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Original Article

Transarterial chemoembolization using callispheres beads in hepatocellular carcinoma therapy

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Abstract: CalliSpheres beads are frequently used in Chinese hepatocellular carcinoma (HCC) patients during transarterial chemoembolization (TACE) procedure. However, the effects of CalliSpheres beads in HCC therapy are still less reported. This study was to examine the efficacy and safety of CalliSpheres beads in HCC treatment. A total of 119 HCC patients were included in this comparative study from June 2016 to June 2017. Among them, 65 patients received conventional TACE using iodized oil and 54 patients treated with TACE using CalliSpheres beads. The clinical efficacy, adverse events, and overall survival were assessed. There were no significant differences for the baseline characteristics, such as gender and overall status. However, higher clinical responses in patients treated with TACE using CalliSpheres beads were observed when compared with cTACE group. Besides, most common complications were lighter in patients using CalliSpheres beads. Patients treated with CalliSpheres beads had a median survival of 14.0 months, which was longer than cTACE group with a median survival of 10.0 months (P = 0.032). The present study supports the use of CalliSpheres beads in TACE treatment for HCC patients due to its higher responses, lighter complications, and the survival benefit compared with cTACE.

Keywords: Hepatocellular carcinoma (HCC), Callispheres beads, TACE

Introduction

Hepatocellular carcinoma (HCC) is a type of fatal cancer, which emerges as a worldwide health problem [1]. Despite patients with hepatitis B were identified as risk predictor, over 50% HCC patients developed to the intermediate/advanced stage when diagnosed [2]. Currently, there are two therapy choices commonly used for HCC patients including hepatic resection and liver transplantation [3]. However, high recurrence rate limits their use for HCC treatment. Moreover, surgical resection is unsuited for most patients at advance stage. Therefore, it's crucial to develop a novel treatment strategy for patients with HCC.

Transarterial chemoembolization (TACE) is an optimized treatment choice for HCC, which blocks tumor-feeding vessels and then leads to ischemia and necrosis of tumors [4, 5]. Conventional TACE (cTACE) was well established by diluting emulsified chemotherapeutic drug (e.g., doxorubicin) with lipiodol. Then, the suspension was injected into the hepatic artery supplying the tumor. However, cTACE usually leads to systemic toxicity due to a peak of chemotherapy drug in the circulation after injection [6]. Recently, some micro-beads were developed, which release anti-cancer drugs slowly in a sustained and steady manner after drugs were injected [7]. To date, a number of clinical studies reported that TACE using beads to absorb/release drugs is a more effective way for HCC treatment; Moreover, such method as a lower incidence of complications when compared with cTACE using lipiodol [8, 9]. CalliSpheres beads, the first commercial beads in China, have been widely used since 2016 [10, 11]. Chemotherapeutic drugs with positive charge can be easily loaded on CalliSpheres beads depending on its negatively charged functional groups [10].

Although most studies have reported that HCC patients undergo TACE treatment have apparent survival benefit, studies evaluating the efficacy and safety of CalliSpheres beads are still limited. To clarify the benefit of TACE treatment using CalliSpheres beads for Chinese HCC patients, the present study performed a retrospective study to evaluate the efficacy, safety and short-term benefits using CalliSpheres beads.

Methods

Patients

This study included two parallel treatment groups: patients received cTACE treatment using iodized oil (N = 65) and patients received TACE treatment using CalliSpheres beads (N = 54). The present research was performed in accordance with the Declaration of Helsinki. This study was approved by the institutional review board at Bengbu Medical College. Written informed-consent forms were obtained from all study participants before entering the study.

The diagnosis of HCC was strictly according to the diagnostic criteria used by the European Association for the Study of the Liver. Clinical data including imaging, serum biochemical parameters, and pathological information were recorded. The TACE surgery was performed during June 2016 to June 2017, and the follow up deadline was 22 December 2018. The inclusion criteria were: (1) aged > 18 years; (2) primary TACE treatment; (3) cancer without obvious distant metastases; (4) Child-Pugh classification with A or B. The following exclusion criteria were adopted: (1) predicted survival time < 3 months; (2) without complete laboratory data or histological grading information; (3) serious portal vein embolizationor fistulas; (4) other systemic disease or uncontrolled infection. After adopted the criteria above, this retrospective research finally included a total of 119 patients (cTACE vs. TACE using CalliSpheres beads = 65:54).

TACE treatment

cTACE was conducted by injecting 80 mg Pirarubicin emulsified with iodized oil into the tumor-supplying vessels as described previously [12]. For TACE using CalliSpheres beads (Hengrui Medicine, Jiangsu, China), microbeads ranged from 300-500 μm or 100-300 μm were used as carrier to absorb and release chemotherapy drugs. Briefly, CalliSpheres beads were diluted with above anti-tumor drugs to allow them fully load drugs. Subsequently, a non-ionic organic, e.g. iodine alcohol contrast medium, was added to the emulsified solution with an equal volume before injection.

Clinical response assessment

After TACE treatment, CT or MRI examination was conducted every 2 months to evaluate the tumor response. The modified response evaluation criteria in solid tumors (mRECIST) guideline was introduced to measure efficacy after treatment [13]. Treatment response was measured by comparing the tumor lesions and sizes pre-TACE to the post-TACE procedure within 4 months. The endpoint of complete remission (CR): the disappearance of arterial for target lesions. Partial remission (PR): > 30% decrease in the sum of diameters for target lesions. Overall response (OR): the sum of CR and PR. Progression of disease (PD): > 20% increase in the sum of the diameters of target lesions. The imaging evaluation results were independently made by two experienced radiologists in our hospital. For those patients undergo several cycles of TACE treatment in cases with tumor progression, only the first cycle TACE treatment outcome was recorded for further analysis.

Safety evaluation

Common complications including nausea, vomiting, fever, and ascites after treatment were recorded. The effect of TACE on liver function were evaluated by measuring serum ALT, GGT, AST, and TBiL levels at 1 week and 1 month post-TACE procedure. Pain visual analogue scale (VAS) score was used to assess the severity of pain [14]. Adverse events within 30 days were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version [15].

Statistical analysis

All parameters collected were presented as count (percentage), median (25th-75th) or mean ± standard deviation. The difference between two groups was analyzed using *t* test or Chi-square test. The overall survival (OS)

Table 1. Comparison of baseline clinical characteristics of study participants

Variables	cTACE (N = 65)	CalliSpheres (N = 54)	*P* value
Gender			0.93
Male	55	46	
Female	10	8	
Age (years)	56 ± 13	57 ± 11	0.65
Child-Pugh stage			0.64
A	52	45	
B	13	9	
BCLC stage			0.51
A	23	16	
B	42	38	
Alcohol			0.88
Yes	32	21	
No	33	23	
HBV			0.69
Yes	35	23	
No	30	31	
HCV			0.50
Yes	10	8	
No	55	46	
WBC (10^9/L)	6.73 ± 3.06	5.94 ± 2.43	0.20
Neutrophil (10^9/L)	4.64 ± 2.58	3.81 ± 2.02	0.11
AFP (IU/mL)			
Abnormal	48	44	0.38
ALT (U/L) (median, Q1-Q3)	42.5 (22.3-79.0)	43.5 (22.8-62.5)	0.91
AST (U/L) (median, Q1-Q3)	53.0 (35.5-69.7)	62.5 (36.2-106.3)	0.24
TBIL (μmol/L)	14.91 ± 5.51	15.68 ± 7.61	0.68
GGT (U/L)	137.5 (87.5-191.5)	144.5 (74.7-208.2)	0.75
Albumin	37.97 ± 5.44	37.55 ± 5.41	0.74

Data were presented as count, mean ± standard deviation or median (25th-75th). BCLC: Barcelona Clinic Liver Cancer; HBV: Hepatic b virus; HCV: Hepatic c virus; WBC: While blood cell; AFP: Alpha fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; GGT: Glutamyl transpeptidase.

time between different TACE treatments were determined using the log-rank test, and then graphed with Kaplan-Meier curve. All the statistical analyses were conducted using SPSS 16.0. *P* value < 0.05 was defined as statistically significant.

Results

Baseline characteristics of HCC patients

From June 2016 to June 2017, a total of 397 patients with HCC treated in our hospital were recorded. According to strict exclusion criteria adopted above, 198 patients were excluded, e.g. portal vein thrombus or fistulas (N = 73), serious distal metastases (N = 59), artery-venous fistulas (N = 34), coagulation disorders (N = 8), and severe live injury (N = 24).

The clinic pathological characteristics and laboratory indexes were presented in **Table 1**. In this retrospective study, 54 patients (males vs. females = 46:8) were treated by TACE using CalliSpheres beads and 65 patients (males vs. females = 55:10) treated by cTACE. The two TACE treatment groups have no significant difference regarding Child-Pugh classification, BCLC stage and hepatic virus infection history before treatment. Among the 119 patients, 57 (47.9%) patients received subsequent treatment after the first cycle of TACE treatment (cTACE group *vs.* TACE using CalliSpheres beads group = 35:22).

Complications

One week after treatment, almost all patients presented with clinical related complications, such as fever. 81.5% patients treated with cTACE and 68.5% patients treated with TACE using CalliSpheres beads presented with pain after treatment. Another common adverse effect observed was transient liver injury, which occurred higher in TACE group using CalliSpheres beads (98.1%) than cTACE group (96.9%). However, the incidence of pain and nausea were significant lower in the TACE group using CalliSpheres beads (**Table 2**). No significant difference for the incidence of other adverse effects was observed, such as coughing and ascites.

Liver function changes after treatment

Then, the differences for the laboratory parameters pre and post-treatment related liver injury

Table 2. Comparison of complications induced by TACE therapy

Complications	cTACE	CalliSpheres-TACE	*P* value
Fever	65 (100%)	54 (100%)	1
Pain	53 (81.5%)	37 (68.5%)	0.005
Coughing	4 (6.15%)	2 (3.70%)	0.515
Nausea	55 (84.6%)	28 (51.9%)	< 0.001
Ascites	12 (18.5%)	7 (13.0%)	0.415
Transient liver injury	63 (96.9%)	53 (98.1%)	0.008

Data were presented as count (%).

were compared. Before treatment, there was no significant difference for liver function parameters between the two TACE groups. Except GGT, the levels of ALT, AST and TBIL were significantly higher compared to those at baseline within 1 week post-treatment (**Figure 1**). However, liver function parameters were improved at 1 month after the TACE procedure.

Response to therapy

As shown in **Table 3**, the tumor response to TACE treatment was evaluated within 6 months. For the TACE group with CalliSpheres beads, the OR rates was 74.1%, among which 21 achieved PR. In addition, 19 (35.2%) patients showed a CR after treatment (**Figure 2**). For the cTACE group, 3 patients achieved CR and 22 achieved PR. Most of patients received cTACE treatment had progressive disease with PD rate of 61.5%. Overall, the tumor response rate within 6 months was significantly higher in the TACE group using CalliSpheres beads when compared to the cTACE treatment.

Survival benefit analysis

Through the clinical records examination, 38 patients including 15 patients treated using the CalliSpheres beads and 23 patients treated by cTACE were expired (P = 0.38). The longest and shortest follow-up time was about 30 and 18 months. The OS rates at 1 and 2 year in the cTACE group were 34.7% and 8.9%, respectively. For patients treated with CalliSpheres beads, OS rate at 1 and 2 year reached 50.6% and 14.6%, respectively. Then, Kaplan-Meier curves were performed to evaluate OS rates (**Figure 3**). An improved median overall survival for patients with TACE treatment using CalliSpheres beads (14.0 months) was observed compared with patients treated with cTACE (10.0 months) (P = 0.032).

Discussion

This study compared TACE using CalliSpheres beads with cTACE in HCC treatment according to tumor response, complications, and the short-term survival benefits. Our data showed that TACE procedure using CalliSpheres beads achieved lower adverse effect rates. Besides, tumor response was higher in TACE group with CalliSpheres beads. Based on our follow-up results, it was demonstrated that CalliSpheres beads group has a longer OS than the cTACE group. Overall, this retrospective study showed that HCC patients treated with TACE treatment using the novel CalliSpheres beads achieved a better efficacy and safety than cTACE treatment.

CalliSpheres beads load chemotherapeutic reagents and then release anti-cancer drugs continuously with a constant concentration [16]. Compared with cTACE, several studies related with HCC therapy had reported a lower toxicity using drug-eluting beads (DEB) [17, 18]. cTACE is gradually replaced by TACE using DEB in HCC treatment, especially for advanced-stage patients [19, 20]. For example, a cohort study in Asian demonstrated that an improvement in OS was observed when unresectable HCC patients were treated with TACE using DEB [21]. In addition, a bigger population study included 212 patients showed that HCC patients received TACE treatment using micro-beads reached a CR of 26.8%, and a PR of 46.3% at 6 months [22]. Importantly, most studies elucidated that the overall incidence of adverse events was significantly decreased in DEB-TACE group than that in cTACE group [23, 24]. These results together demonstrated that TACE therapy using DEB has the lower complications and higher efficacy in the HCC treatment. However, there are still conflict results for the efficacy and safety of cTACE *vs.* DEB-TACE according to previous studies [25, 26]. Several reasons may account for such consistent results including the sample size analyzed and different stages of HCC patients enrolled.

The observational study compared the effects of lipiodol and CalliSpheres beads in the HCC

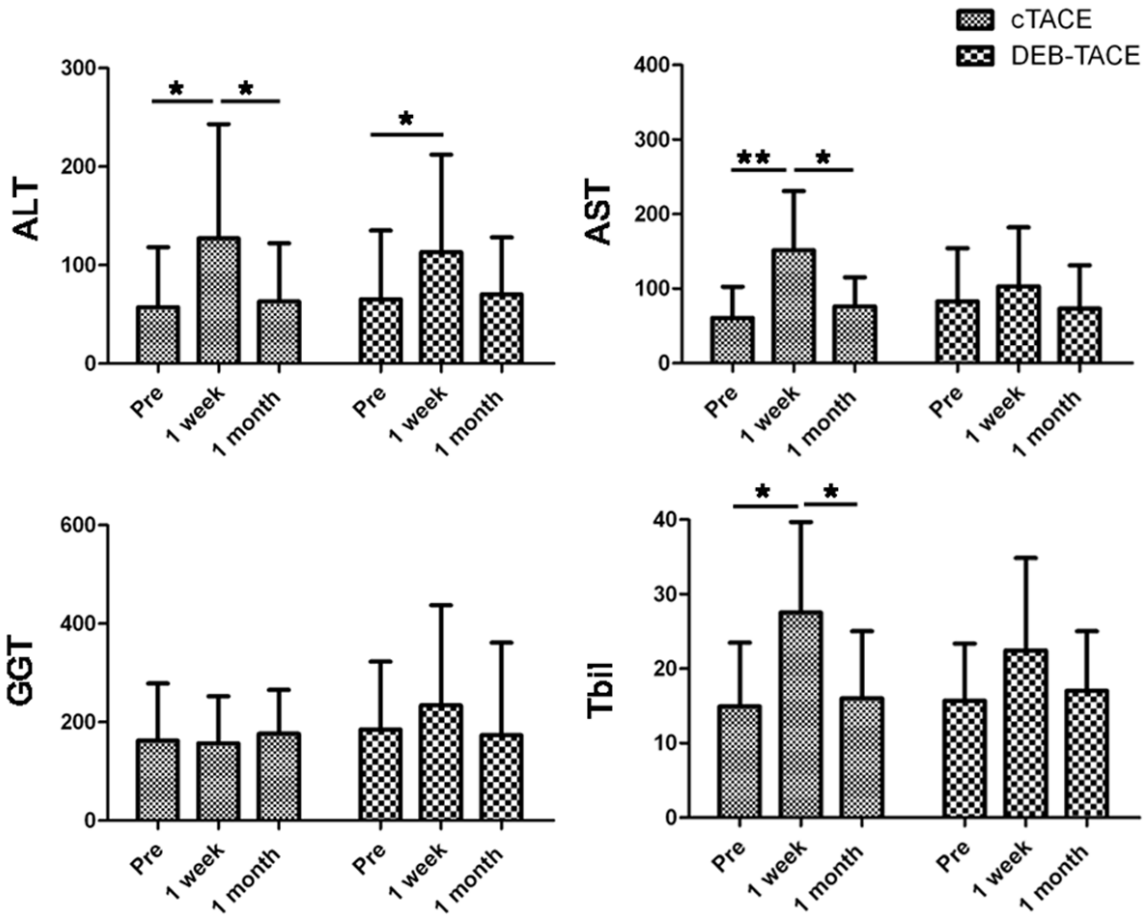

Figure 1. The liver functional parameters in patients with HCC treated with cTACE and TACE using CalliSpheres beads pre and post-treatment. *represents P < 0.05, **represents P < 0.01.

Table 3. Tumor response at 6 months after treatment

	cTACE	CalliSpheres-TACE	*P* value
CR	3 (4.6%)	19 (35.2%)	< 0.01
PR	22 (33.8%)	21 (38.9%)	0.57
OR	25 (38.5%)	40 (74.1%)	< 0.01
PD	40 (61.5%)	14 (25.9%)	< 0.01

Data were presented as count (%). CR: complete response; PR: partial response; OR: objective response; PD: progressive disease.

treatment. CalliSpheres beads were recently developed to load anti-cancer drugs based on the negatively charged groups [27]. As the first DEB, CalliSpheres beads were widely used in clinical practice in China [11, 27]. A previous study has compared the pharmacokinetics of TACE procedure using lipiodol or CalliSpheres beads in animal experiment [28]. Their results also supported the concept that CalliSpheres beads could prolong and sustain chemotherapeutic drugs release at a constant concentration as far as 200 μm at least 1 month around the micro-beads. In this study, we thoroughly determined the advantage of CalliSpheres beads in the HCC treatment. Our data further demonstrated that CalliSpheres beads could achieve a better tumor response and was better tolerated for HCC patients.

Several limitations still existed in this retrospective study: (1) this study was a single-center study; (2) a relatively high percentage of patients received some other treatments after the first cycle TACE procedure, thus many compounding factors can't be ignored; (3) due to small sample size adopted in this research, we can't make definitive conclusions; (4) the follow-up time is short. Therefore, further large cohorts, long-term studies are still required to validate these preliminary findings.

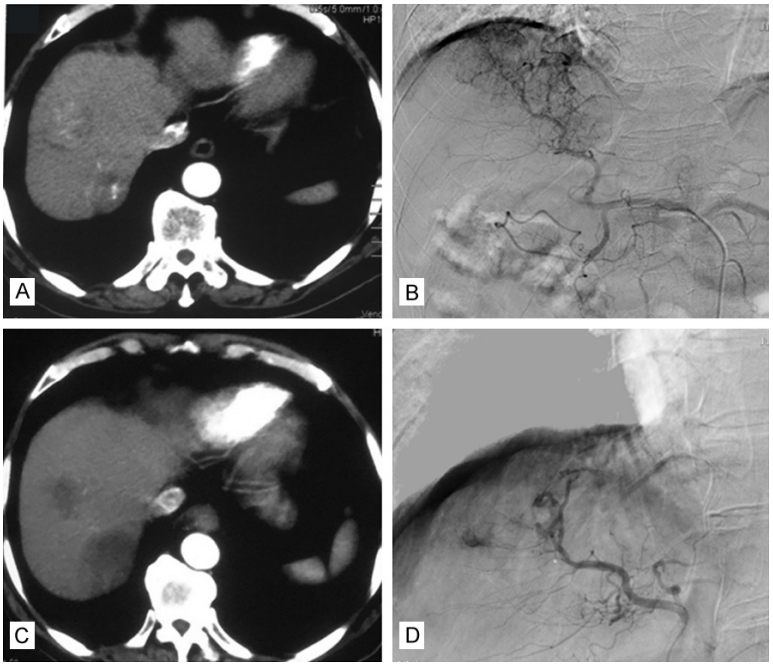

Figure 2. A complete remissions in a 75-year-old patient with HCC treated by TACE using CalliSpheres beads. A. The enhanced CT scan shows a huge tumor before treatment; B. Artery angiography showed the branch of the right hepatic artery supplying the tumor before treatment; C. The enhanced CT scan performed at 40 days after treatment showed the tumor was significantly reduced; D. Angiography after the TACE treatment using CalliSpheres beads showed the branch of the hepatic artery supplying the tumor disappeared.

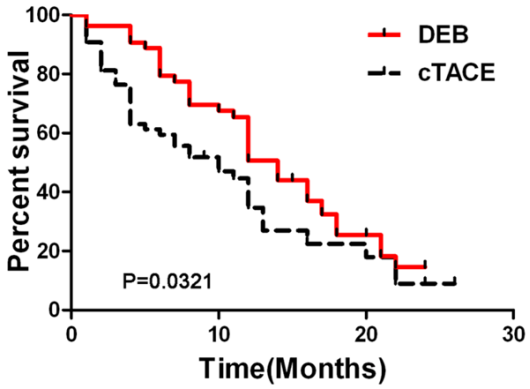

Figure 3. Kaplan-Meier curves of OS in patients with HCC treated with cTACE and TACE using CalliSpheres beads.

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Disclosure of conflict of interest

None.

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