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Time-to-progression following conventional compared with drug-eluting-bead transcatheter arterial chemoembolisation in patients with large hepatocellular carcinoma

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AIMS: To identify the optimal transarterial chemoembolisation (TACE) approach in patients with large hepatocellular carcinoma (HCC; >5 cm) by comparing conventional TACE (cTACE) and drug-eluting-bead (DEB)-TACE.

MATERIALS AND METHODS: This retrospective study included 63 consecutive HCC patients who received TACE at a single medical centre from September 2009 to October 2015. Primary endpoints were 3-year overall survival (OS) rate and time-to-progression (TTP). Hazard ratios (HRs) from Kaplan–Meier curves were calculated to compare survival estimates.

RESULTS: The median OS was shorter in the cTACE group, but was not significantly different from the DEB-TACE group (33.9 versus 35.6 months, respectively; p=0.52). The mean TTP was shorter in the cTACE group than in the DEB-TACE group (13.9 versus 17.5 months, respectively; p=0.01). There was no difference in 3-year survival (HR=0.95, 95% confidence interval [CI]: 0.51–1.78; p=0.880) and TTP (HR=0.70, 95% CI: 0.42–1.16; p=0.147) between the groups; however, patients treated with DEB-TACE were more likely to have longer TTP in the first 2 years following treatment (HR=0.51, 95% CI: 0.29–0.88; p=0.009).

CONCLUSION: Although DEB-TACE is not superior in terms of TTP or OS in patients with large HCC, it may have greater efficacy in the first 24 months following therapy.

Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy worldwide,[1] with more than 700,000 new cases diagnosed each year.[2,3] It is also the third leading cause of cancer-related death worldwide and in China,[4,5] where approximately 50% of the cases and deaths occur.[1] The Barcelona Clinic Liver Cancer (BCLC) staging guidelines are currently used for both HCC staging and treatment decisions, and are recommended by both the American Association for the Study of Liver Diseases (AASLD)[6] and the European Association for the Study of the Liver (EASL).[7] Improved clinical surveillance strategies have increased the detection rate of small HCC, and surgical resection is

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currently recommended for these patients (BCLC stage A, tumours of ≤5 cm or three nodules of <3 cm each); however, up to one-third of patients present with large HCC (single tumour of >5 cm diameter) at diagnosis.[8]

The management of large HCC represents a unique challenge as there are no universally recognised guidelines.[8] For HCC patients with a single tumour >5 cm in diameter (intermediate stage[9]), surgical resection remains the primary option according to EASL guidelines[7]; however, for patients with a single tumour >5 cm and portal hypertension, decreased liver function, or an unresectable tumour, transarterial chemoembolisation (TACE) is recommended, and has been shown to improve patient survival,[10] even in those with tumours >10 cm in diameter.[11] Conventional TACE (cTACE) selectively obstructs tumour-feeding arteries, leading to ischaemic necrosis of the target tumour via cytotoxic and ischaemic effects.[12] Drug-eluting beads (DEBs) have been introduced as novel drug-delivering agents for TACE (DEB-TACE), and produce higher concentrations of chemotherapeutic drugs in the target tumour and lower systemic concentrations as compared with cTACE.

Despite the theoretical advantages of DEB-TACE, it is still undetermined if DEB-TACE is superior to cTACE with respect to overall survival (OS) and treatment response. Recent meta-analyses have reported that DEB-TACE provides a significantly better tumour response compared with cTACE: 1-, 2-, and 3-year OS is superior with DEB-TACE with the same safety profile as cTACE.[13,14] In contrast, other studies,[15–17] as well as a meta-analysis that included 12 studies and 1,449 patients,[18] failed to demonstrate the superiority of DEB-TACE over cTACE in terms of treatment efficacy, although DEB-TACE appeared to be safer with fewer complications than cTACE.[17,19] Furthermore, Lee *et al.*[17] showed that the median time-to-progression (TTP) in patients treated with cTACE was longer than in those receiving DEB-TACE (13.3 versus 10.8 months, respectively; $p=0.023$). The discrepancies in these reports may be due to differences of disease stage and length of follow-up. Specifically, in a randomised controlled trial comparing cTACE with DEB-TACE, the response at 6 months was comparable overall; however, patients who were Child–Pugh class B, had an Eastern Cooperative Oncology Group (ECOG) performance score of 1, had bilobar disease, and recurrent disease had a significantly increased objective response rate.[20]

Because the treatment efficacy of cTACE has not been compared with DEB-TACE in patients with large HCC, this retrospective cohort study was undertaken to compare the efficacy of DEB-TACE to cTACE in the management of treatment-naive HCC patients with large tumours (>5 cm).

Materials and methods

Study participants

This retrospective study included 63 consecutive HCC patients who received TACE at a single medical centre from September 2009 to October 2015. This study was approved by the Institutional Review Board. The informed patient consent requirement was waived due to the retrospective study design.

The primary endpoints were 3-year survival rate and TTP. Prior to receiving TACE, the following baseline assessments were conducted in all patients: medical history, physical examination, laboratory assessments, and imaging analyses, including contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Demographic data, the presence of chronic hepatitis viral infection, tumour number/size/classification (BCLC stage) and clinical stage (Child–Pugh) were collected from the patients' medical records.

The inclusion criteria were: (1) ≥18 years of age; (2) diagnosis of HCC on the basis of histopathology or non-invasive criteria; (3) one or more tumour that was treatment-naive and >5 cm in diameter; (4) BCLC stage B; (5) ECOG performance score of 0 or 1; (6) serum creatinine <1.2 mg/dl (normal range, 0.6–1.2 mg/dl); (7) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <200 IU/l (normal range, 0–40 IU/l and 0–45 IU/l, respectively); and (8) total bilirubin <3 mg/dl (normal range, 0.1–1 mg/dl). Exclusion criteria were: (1) tumour invasion of the portal vein, hepatic vein, or biliary duct; (2) a tumour with an extrahepatic arterial supply; and (3) atypical HCC (e.g., infiltrative).

Treatment

Treatment was conducted as previously described.[19] Patients were treated with one cycle of either cTACE with a gelatin sponge or chemoembolisation with doxorubicin-loaded DEB (DEB-TACE; DC Beads; Biocompatibles, Farnham, UK). The choice of treatment was selected by the patient once the attending physician explained the tumour response and complication rates of each treatment.

To evaluate the vascular anatomy and portal flow, diagnostic angiographic of the coeliac trunk, superior mesenteric artery, and hepatic artery was performed on the treatment day. Super-selective angiography was then performed to catheterise the segmental or subsegmental arteries of the tumour. In patients in whom the right hepatic artery arose from the superior mesenteric artery, the right hepatic artery was selected. In cases where the phrenic artery was suspected of supplying the target tumour, it was further analysed.

Patients in the cTACE group were treated with a Lipiodol/doxorubicin mixture consisting of 50 mg of doxorubicin mixed with 10 ml of Lipiodol to achieve a consistent concentration. The Lipiodol/doxorubicin mixture was injected into a segmental or subsegmental artery followed by injection of 500–750 μm gelatin sponges (Spongostan Standard, Johnson & Johnson, Gargrave, Skipton, UK). The amount injected was based on tumour diameter.[21]

Patients in the DEB-TACE group were treated with 2 ml of DEB (300–500 μm in diameter) loaded with 70 mg of doxorubicin.[22] In the event that "near-stasis" was not achieved following the first dose of DEB, an additional volume of DEB was injected until the contrast column was found

clear within 2–5 heartbeats.[23] The amount of beads recommended by the manufacturer was used, and 300–500 μm DEB was used as 100–300 μm beads have not been approved in the Republic of China. After drug binding, the beads shrunk to 240–400 μm in size (i.e., close to the size of the embospheres).

Response evaluation and follow-up

Patients received triple-phase contrast-enhanced CT at 3 months following the procedure as recommended by the modified Response Evaluation Criteria in Solid Tumours (mRECIST).[24] Tumour response assessment was performed every 2–4 months, with follow-up every 3 months in cases with a partial response (PR; ≤30% decrease in the sum of the diameters of the visible target lesions) or stable disease by mRECIST criteria. In cases of progressive disease, another treatment was administered according to BCLC guidelines and disease status.[25] Complete response (CR) was defined as the disappearance of any intra-tumour enhancement on CT. Because target and non-target lesions were simultaneously treated, target tumour response was not separated from the overall tumour response. Progressive disease was defined as at least a 20% increase in the sum of the diameters of the visible target lesions, and stable disease was defined as any case that did not meet the definition of either PR or progressive disease.[24] All images were evaluated by two experienced radiologists, who resolved discrepancies in consensus.

Statistical analysis

Continuous variables were presented as mean and standard deviation, and categorical variables were presented as count and percentage and tested by thechi-square or Fisher's exact test. The Mann–Whitney *U*-test was used to examine differences between groups when data were non-normally distributed, and the *t*-test was used for normal distributed data. Kaplan–Meier curves were used to compare the 3-year survival rate and TTP of the cTACE and DEB-TACE groups. Differences of Kaplan–Meier curves between two groups were tested by the log-rank test. The effect of DEB-TACE compared to cTACE on 3-year survival and TTP was evaluated by Cox proportional hazard regression analysis. The significance level was set as a two-sided value of $p<0.05$. All statistical analyses were performed with SAS® version 9.4 (Windows NT version, SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 63 HCC patients were included in the analysis: 32 patients were treated with cTACE and 31 treated with DEB-TACE. Patient baseline characteristics are summarised in Table 1. No differences in age, sex, previous treatment, and hepatitis B virus (HBV) and hepatitis C virus (HCV) status were detected between the two groups. Although

Table 1
Patient characteristics.

	cTACE (n=32)	DEB-TACE (n=31)	*p*-Value[a,b]
	Mean ± SD		
Age, years	65.8±10.2	65.6±11.7	0.93[c]
GOT	97.9±81.7	92.7±59.4	0.59
GPT	108.1±162.7	72.9±41.5	0.45
Bilirubin	0.7±0.4	0.8±0.4	0.39
AFP	2721.1±10722.5	2025.5±5271.8	0.58
Albumin	3.9±0.5	3.9±0.5	0.69[c]
Largest target lesion, cm	7.5±2.4	8.5±3.6	0.43
Overall survival time, months	33.9±26.9	35.6±23.0	0.52
Time-to-progression, months	13.9±16.1	17.5±15.0	0.01[d]
Procedure time	56.3±12.9	63.3±10.9	0.02[c,d]
	Number (%)		
Sex			
Female	9 (28.13%)	12 (38.71%)	0.37[d]
Male	23 (71.88%)	19 (61.29%)	
Previous treatment			
None	32 (100%)	29 (93.55%)	0.24
Operation	0 (0%)	2 (6.45%)	
Uni-/bilobar			
Unilobar	17 (53.13%)	9 (29.03%)	0.05[d]
Bilobar	15 (46.88%)	22 (70.97%)	
HBV/HCV			
Negative	7 (21.88%)	3 (9.68%)	0.15
HBV	12 (37.50%)	20 (64.52%)	
HCV	10 (31.25%)	5 (16.13%)	
HBV+HCV	3 (9.38%)	3 (9.68%)	
Ascites			
No ascites	30 (93.75%)	27 (87.1%)	0.43
Mild ascites	2 (6.25%)	4 (12.9%)	
PVT			
No PVT	32 (100%)	30 (96.77%)	0.49
PVT not involving the main and first-order branch	0 (0%)	1 (3.23%)	
Child–Pugh score			
5	25 (78.13%)	24 (77.42%)	1.00
6	6 (18.75%)	5 (16.13%)	
7	1 (3.13%)	2 (6.45%)	
BCLC			
B1	5 (15.63%)	3 (9.68%)	0.78
B2	26 (81.25%)	26 (83.87%)	
B3	1 (3.13%)	2 (6.45%)	
Tumour number			
1	6 (18.75%)	7 (22.58%)	0.72
2	7 (21.88%)	5 (16.13%)	
3	2 (6.25%)	2 (6.45%)	
4	1 (3.13%)	3 (9.68%)	
5	4 (12.5%)	1 (3.23%)	
≥6	12 (37.5%)	13 (41.94%)	
Pain during procedure			
No	25 (78.13%)	28 (90.32%)	0.32
Yes	7 (21.88%)	3 (9.68%)	
PES: abdominal pain			
No	19 (59.38%)	27 (87.10%)	0.01[d,e]
Yes	13 (40.63%)	4 (12.90%)	
PES: nausea/vomiting			
No	22 (68.75%)	28 (90.32%)	0.03[d,e]
Yes	10 (31.25%)	3 (9.68%)	
PES: low-grade fever			
No	21 (65.63%)	26 (83.87%)	0.09
Yes	11 (34.38%)	5 (16.13%)	
Major complication: severe abdominal pain			
No	26 (81.25%)	31 (100%)	0.02[d]
Yes	6 (18.75%)	0 (0%)	

(*continued on next page*)

Table 1 (*continued*)

	cTACE (n=32)	DEB-TACE (n=31)	*p*-Value[a,b]
	Mean ± SD		
Major complication: fever[f]			
No	28 (87.50%)	30 (96.77%)	0.35
Yes	4 (12.50%)	1 (3.23%)	

GOT, glutamate oxaloacetate transaminase; GPT, glutamic pyruvic transaminase; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; PVT, portal vein thrombosis; BCLC, Barcelona Clinic Liver Cancer; PES, post-embolisation syndromes.

[a] Mann–Whitney *U*-test.

[b] Fisher's exact test.

[c] *t*-Test.

[d] Statistically significant difference between groups ($p<0.05$).

[e] Chi-square test.

[f] Need antibiotics drug for treatment.

patients in both groups had similar portal vein thrombosis (PVT) status, Child–Pugh score, BCLC stage, and number of tumours, the mean TTP was shorter in the cTACE group than in the DEB-TACE group (13.9 versus 17.5 months, respectively; $p=0.01$). Although the OS time was also shorter in the cTACE group, the difference from the DEB-TACE group did not reach statistical significance (33.9 versus 35.6 months, respectively; $p=0.52$). In addition, a greater proportion of patients in the cTACE group had unilobar involvement, while a greater proportion of patients in the DEB-TACE group had bilobar HCC ($p=0.05$; Table 1). Patients in the DEB-TACE group had a significantly longer procedure time, and lower proportion of post-embolisation syndromes (PES) including abdominal pain, nausea/vomiting, and the major complication, severe abdominal pain, as compared to cTACE group.

OS and TTP analysis

Results of the Kaplan–Meier analysis and log-rank tests for the 3-year OS and TTP are shown in Fig 1. The 3-year OS rate was 37.5% in the cTACE and 35.5% in the DEB-TACE group. The 3-year TTP rate was 3.2% in the cTACE group and 3.5% in the DEB-TACE group. Thus, there was no significant difference in 3-year OS (hazard ratio [HR]=0.95, 95% confidence interval [CI]: 0.51–1.78; $p=0.880$) and TTP (HR=0.70, 95% CI: 0.42–1.16; $p=0.147$) between the treatments.

To determine if DEB-TACE impacts patient outcomes sooner in the disease course, 2-year TTP was further examined by log-rank tests. The 2-year TTP rate was 3.7% in the cTACE group and 4.1% in the DEB-TACE group (Fig 2). Thus, patients treated with DEB-TACE were more likely to have longer TTP in the first 2 years following treatment as compared to those treated with cTACE (HR=0.51, 95% CI: 0.29–0.88; $p=0.009$).

Discussion

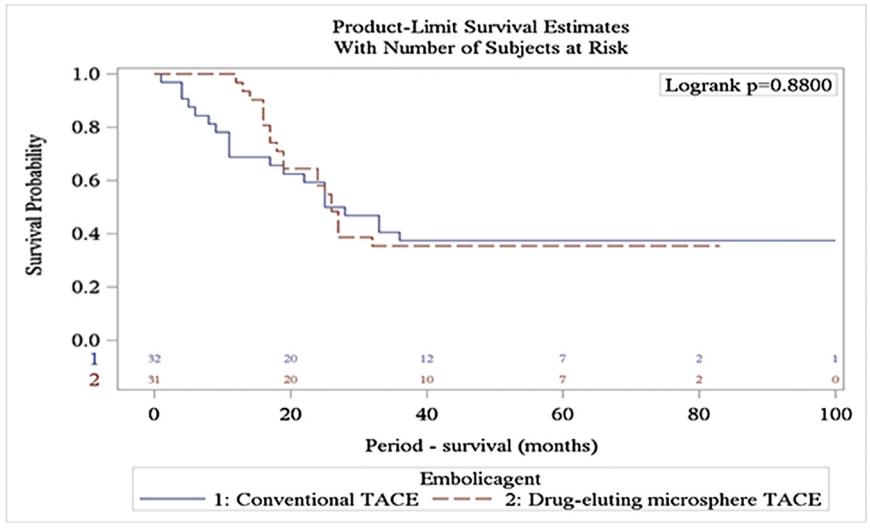
Because the benefit of DEB-TACE over cTACE is controversial, with some studies reporting significantly better patient outcomes,[13,14] while others report no such superiority,[15–18] this study aimed to compare the efficacy of DEB-TACE to cTACE in treatment-naive patients with large HCC (>5 cm). There was no statistical difference in 3-year OS and TTP between the cTACE and DEB-TACE groups, which is consistent with previous studies showing similar clinical efficacy between the approaches[15–18,26] irrespective of tumour size or BCLC stage[17]; however, analysing the 2-year TTP showed that it was longer in patients treated with DEB-TACE. Thus, treatment with DEB-TACE may only be superior within the first 24 months following therapy.

The TTP differences with cTACE and DEB-TACE between the 2- and 3-year time points observed in the present study are consistent with relapse-free survival (RFS) rates reported in a recent meta-analysis of 16 studies that included a total of 1,832 patients.[13] Specifically, patients treated with DEB-TACE had significantly higher 1- and 2-year RFS rates; however, there was no difference in the 3-year RFS rates.[13] Similarly, another meta-analysis of seven studies and 700 patients found significant 1- and 2-year survival benefits with DEB-TACE; however, the 6-month and 3-year survival rates were similar between the groups, leading the authors to conclude that DEB-TACE may not truly be superior.[14]

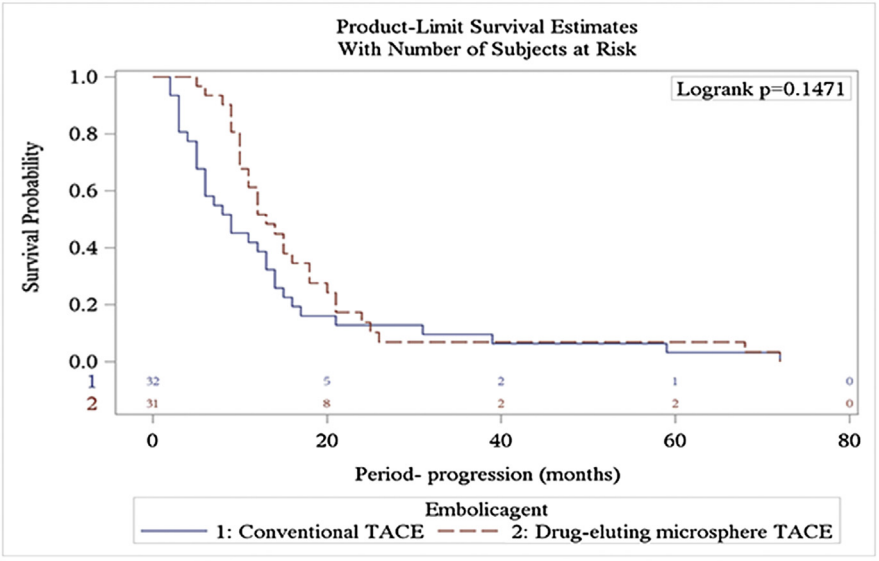
In the present study, the mean survival time was longer in the DEB-TACE group than in the cTACE group, although the difference did not reach statistical significance (35.6 versus 33.9 months, respectively). These survival times are similar to those in another study comparing cTACE with DEB-TACE in Korean patients; those with tumours >5 cm had a median OS of 36.3 versus 33.4 months, respectively.[17]

We also found that the mean TTP was significantly shorter in the cTACE group than in the DEB-TACE group (13.9 versus 17.5 months, respectively). Although these results are in contrast with those of Lee *et al.*,[17] in which the TTP of patients with tumours >5 cm in the cTACE group was similar to the present study (13.4 versus 13.9 months, respectively). On the other hand, the Precision Italia study randomised 177 patients with HCC unsuitable for curative treatment or had failed/recurred after resection/ablation to receive either cTACE or DEB-TAC.[27] Patients were followed for 2 years or until death. Local and overall tumour response was the same in both groups, and the median TTP was 9 months in both groups. The 1- and 2-year survival rates were 86.2% and 56.8% after DEB-TACE and 83.5% and 55.4% after cTACE ($p=0.949$). The only benefit of DEB-TACE noted was less procedural pain. The longer TTP at 2-years following DEB-TACE observed in the present study may be meaningful, especially in the context of additional treatments, including resection, radiotherapy, and radiofrequency ablation. Indeed, initial TACE may be useful in selecting patients for whom surgical resection may offer additional survival benefits.[28] Given the impact of additional treatments on the survival outcomes of patients, especially those with tumours >10 cm,[11] further studies are required to determine the effect of additional treatments.

Selecting the optimal therapeutic approach for patients with solitary HCC ≥5 cm is important, as either surgical resection or TACE may be viable options. A recent meta-analysis that included 861 patients in four studies showed that surgical resection resulted in better OS and greater TTP



(a)



(b)

Figure 1 Kaplan–Meier curves of (a) 3-year OS and (b) TTP.

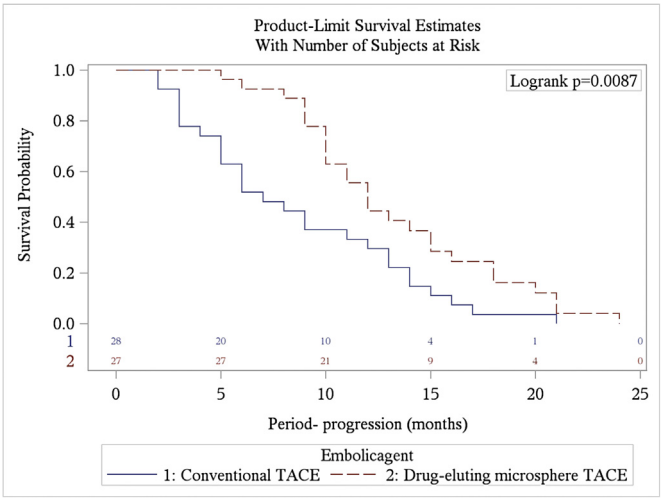


Figure 2 Kaplan–Meier curve of 2-year TTP.

as compared to TACE.[29] Similarly, patients with solitary large HCC treated with surgical resection had better 1-, 3-, and 5-year OS rates[8,30] and longer TTP[30] as compared to those treated with TACE. Following propensity score matching, the authors claimed that both therapies were similar in terms of OS, but not TTP[30]; however, further studies with larger samples sizes are required to confirm the findings.[31] Thus, although the present study found no differences in the 2- and 3-year OS and TTP between cTACE and DEB-TACE, these therapies should be considered only in those patients for whom surgical resection is not an option. Further studies are required to examine the clinical efficacy of combining both strategies for patients with large HCC.

In addition to its retrospective design, the present study is limited by its small sample size. In addition, all of the patients were treated at a single centre, and objective response rates and adverse events were not analysed. In addition, neither the costs of the two procedures nor the

cost-effectiveness were compared (for example, is one treatment associated with more recurrences and follow-up procedures than the other, making the overall cost higher).

In conclusion, DEB-TACE is not superior to cTACE with respect to OS or TTP in patients with large HCC; however, DEB-TACE may have greater efficacy in the first 24 months following therapy, which may be clinically significant in the context of additional treatments (e.g., surgical resection). Further studies are required to determine if specific combination strategies are superior in terms of efficacy for HCC patients with tumours >5 cm.

Conflict of interest

There is no conflict of interest.

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