Huang, Mingji He, Hui Lian, Yongjian Guo, Jingjun Huang, Jingwen Zhou, and Kangshun Zhu

Department of Minimally Invasive Interventional Radiology,
The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, P.R. China

This study aimed to investigate the efficacy and safety of drug-eluting beads transarterial chemoembolization (DEB-TACE) treatment in Barcelona Clinic Liver Cancer (BCLC) stage C liver cancer patients. In 39 patients with BCLC stage C liver cancer, after the first cycle of DEB-TACE, 2 (5.1%) and 24 (61.5%) patients achieved complete response (CR) and partial response (PR) to give an overall objective response rate (ORR) of 66.7%. With respect to the second cycle of therapy, the ORR was higher in patients receiving DEB-TACE compared with those receiving cTACE (57.1% vs. 11.1%). After the first cycle of DEB-TACE treatment, the percentages of abnormal albumin (ALB), total protein (TP), total bilirubin (TBIL), and alanine aminotransferase (ALT) worsened at 1 week and recovered at 1 month. The number of patients with abnormal aspartate aminotransferase (AST) did not increase at 1 week but elevated at 1 month. After the second cycle of DEB-TACE or cTACE treatment, no difference was observed between cTACE and DEB-TACE in terms of all adverse events (AEs) at all visits, and most of the AEs did not change after the second cycle in both groups. The most common AEs after the first and second treatment cycles were pain, fever, and nausea/vomiting. These results demonstrate that DEB-TACE offers patients with BCLC stage C liver cancer a clinically active short-term treatment that is safe and relatively well tolerated.

**Key words: Clinical efficacy; Safety; Drug-eluting beads transarterial chemoembolization (DEB-TACE); Barcelona Clinic Liver Cancer (BCLC) stage C; Liver cancer**

## INTRODUCTION

Liver cancer is a malignancy with an extremely poor prognosis. This cancer is a major public health problem as it accounts for the majority of cancer deaths worldwide and is the most frequent cancer in Chinese males[1]. Patients with advanced liver cancer, according to the Barcelona Clinic Liver Cancer (BCLC) staging system, are those with BCLC stage C who are characterized by poor performance status, large or multifocal tumor, vascular invasion or extrahepatic metastasis, and inadequate liver function. Patients with BCLC stage D disease have an extremely poor performance status and poor liver function[2]. Therapies for advanced liver cancer remain limited. The small molecule tyrosine kinase inhibitor sorafenib is currently recommended as a standard treatment for BCLC stage C patients. Unfortunately, because of financial costs, its use in China has been somewhat restricted[2].

Drug-eluting beads transarterial chemoembolization (DEB-TACE) is local regional therapy recently developed to improve the efficacy and safety of conventional transarterial chemoembolization (cTACE), which is now universally used to treat patients with unresectable liver cancer[3,4]. Cohort studies, clinical trials, and meta-analysis have shown DEB-TACE to be associated with favorable treatment responses, prolonged survival, and at least similar safety profile when compared with cTACE[5,6]. Despite the fact that DEB-TACE is considered to be appropriate for intermediate stage liver cancer, there is still only a small number of patients with advanced liver cancer that are treated with DEB-TACE in clinical practice and in clinical studies. A retrospective cohort study revealed that DEB-TACE could be used as an effective bridge therapy for liver transplantation in patients with advanced liver cancer and inadequate liver function[7]. However, currently available evidence for the

Address correspondence to Kangshun Zhu, Department of Minimally Invasive Interventional Radiology, The Second Affiliated Hospital of Guangzhou Medical University, 250 Changgang East Road, Guangzhou 510260, Guangdong, P.R. China. Tel: +86-020-34152781; Fax: +86-020-34153709; E-mail: kangshunzhu@yeah.net

use of DEB-TACE in the setting of BCLC stage C liver cancer is limited.

With this in mind, our study was focused on investigating the clinical efficacy and safety of DEB-TACE treatment in BCLC stage C liver cancer patients.

## MATERIALS AND METHODS

### *Patients*

A total of 39 patients with liver cancer were seen and were enrolled in this study at the Department of Minimally Invasive Interventional Radiology in The Second Affiliated Hospital of Guangzhou Medical University Hospital from January 2016 to March 2017. The study inclusion criteria were as follows: (1) patients diagnosed with liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), according to the American Association for the Study of the Liver Diseases (AASLD) guidelines[8]; (2) patients who were classified as BCLC stage C according to the BCLC staging system; (3) age above 18 years; and (4) patients who received DEB-TACE treatment. In addition, patients with liver or renal failure, contraindications for the arterial procedure, HIV infection or AIDS-related or serious acute or chronic illness, ascites, liver abscess, allergy to the chemoembolization reagents, incomplete laboratory indexes, cognitive impairment, and were pregnant or in the lactation period were excluded from this study.

This study was conducted according to the basic principles of the Declaration of Helsinki and approved by the ethical committee of The Second Affiliated Hospital of Guangzhou Medical University Hospital. Written informed consent was collected from all patients.

### *TACE Procedures*

All the TACE procedures were conducted in the Digital Subtraction Angiography (DSA) room in our hospital, and the DEB-TACE operation was carried out as follows. (1) CalliSpheres® beads (Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, P.R. China) with diameters of 100–300 μm were loaded with Pirarubicin (ShenZhen Main Luck Pharmaceuticals Inc., ShenZhen, P.R. China) 60 mg through the following method: first, preparing one bottle of CalliSpheres® beads by extracting the supernatant, afterward dissolving the Pirarubicin to the solution with concentration of 20 mg/ml, then subsequently using the tee joint to mix the beads and the Pirarubicin solution, and finally adding the nonionic contrast agent to the mixed solution. (2) Angiography was performed to detect the tumor-supplying vessels, and the microcatheter and microwire were superselectively catheterized into the tumor-supplying vessels for the embolization. (3) The embolization was stopped until the stasis of the flow of contrast agent existed. (4) After 5 min of the delivery, another angiography was performed to detect the blushed/tinted tumor, and the embolization procedure was repeated if the blushed/tinted tumor still appeared. Lobaplatin (20 mg; Hainan Changan International Pharmaceuticals Co. Ltd., Haikou City, Hainan Province, P.R. China) was given through arterial embolization. In addition, if one bottle of CalliSpheres® beads was not enough for the embolization, the 300- to 500-μm Embosphere® beads (Biosphere Medical, Roissy En, France) and polyvinyl alcohol (PVA; Cook Inc., Bloomington, IN, USA) were used for further embolization.

cTACE was performed as follows. Angiography was conducted to detect the tumor-supplying vessels, and percutaneous femoral arterial puncture was performed using the Seldinger technique under topical anesthesia; afterward the microcatheter and microwire were super selectively catheterized into the tumor-supplying vessels for the delivery of the mixed solution of Pirarubicin (60 mg) and lipiodol (Yantai Luyin Pharmaceuticals Co. Ltd., Yantai City, Shandong Province, P.R. China). Under x-ray, the embolization was stopped until stenosis of the flow of lipiodol existed. Another angiography was performed to ensure the lipiodol was deposited and to detect if there was inadequate embolization.

### *Pre- and Postoperation Treatment*

Before operation, patients received analgesia treatment using flurbiprofen axetil (Beijing Tide Pharmaceutical Co. Ltd., Beijing, P.R. China) injected intravenously (IV; 50 mg), antiemetic treatment using tropisetron citrate (5 mg; Huiyinbi Co. Ltd., Fuzhou City, Jiangxi Province, P.R. China) injected IV, and treatment for protecting the stomach using omeprazole IV (40 mg; Jiangsu Aosaikang Pharmaceutical Co. Ltd., Nanjing City, Jiangsu Province, P.R. China).

Postoperation, patients were treated with metoclopramide dihydrochloride (40 mg; The Seventh Pharmaceutical Co. Ltd. of Wuxi, Wuxi City, Jiangsu Province, P.R. China) injected IV to prevent nausea/vomiting, loxoprofen sodium [Daiichi Sankyo (China) Holdings Co. Ltd., Shanghai, P.R. China] per os (60 mg) for fever, and tramadol (10 mg; Grünenthal GmbH, Aachen, Germany) intramuscularly (IM) or flurbiprofen axetil (50 mg; Beijing Tide Pharmaceutical Co. Ltd.) injected IV in combination with normal saline (100 mg) for analgesia.

### *Treatment Response Assessment*

Treatment responses were assessed within 1–3 months after both the first cycle of DEB-TACE and the second cycle of cTACE or DEB-TACE procedures according to imaging results by modified Response Evaluation Criteria in Solid Tumors (mRECIST)[9]: (1) complete response (CR): the loss of any intratumoral arterial enhancement in all target nodules; (2) partial response (PR): at

least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target nodules, taking as reference the baseline sum of the diameters of target nodules; (3) stable disease (SD): any patient that do not measure up either PR or progressive disease (PD); (4) PD: an increase of at least 20% in the sum of the diameters of viable (enhancing) target nodules, taking as reference the smallest sum of the diameters of viable (enhancing) target nodules recorded since treatment started. Objective response rate (ORR) was defined as the percentage of patients who achieved CR and PR.

*Liver Function and Safety Assessment*

Liver function was assessed by evaluating the liver function-related laboratory indexes, including albumin (ALB), total protein (TP), total bilirubin (TBIL), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). In addition, adverse events (AEs) including pain, fever, nausea/vomiting, and others were recorded.

*Statistics*

SPSS software 22.0 (IBM, USA) and Office 2016 software (Microsoft, USA) were used for the statistical analysis. Data are presented as count (%), mean ± standard deviation, or median (25th–75th). A comparison between the two treatment groups was determined by chi-square test. The McNemar test was performed to compare the difference of liver function indexes at each visit. A value of $p < 0.05$ was considered significant.

## RESULTS

*Study Design*

As presented in Figure 1, 185 liver cancer patients received their first cycle treatment with DEB-TACE in our hospital from January 2016 to March 2017, and 146 patients were excluded due to secondary liver cancer, BCLC stage A, or BCLC stage B. In the remaining 39 patients with BCLC stage C who received their first cycle treatment with DEB-TACE, the blood routine of 4 patients was not recorded and image assessment of 1 patient was not evaluated. After the first cycle of DEB-TACE, 23 patients received a second cycle treatment with DEB-TACE or cTACE. In 14 patients who received a second cycle DEB-TACE, the blood work of 3 patients was not performed, while 1 patient did not have imaging assessment. For the 9 patients who received cTACE therapy, 1 patient did not have routine blood work performed and 1 patient did not undergo imaging assessment. The treatment responses were assessed after the completion of each procedure.

*Patient Characteristics*

The mean age was 56.74 ± 14.73 years in 39 liver cancer patients, among which there were 28 males and 11 females (Table 1). The numbers of HCC and ICC

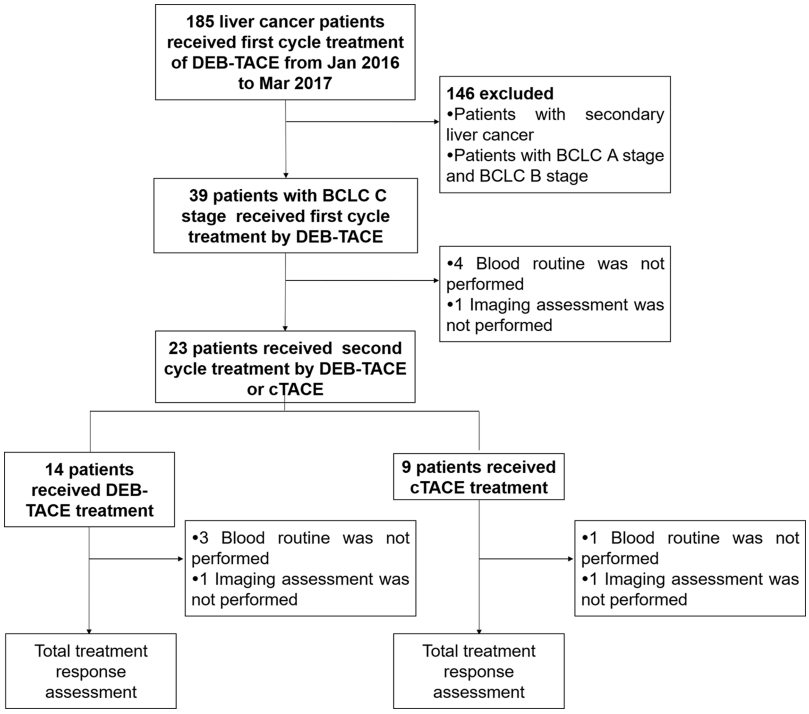


**Figure 1.** Study flow.

**Table 1.** Baseline Patient Characteristics

| Parameters | Patients ($N=39$) |
|---|---|
| Age (years) | 56.74±14.73 |
| Gender (male/female) | 28/11 |
| History of hepatitis B, *n* (%) | 25 (64.1) |
| History of drink, *n* (%) | 4 (10.3) |
| Histology | |
| Hepatocellular carcinoma (HCC), *n* (%) | 34 (87.2) |
| Intrahepatic cholangiocarcinoma (ICC), *n* (%) | 5 (12.8) |
| Tumor distribution, *n* (%) | |
| Multiple lesions | 16 (41) |
| Single lesion | 23 (59) |
| Tumor location, *n* (%) | |
| Left liver | 3 (7.7) |
| Right liver | 28 (71.8) |
| Bilobar | 8 (20.5) |
| Largest tumor size (cm) | 9 (5.7–12.5) |
| Largest tumor size distribution, *n* (%) | |
| <5 cm | 4 (10.3) |
| 5–7 cm | 7 (17.9) |
| >7 cm | 28 (71.8) |
| Portal vein invasion, *n* (%) | 35 (89.7) |
| ECOG performance status, *n* (%) | |
| 0 | 35 (89.7) |
| 1 | 4 (10.3) |
| Child–Pugh stage, *n* (%) | |
| A | 31 (79.5) |
| B | 8 (20.5) |
| Liver function | |
| Albumin (ALB) (g/L) | 36.4 (31.9–38.7) |
| Total protein (TP) (g/L) | 69.4 (65.1–73.6) |
| Total bilirubin (TBIL) (μmol/L) | 17.1 (10.6–22.4) |
| Total bile acid (TBA) (I/L) | 4.0 (0.0–13.4) |
| Alanine aminotransferase (ALT) (U/L) | 32 (20–57) |
| Aspartate aminotransferase (AST) (U/L) | 46 (24–87) |
| Alkaline phosphatase (ALP) (U/L) | 110 (74–139) |
| Tumor markers | |
| Alpha fetoprotein (AFP) (μg/L) | 154.2 (5.2–3028.1) |
| Carcino-embryonic antigen (CEA) (μg/L) | 1.6 (0.0–3.6) |
| Carbohydrate antigen (CA199) (kU/L) | 2.2 (0.0–15.5) |
| Previous treatments, *n* (%) | |
| Surgery | 1 (2.6) |
| History of interventional therapy | 16 (41.0) |
| Systemic chemotherapy | 2 (5.1) |
| Combination of ordinary embolization agent | 18 (46.2) |

Data are presented as mean±standard deviation, median (25th–75th), or count (%). ECOG, Eastern Cooperative Oncology Group.

were 34 (87.2%) and 5 (12.8%), respectively. Sixteen (41%) patients had multiple lesions and 23 (59%) patients had a single lesion. The numbers of patients with tumor located in the left liver, right liver, and both lobes of the liver were 3 (7.7%), 28 (71.8%), and 8 (20.5%), respectively. The median tumor size was 9 cm (5.7–12.5 cm), among which the numbers of patients with largest tumor size <5 cm, 5–7 cm, and >7 cm were 4 (10.3%), 7 (17.9%), and 28 (71.8%), respectively. With respect to performance status, 35 (89.7%) patients had Eastern Cooperative Oncology Group (ECOG) performance status 0, and 4 (10.3%) patients had ECOG performance status 1. Other disease history, clinicopathological characteristics, laboratory indexes, previous treatments, and information on combination of ordinary embolization agents are listed in Table 1.

*Treatment Responses*

As seen in Table 2, after the first cycle of DEB-TACE, 2 (5.1%) and 24 (61.5%) achieved CR and PR, to give an ORR of 66.7%. In addition, in all patients who received a second cycle of TACE treatment, the numbers of patients who achieved CR and PR were 1 (7.1%) and 7 (50.0%) after DEB-TACE, and 0 (0.0%) and 1 (11.1%) after cTACE (Table 3). The ORR was significantly higher in patients treated with DEB-TACE compared with patients treated with cTACE (57.1% vs. 11.1%, $p=0.040$).

The total treatment response was also assessed, which disclosed that 1 (7.1%) patient achieved CR and 9 (64.3%) patients achieved PR in the DEB-TACE group; the ORR was 71.4% (Table 4). In the cTACE group, CR and PR were 0 (0.0%) and 4 (44.4%), respectively, to yield and ORR of 44.4%. There was no difference in total treatment response in patients treated with two cycles of DEB-TACE or one cycle of DEB-TACE followed by the second cycle of cTACE (all $p>0.05$).

*Liver Function Before and After Treatment*

As presented in Table 5, after the first cycle of DEB-TACE treatment, the percentages of abnormal ALB, TP, TBIL, and ALT increased at 1 week postoperation (all

**Table 2.** Treatment Response to First Cycle of Drug-Eluting Bead Transarterial Chemoembolization (DEB-TACE)

| Parameters | Patients ($N=39$) |
|---|---|
| Complete response (CR) | 2 (5.1) |
| Partial response (PR) | 24 (61.5) |
| Overall response rate (ORR) | 26 (66.7) |
| Stable disease (SD) | 10 (25.6) |
| Progressive disease (PD) | 2 (5.1) |
| Not assessed | 1 (2.6) |

Data are presented as count *n* (%).

**Table 3.** Treatment Response to Second Cycle Treatment With DEB-TACE or Conventional Transarterial Chemoembolization (cTACE)

| Parameters | DEB-TACE Group ($N=14$) | cTACE Group ($N=9$) | $p$ Value |
|---|---|---|---|
| Complete response (CR) | 1 (7.1) | 0 (0.0) | 1.000 |
| Partial response (PR) | 7 (50.0) | 1 (11.1) | 0.086 |
| Overall response rate (ORR) | 8 (57.1) | 1 (11.1) | **0.040** |
| Stable disease (SD) | 2 (14.3) | 5 (55.6) | 0.066 |
| Progressive disease (PD) | 1 (7.1) | 2 (22.2) | 0.538 |
| Not assessed | 3 (21.5) | 1 (11.1) | – |

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

$p<0.05$) and were similar to that at before operation and at 1 month postoperation (all $p>0.05$). In addition, the percentage of abnormal TBA and abnormal ALP did not change at 1 week postoperation and 1 month postoperation (all $p>0.05$). However, although the number of patients with abnormal AST did not increase at 1 week postoperation, it was notably elevated at 1 month ($p=0.125$ and $p=0.031$, respectively).

No differences were observed between cTACE and DEB-TACE in terms of the proportions of abnormal ALB, TP, TBIL, TBA, ALT, AST, and ALP before, at 1 week, and at 1 month after the second cycle of treatments (all $p>0.05$) (Table 6). However, the percentage of abnormal ALB in the DEB-TACE group was elevated both at 1 week and 1 month postoperation ($p=0.007$ and $p=0.039$, respectively). Only the proportion of abnormal ALB in cTACE group as well as the percentage of abnormal AST in the DEB-TACE group increased at 1 week postoperation ($p=0.021$ and $p=0.022$, respectively), and there were no differences observed with these liver function tests at 1 month compared with that before treatment (all $p>0.05$).

*Safety Profiles*

After the first cycle of DEB-TACE treatment, 21 (53.8%) patients had pain, 21 (53.8%) patients had fever, 5 (12.8%) patients had nausea, 5 (12.8%) patients had vomiting, and 2 patients (5.1%) experienced other AEs during DEB-TACE operation (Table 7). After 1 month postoperation, only 8 (20.5%) patients had pain, and no other AEs were observed.

As seen in Table 8, after the second cycle of DEB-TACE or cTACE treatment, the numbers of patients who presented with pain, fever, and vomiting in DEB-TACE group were 7 (50.0%), 7 (50.0%), and 1 (7.1%); no nausea and other AEs were observed during operation, and no pain or fever was observed at 1 month postoperation. In contrast, in the cTACE group, 4 (44.4%) patients had pain, 3 (33.3%) patients presented with fever, and 1 (11.1%) patient experienced nausea during operation. In addition, 1 month postoperation, 2 patients (22.2%) had pain and 1 (11.1%) patient had fever.

## DISCUSSION

Patients with early and intermediate stage liver cancer are usually underdiagnosed as a consequence of the absence of symptoms. As a result, a large number of patients presented with advanced stage disease when they received their first cycle of transarterial chemoembolization therapy. Moreover, a high proportion of patients with BCLC stage C disease have hepatic or portal vein

**Table 4.** Total Treatment Response in Patients Receiving Two Cycles of TACE Treatments

| Parameters | DEB-TACE Group ($N=14$) | cTACE Group ($N=9$) | $p$ Value |
|---|---|---|---|
| Complete response (CR) | 1 (7.1) | 0 (0.0) | 0.412 |
| Partial response (PR) | 9 (64.3) | 4 (44.4) | 0.349 |
| Overall response rate (ORR) | 10 (71.4) | 4 (44.4) | 0.196 |
| Stable disease (SD) | 0 (0) | 2 (22.2) | 0.624 |
| Progressive disease (PD) | 1 (7.1) | 2 (22.2) | 0.295 |
| Not assessed | 3 (11.1) | 1 (11.1) | – |

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

**Table 5.** Liver Function Before and After the First Cycle of DEB-TACE

| | Before Operation | 1 Week Postoperation | 1 Month Postoperation | *p* Value* | *p* Value† |
|---|---|---|---|---|---|
| Albumin (ALB) abnormal | 30/38 (78.9) | 36/37 (97.3) | 29/35 (82.9) | **0.039** | 1.000 |
| Total protein (TP) abnormal | 9/39 (23.1) | 19/39 (48.7) | 12/35 (34.4) | **0.021** | 0.289 |
| Total bilirubin (TBIL) abnormal | 11/39 (28.2) | 25/39 (64.1) | 13/35 (37.1) | **0.001** | 0.754 |
| Total bile acid (TBA) abnormal | 11/28 (39.3) | 7/16 (43.8) | 10/24 (41.7) | 1.000 | 1.000 |
| Alanine aminotransferase (ALT) abnormal | 13/39 (33.3) | 23/39 (59.0) | 2/24 (8.3) | **0.006** | 0.125 |
| Aspartate aminotransferase (AST) abnormal | 28/39 (71.8) | 33/39 (84.6) | 10/24 (41.7) | 0.125 | **0.031** |
| Alkaline phosphate (ALP) abnormal | 19/39 (48.7) | 20/39 (51.3) | 12/23 (52.2) | 1.000 | 1.000 |

Data are presented as count *n*/*N* (%). Comparison between baseline and 1 week postoperation and 1 month postoperation was determined by McNemar test. A value of $p<0.05$ was considered significant.
*The *p* value of liver function-related biochemical indexes of patients from baseline to 1 week postoperation.
†The *p* value of liver function-related biochemical indexes of patients from baseline to 1 month postoperation.

**Table 6.** Liver Function Before and After Operation Following the Second Cycle Treatment of DEB-TACE or cTACE

| | Before Operation | 1 Week Postoperation | 1 Month Postoperation | *p* Value* | *p* Value† |
|---|---|---|---|---|---|
| Albumin (ALB) abnormal | | | | | |
| DEB-TACE | 10/12 (83.3) | 13/13 (100.0) | 10/11 (90.9) | **0.007** | **0.039** |
| cTACE | 8/9 (88.9) | 9/9 (100.0) | 7/8 (87.5) | **0.021** | 0.070 |
| *p* Value‡ | 1.000 | – | 1.000 | | |
| Total protein (TP) abnormal | | | | | |
| DEB-TACE | 3/12 (25.0) | 6/14 (42.9) | 6/11 (54.5) | 0.607 | 0.607 |
| cTACE | 2/9 (22.2) | 3/8 (37.5) | 3/8 (37.5) | 0.344 | 0.344 |
| *p* Value‡ | 1.000 | 1.000 | 0.650 | | |
| Total bilirubin (TBIL) abnormal | | | | | |
| DEB-TACE | 5/12 (41.7) | 7/14 (50.0) | 3/11 (27.3) | 1.000 | 0.344 |
| cTACE | 2/9 (22.2) | 7/8 (75.0) | 5/8 (62.5) | 1.000 | 0.774 |
| *p* Value‡ | 0.642 | 0.380 | 0.181 | | |
| Total bile acid (TBA) abnormal | | | | | |
| DEB-TACE | 2/8 (25.0) | 3/5 (60.0) | 4/8 (50.0) | 0.508 | 0.754 |
| cTACE | 5/7 (71.4) | 2/5 (40.0) | 2/6 (33.3) | 1.000 | 1.000 |
| *p* Value‡ | 0.132 | 1.000 | 0.627 | | |
| Alanine aminotransferase (ALT) abnormal | | | | | |
| DEB-TACE | 2/8 (25.0) | 9/14 (64.3) | 2/8 (25.0) | 0.607 | 0.289 |
| cTACE | 0/7 (0.0) | 5/8 (62.5) | 1/6 (16.7) | 0.774 | 0.070 |
| *p* Value‡ | 0.467 | 1.000 | 1.000 | | |
| Aspartate aminotransferase (AST) abnormal | | | | | |
| DEB-TACE | 6/8 (75.0) | 11/14 (78.6) | 5/8 (62.5) | **0.022** | 0.453 |
| cTACE | 2/7 (28.6) | 6/8 (75.0) | 4/6 (66.7) | 1.000 | 1.000 |
| *p* Value‡ | 0.132 | 1.000 | 1.000 | | |
| Alkaline phosphatase (ALP) abnormal | | | | | |
| DEB-TACE | 6/8 (75.0) | 8/14 (57.1) | 4/8 (50.0) | 0.109 | 0.687 |
| cTACE | 3/6 (50.0) | 4/8 (50.0) | 2/6 (33.3) | 1.000 | 1.000 |
| *p* Value‡ | 0.580 | 1.000 | 0.627 | | |

Data are presented as count *n*/*N* (%). Comparison between baseline and 1 week postoperation and 1 month postoperation was determined by McNemar test. Comparison between DEB-TACE group and cTACE group was determined by chi-square test. A value of $p<0.05$ was considered significant.
*The *p* value of liver function-related biochemical indexes of patients from baseline to 1 week postoperation.
†The *p* value of liver function-related biochemical indexes of patients from baseline to 1 month postoperation.
‡Comparison between DEB-TACE and cTACE at each visit.

**Table 7.** Safety Profile of First Cycle of DEB-TACE Treatment ($N=39$ Records)

| Parameters | *n* (%) |
|---|---|
| During DEB-TACE operation | |
| Pain | 21 (53.8) |
| Fever | 21 (53.8) |
| Nausea | 5 (12.8) |
| Vomiting | 5 (12.8) |
| Others | 2 (5.1) |
| 1 month after DEB-TACE operation | |
| Pain | 8 (20.5) |

invasion and poor liver function, leading to an extremely poor median survival, which is reported to be on the order of several months without any treatment[10,11]. To prolong the survival of these patients, systemic chemotherapy and sorafenib are now viewed as standard treatment options[12,13]. As an emerging type of TACE treatment, DEB-TACE has been shown to be efficient and capable of prolonging survival with less associated chemoembolization syndrome compared with cTACE. For this reason, we conducted this study to further investigate its potential in BCLC stage C patients[14–16].

In our study, the CR and ORR at 1 month after the first cycle of DEB-TACE were 5.1% and 66.7%, and after the second cycle of DEB-TACE or cTACE treatments the ORR was higher in patients treated by DEB-TACE. However, it should be noted that there was no difference regarding the total treatment responses after the second treatment cycles. The ORR in our study was higher than what has been previously reported in a study conducted on HCC patients in the intermediate and advanced stages using hepatic arterial infusion chemotherapy with fine powder cisplatin and iodized oil suspension. In this particular study, the overall response at 3 months was 23%[17]. Our study was not the first study to evaluate the efficacy of DEB-TACE in advanced liver cancer. In 2012, Kalva et al. conducted a retrospective cohort study on 80 patients with advanced HCC, and they demonstrated a CR of 2.5% and an ORR of 11.2% at 1 month after DEB-TACE using doxorubicin[18]. This level of clinical activity is much lower than what is reported in our present study. In another retrospective study, the treatment response was not assessed; however, a survival benefit was reported[19]. In addition, 12.8% patients in our study were ICC patients. Besides primary liver cancer, DEB-TACE is rarely used in ICC patients. In a retrospective study analyzing three prospective trials that focused on ICC patients treated by DEB-TACE, cTACE, and systemic chemotherapy, the CR and ORR in patients treated by DEB-TACE at 2 months post-treatment were 0.0% and 4.0%. These results are quite poor and probably due to the fact that ICC is considered to be an even more malignant disease when compared with primary liver cancer[20]. However, they observed that the disease control rate (DCR) was 46%[20]. The variable response rates may be explained by different patient eligibility criteria, different patient populations, and the use of different chemoembolization agents.

In general, advanced liver cancer patients have reduced liver function, which is often considered a key criteria used in the decision-making process before treatment. Underlying diseases, such as cirrhosis, viral hepatitis, or alcoholic hepatitis, contribute to the poor liver function, and they limit the treatment options for patients with advanced stage liver cancer. In this current study, the majority of liver function-related laboratory indexes worsened rapidly after the chemoembolization procedure and recovered at 1 month after the first cycle, while after the second cycle, most of the liver function-related indexes were similar to baseline level both at 1 week and 1 month postoperation. A single-center, retrospective

**Table 8.** Safety Profile Following Second Cycle Treatment of DEB-TACE or cTACE ($N=23$ Records)

| Parameters | DEB-TACE ($N=14$) *n* (%) | cTACE ($N=9$) *n* (%) | *p* Value |
|---|---|---|---|
| During operation | | | |
| Pain | 7 (50.0) | 4 (44.4) | 0.795 |
| Fever | 7 (50.0) | 3 (33.3) | 0.431 |
| Vomiting | 1 (7.1) | 1 (11.1) | 0.742 |
| Nausea | 0 (0.0) | 0 (0.0) | – |
| Others | 0 (0.0) | 0 (0.0) | – |
| 1 month after operation | | | |
| Pain | 0 (0.0) | 2 (22.2) | 0.142 |
| Fever | 0 (0.0) | 1 (11.1) | 0.391 |

Comparison between two groups was determined by chi-square test. A value of $p<0.05$ was considered significant.

study revealed a milder liver function index elevation in patients treated with DEB-TACE compared with cTACE, indicating that DEB-TACE might be a preferred approach for patients with impaired liver function, which is partly in line with the findings from our study[21]. Another study assessing the combination of TACE and sorafenib for HCC patients with portal vein tumor thrombus (PVTT) reported that liver function was worsened only in patients with PVTT in the main portal vein[22]. However, to our knowledge, there is still no definitive study that has evaluated the change of liver function in ICC patients receiving DEB-TACE. Our results suggest that DEB-TACE may have the advantage in protecting the liver function of advanced stage liver cancer patients. However, the AST levels worsened at 1 month after the first cycle, and ALB kept worsening after the second cycle. The probable explanations are as follows: there were 20.5% patients with Child–Pugh stage B disease who presented with high ALB and AST levels, indicating a decompensated liver function, and the indexes of these patients may not be able to recover.

After the first and second cycles of treatments, the most common AEs in our study were pain, fever, nausea, and vomiting, and all other AEs were relatively rare. Previous studies identified the embolization syndrome as the most frequent AE associated with DEB-TACE and cTACE. This syndrome is induced by the necrosis of tumor tissue and involves an inflammatory response, leading to abdominal pain, fever, nausea, and vomiting[23]. As to the safety profile of other standard therapies, a study using sorafenib combined with DEB-TACE shows the AEs were fatigue (94%), anorexia (67%), elevations in liver enzymes (64%), and dermatologic side effects (48%), and the overall incidence of AEs is increased when compared to what we have observed in our study[24]. In a single institutional retrospective study of 121 HCC patients in BCLC stage C receiving DEB-TACE, AEs were present in 30.2% of patients, and all AEs were no more than grade III as determined by the Common Adverse Event Evaluation Criteria (CTCAE). In a previous study, the incidence of nausea and vomiting was 7.8% and that of abdominal pain was 23.8%, all of which were grade I and II AEs, and no procedure-related deaths occurred within 1 month, which is consistent with our findings[19]. With respect to ICC patients, in a prior study evaluating the AEs in ICC patients treated by DEB-TACE, the majority of AEs were related to the chemoembolization syndrome with low CTCAE grades (CTCAE I–III)[20]. In our study, prophylaxis and treatment for the AEs were performed, and the results of AEs after each cycle of DEB-TACE or cTACE treatments reveal a favorable safety profile, which indicates that DEB-TACE is a safe and well-tolerated treatment strategy in patients with advanced stage liver cancer.

There were several limitations in this study: (1) the sample size was relatively small, which might lead to a relatively insufficient statistical power; (2) we only assessed short-term efficacy and liver function, and the long-term follow-up of patients should be expanded in future studies; and (3) as a single-center, retrospective cohort study, there may be some bias that might interfere with the results. Thus, a multicenter, prospective study with a larger patient sample size is needed to confirm the results of our study.

In conclusion, DEB-TACE is a clinically active and safe treatment option for patients with BCLC stage C liver cancer. Our findings provide the rationale for further studies investigating this transarterial chemoembolization treatment strategy either alone or in combination with other novel systemic therapies.

*ACKNOWLEDGMENTS: This study was supported by the National Natural Science Foundation of China (Grant Nos. 81371655 and 81571774) and the Natural Science Foundation of Guangdong Province, P.R. China (Grant No. 2014A030313171). The authors declare no conflicts of interest.*

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