

Repeated transcatheter arterial chemoembolization is safe for hepatocellular carcinoma in cirrhotic patients with transjugular intrahepatic portosystemic shunt

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PURPOSE

We aimed to investigate the safety and long-term outcomes of repeated transcatheter arterial chemoembolization (TACE) in cirrhotic patients with transjugular intrahepatic portosystemic shunt (TIPS).

METHODS

Data of patients with hepatocellular carcinoma, who had previous TIPS implantation and received TACE between January 2010 and December 2012, were reviewed retrospectively. The primary outcome measure was liver function, which was represented by model for end-stage liver disease score, Child-Pugh-Turcotte score, serum total bilirubin, alanine aminotransferase, and aspartate aminotransferase. Changes in liver function before and after the initial TACE procedure and hepatobiliary severe adverse events (SAEs) were compared. Liver function following the initial TACE session was compared with that obtained in later TACE sessions. The secondary outcome measures were tumor response to multiple TACE sessions and survival.

RESULTS

Seventeen patients underwent at least two TACE sessions, while nine patients underwent at least three sessions during the follow-up period. There was no statistically significant difference between the liver function tests performed before and one-month after the TACE procedure. Grade 3 or 4 SAEs occurred in six (31.6 %) patients within one month. The one-, two-, and three-year survival rates were 88%, 53%, and 32%, respectively. Tumor response of multiple TACE sessions was the only predictive risk factor of mortality (OR=4.40; $P=0.030$; 95% CI, 1.15–16.85).

CONCLUSION

Our results suggest that repeated TACE is safe in selected patients with TIPS.

Trascatheter arterial chemoembolization (TACE) is an established method for the management of unresectable hepatocellular carcinoma (HCC) (1). Since HCC is likely to develop in individuals with uncompensated liver cirrhosis, TACE may be required in patients with transjugular intrahepatic portosystemic shunt (TIPS). The safety profile of TACE in patients with TIPS remains unclear. Theoretically, TACE can further reduce liver perfusion, thereby potentially increasing the risk of liver deterioration (2, 3). Previous studies have investigated the safety of TACE in cirrhotic patients with TIPS, and the results have shown that TACE may be beneficial in patients with adequate liver function (4–9). However, these studies only investigated the patients' adverse events after a single TACE procedure, and thus they cannot reflect the dynamic changes of liver function from multiple sessions of TACE over time. Hence, the purpose of this study was to investigate the safety and long-term outcomes of repeated TACE in cirrhotic patients with TIPS.

Methods

Study design

This study was approved by our institutional review board, and written informed consent was acquired from all patients before the procedure. Data of patients, who were diagnosed with HCC and received TACE procedure between January 2010 and December 2012, were retrospectively reviewed using our institutional database. Patients with previous TIPS implantation were included in the present study. HCC was diagnosed according to the European Association for the Study of Liver criteria (10). Exclusion criteria included patients without cirrhosis, patients with Model for End-Stage Liver disease (MELD) score >18 or Child-Pugh-Turcotte (CPT) score >13, patients with shunt dysfunction as diagnosed by Doppler ultrasonography (defined as invisible intrasent blood flow or midshunt velocity <60 cm/s) or angiography before initial TACE procedure, and patients with previously surgical resection or other liver-directed therapy. The main outcome measure was liver function, which was represented by MELD and CPT scores, serum total bilirubin (TBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Liver function was compared before and after the first TACE procedure. Hepatobiliary severe adverse events (SAEs; Grade 3 or 4 according to the National Cancer Institute Common Terminology Criteria, version 4.03 criteria) occurring within one month were documented. Postprocedural liver function of the first TACE session was compared with the postprocedural liver function obtained in later TACE sessions. Secondary outcome measures were tumor response and survival. The tumor response of multiple TACE sessions was evaluat-

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ed by comparing contrast-enhanced computed tomography (CT) images obtained before the first TACE and after the last TACE, using modified response evaluation criteria in solid tumors (mRECIST) criteria (11).

Patients

Nineteen patients consisting of 17 men and two women with a mean age of 54 years (range, 36–70 years) were included in this study. The etiology of cirrhosis was hepatitis B virus infection in 18 patients and hepatitis C virus infection in one patient. Seventeen patients had undergone TIPS for the secondary prophylaxis of variceal bleeding, and two patients had undergone emergent TIPS to manage acute variceal bleeding. TIPS was created using 10 mm stent-grafts (Fluencyplus; Bard, Tempe, Arizona, USA) in the right lobe in 17 patients and the left lobe in two patients. In two patients, the tumor lesion was in the same lobe where the shunt was created, and these patients received treatment with TIPS on an emergency basis. The mean time between TIPS implantation and initial TACE was 7.16 months (range, 0.2–39.4 months). At the time of first TACE, patients were classified as CPT class A (n=5), class B (n=9), and class C (n=5). The average CPT score was 8.11±1.76 (range, 6–11), and the average MELD score was 13.37±2.57 (range, 10–18). According to the Barcelona Clinic Liver Cancer (BCLC) staging system seven patients were stage A and seven patients were stage B. Five patients were classified as stage D because they had an end-stage liver disease.

TACE technique

With the patient under local anesthesia, the right femoral artery access was obtained, and superior mesenteric arteriography and celiac arteriography was performed to assess patency of portal venous system and tumor characteristics. A 3 F microcatheter (MicroFerret, Cook, Bloomington, Indiana, USA) was coaxially placed into second-order or third-order branch of the right or left hepatic artery. Chemoembolization was performed with a 20 mL mixture consisting of 10 mL ethiodized oil (Lipiodol; Guerbet, Villepinte, France) emulsified with 10 mL of aque-

Table 1. Comparison of liver function before and after the initial TACE procedure

	Before TACE	Two weeks after TACE	<i>P</i> ^a	One month after TACE	<i>P</i> ^b
MELD score	13.37±2.57	16.42±3.36	<0.001	13.68±2.77	0.522
CPT score	8.11±1.76	8.74±1.63	0.169	7.89±1.49	0.578
TBIL (μmol/L)	35.47±13.08	61.33±31.56	0.002	37.84±16.75	0.551
ALT (IU/L)	39.26±29.88	122.74±81.64	0.001	69.48±90.27	0.078
AST (IU/L)	51.16±25.53	131.00±91.66	0.001	98.84±111.142	0.069

TACE, transcatheter arterial chemoembolization; MELD, Model for end-stage liver disease; CPT, Child-Pugh-Turcotte score; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
^aBefore vs. two weeks after the initial TACE.
^bBefore vs. one month after the initial TACE.

ous drugs containing 50 mg each of doxorubicin and 5-fluorouracil. The endpoint of the procedure was stasis flow in the targeted branches of the selected hepatic artery. After complete drug delivery gelform slurry was utilized to achieve stasis flow.

Follow-up

Clinical status and liver function tests were evaluated at two weeks and one month after the first TACE. Contrast-enhanced CT scan and liver function tests were performed at one month after each TACE session to assess the tumor response (mRECIST). Patients with partial response, stable disease, and progressive disease underwent additional TACE sessions, if their MELD score was ≤18 and CPT score was ≤13. The patency of TIPS was evaluated by Doppler ultrasonography during post-TIPS follow-up period and before each TACE procedure.

Statistical analysis

Liver function tests of individuals were analyzed using the paired t-test. The cumulative rate of survival was calculated using the Kaplan-Meier method. Cox regression analysis was performed including age, BCLC-stage, CPT class, MELD score, TACE sessions, and side effects of TACE procedure to assess the prognostic factors for survival. All tests of significance were two-sided, and a *P* value less than 0.05 was considered significant. SPSS 19.0 software (IBM Corp., Armonk, New York, USA) was used for statistical analysis.

Results

Nineteen patients underwent a total of 54 TACE sessions (mean, 2.84 sessions; range, 1–7 sessions). Seventeen

patients underwent at least two TACE sessions, while nine patients underwent at least three TACE sessions. The initial target tumor size was 3.72±1.74 cm (range, 2.0–8.8 cm), and multiple tumors were present in seven patients. There were no suspected parasitic tumor feeding arteries and arterial-portal shunts during repeated procedures. Stasis flow was achieved using the lipiodol mixture (≤20 mL) in 14 patients, and gelfoam in five patients with CPT class A or B. Ten patients with TIPS created in the right portal vein underwent right-lobe TACE, and one patient with TIPS created in the left portal vein underwent left-lobe TACE.

MELD score, TBIL, ALT, and AST significantly increased two weeks after the first TACE procedure. However, liver function parameters returned to pre-procedural levels within one month (Table 1). Grade 3 or 4 SAEs occurred in six (31.6%) patients within one month after the first TACE procedure. In addition, the one-month postprocedural liver function was not significantly different between the first, second, and third TACE sessions (Table 2).

One patient (BCLC-D) died of acute gastrointestinal rebleeding 34 days after the first TACE procedure. Another patient (BCLC-B) refused treatment after the first TACE procedure. These two patients were excluded from the final analysis, since their outcomes would not contribute to the analysis of the safety of repeated TACE. No patient was lost to follow-up, and the mean follow-up time was 20.9 months (range, 4.1–50.1 months). During the follow-up, three patients developed shunt dysfunction, which was successfully relieved by balloon angio-

plasty (n=1) or stent placement (n=2). After multiple TACE sessions tumor response was progressive disease in eight patients (42%), stable disease in five patients (26%), partial response in three patients (16%) and complete response in three patients (16%). One patient with BCLC-B underwent liver transplantation after the second TACE session, and this patient's survival data was censored at 4.2 months. Another patient with BCLC-D HCC (Fig.) underwent liver transplantation after the third TACE session, and this patient's survival data was censored at 11.9 months. Nine patients died during the follow-up: three patients (CPT class B [n=1] and class C [n=2]) died of mul-

tipple organ failure associated with HCC metastasis, two patients (CPT class B and C) died of hepatic failure, two patients (CPT class A and B) died of acute gastrointestinal rebleeding, one patient (CPT class B) died of HCC rupture, and one patient (CPT class B) died of sepsis (Table 3). The one-, two-, and three-year survival rates were 88%, 53%, and 32%, respectively. Tumor response after multiple TACE sessions was the only predictive risk factor of mortality (OR=4.40; $P = 0.030$; 95% CI, 1.15–16.85).

Discussion

TACE has been widely accepted as an effective therapy for unresectable HCC

(1). Generally, hepatic arterial flow increases after TIPS is created to compensate the reduced portal flow (12, 13). Thus, the risk of liver deterioration from hepatic ischemia is a concern for patients with functional TIPS undergoing TACE. In the present study, though an obvious fluctuation of liver function was observed within one month after the initial TACE procedure, repeated TACE was still well-tolerated in selected patients with TIPS.

Several previous studies investigating the safety of TACE in patients with cirrhosis having TIPS have shown contrasting results (4–8, 14). Tesdal et al. (7) described six patients with TIPS treated with either TACE or TACE combined with percutaneous ethanol injection. During an average follow-up of 26.2 months, no procedure-related severe complications occurred after 17 TACE sessions. Four other studies, including a total of 28 patients, have also shown that TACE is safe in patients with cirrhosis having TIPS (4–6, 14). On the other hand, a recent case-control study showed that the occurrence of SAEs within 30 days was significantly higher in patients with TIPS than those without TIPS (70% vs. 36%), but this variation was not statistically significant after 1–7 months (29% vs. 20%) (9). In response to this study, Gaba et al. (15) shared their results of a research in seven patients and showed a much lower rate of SAEs (11%), all of which resolved within two weeks. The two main reasons that could have contributed to the difference in

Table 2. Comparison of liver function one-month after initial TACE vs. after multiple sessions of TACE

	≥2 sessions of TACE (n=17)		
	1st TACE	2nd TACE	<i>P</i>
MELD score	13.29±2.57	13.65±3.16	0.496
TBIL (μmol /L)	35.84±15.68	36.98±19.92	0.775
ALT (IU/L)	51.36±49.70	35.47±21.80	0.186
AST (IU/L)	65.65±52.32	51.71±22.84	0.307
	≥3 sessions of TACE (n=9)		
	1st TACE	3rd TACE	<i>P</i>
MELD score	13.00±3.04	13.44±4.10	0.609
TBIL (μmol/L)	37.46±19.83	36.37±13.81	0.877
ALT (IU/L)	63.33±67.1	32.89±12.17	0.183
AST (IU/L)	77.56±67.64	51.56±21.30	0.308

TACE, transcatheter arterial chemoembolization; MELD, Model for end-stage liver disease; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. Deaths during the follow-up period

Patient no.	Age (years)	BCLC stage	CPT class	MELD score	No. of TACE sessions	Ipsilateral TACE*	Duration (months)	Cause of death
2	58	A	B	13	2	No	29.9	Metastasis MODS
4	57	A	A	12	2	Yes	17.5	Gastrointestinal bleeding
6	65	D	C	18	3	No	12.8	Liver failure
7	56	D	C	13	2	Yes	27.8	Metastasis MODS
8	48	B	B	17	3	Yes	17.9	Liver failure
9	47	D	C	12	2	Yes	18.5	Metastasis MODS
11	36	A	B	15	3	Yes	9	HCC rupture
13	58	B	B	16	2	No	39.3	Sepsis
18	40	B	B	17	1	No	1.13	Gastrointestinal bleeding

BCLC, Barcelona clinic liver cancer; CPT, Child-Pugh-Turcotte; MELD, Model for end-stage liver disease; TACE, transcatheter arterial chemoembolization; MODS, multiple organ dysfunction syndrome; HCC, hepatocellular carcinoma.

*TACE performed in the same lobe where the shunt was created.

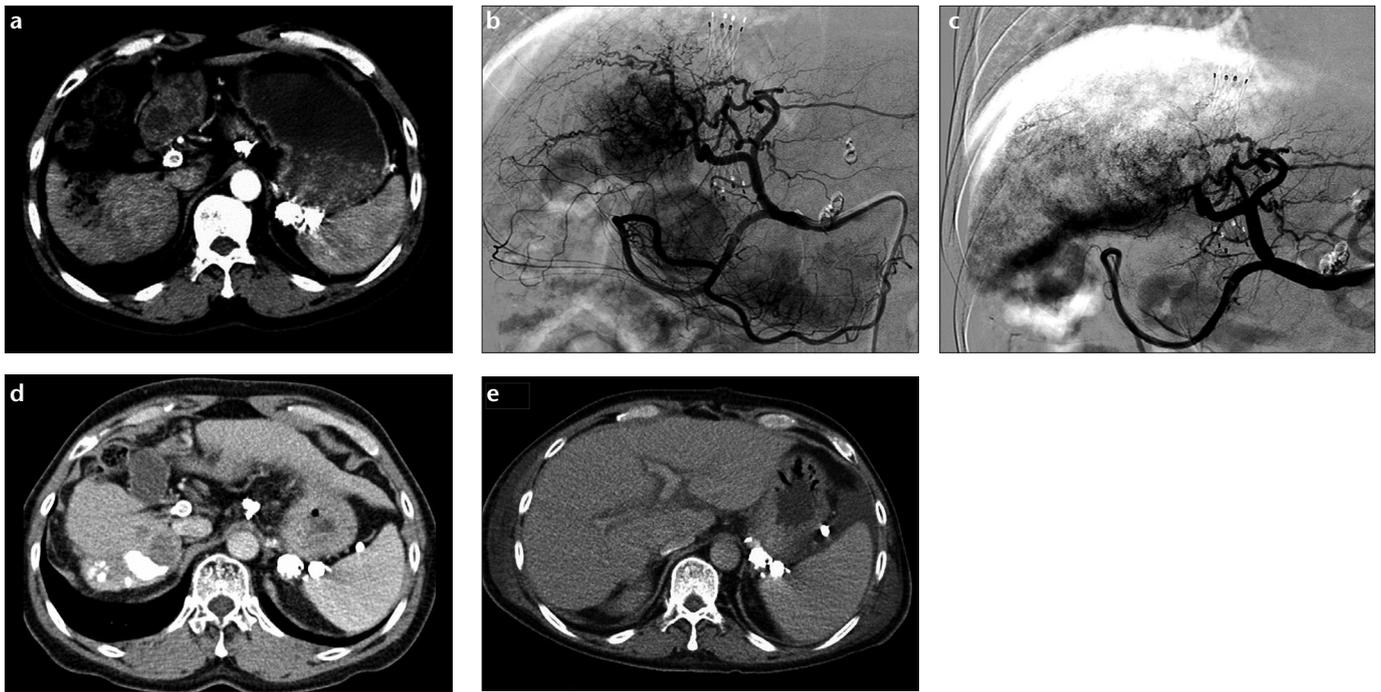


Figure. a–e. A 50-year-old male patient with cirrhotic hepatitis received transjugular intrahepatic portal systemic shunt in our unit for prevention of variceal bleeding. Enhanced computed tomography (CT) axial images (a) showed a typical image of hepatocellular carcinoma (about 6.5 cm in diameter) and his condition was graded as Barcelona Clinic Liver Cancer-D for his poor liver function (Child-Pugh class C). Angiographic images (b) prior to the initial session of transcatheter arterial chemoembolization (TACE) showed tumor stains which almost disappeared after occlusion of feeding arteries by three consecutive sessions of TACE (c). The postprocedural enhanced-CT (d) showed that the long-term tumor response was partial according to mRECIST guidelines. After 11.9 months following TACE, he successfully received liver transplantation (e) and presently survives without tumor recurrence after 26 months of follow-up.

their results may be the difference in the TACE technique used and different patient selection criteria. First, in order to achieve vascular stasis, Kohi et al. (9) injected additional gelatin sponge, which was not performed in the series reported by Gaba et al. (9, 15); and this could result in a much higher hepatotoxicity. The occurrence of SAEs (31.6%) in the current study was between the SAE rates reported in those two studies, which might be because an additional embolization was performed in only five patients with preserved liver function in this study, as previous studies have suggested (14, 16, 17). Second, it is considered that the preprocedural liver function is correlated with the postprocedural hepatotoxicity. There were five CPT class C patients who underwent TACE in the present series. Only one died of liver failure after three sessions of TACE. Multiple TACE sessions might be correlated with progressive deterioration of liver function, but it is not likely to cause hepatotoxicity directly.

TIPS was performed in two patients with concomitant HCC. It is technically possible to perform TIPS in patients

with HCC, unless the tumor transverse the intrahepatic puncture path, as previously described (14). In this study, TACE was performed following TIPS implantation without any severe complications, but we believe TACE or other liver-directed therapies should be performed prior to TIPS in patients with cirrhosis and HCC, unless TIPS is regarded as a salvage option.

TACE is considered to be an advisable therapy, but requires repeat sessions; few previous studies have described the safety of repeated TACE in patients with TIPS (4–9, 14). Existing studies have investigated the safety of repeated TACE in cirrhosis without TIPS, and results have shown that most of the postprocedural impairments are reversible within two weeks to four months (18–22). The current study also found that the reserved liver function in patients with TIPS does not worsen after repeated sessions of TACE. These results suggest that in patients with reduced portal nutrition compensatory mechanisms may arise after TACE. Portal vein invasion could also reduce the portal blood flow and increase the potential risk of hepatic

insufficiency. Previous studies showed that TACE could be safely performed in patients with main portal vein obstruction, provided that the patients have adequate collateral circulation and conserved liver function (23, 24). More TACE sessions were tolerated in patients with portal branch invasion rather than main portal vein invasion over the long-term, which suggested a compensatory role for the intrahepatic vein (24). Nourishment of hepatic tumor by portal blood flow has also been observed in patients who underwent repeated TACE sessions (25, 26). Thus, the reserved portal flow in the intrahepatic branch may play a role in protecting the liver function. In the present study, performing TACE in the same lobe, where the shunt was created, did not predict poor prognosis. However, because of the limited sample size, the risk of performing TACE in the same lobe of TIPS should be weighed against the benefits. Though survival benefit analysis was not the main purpose in the present study, we found that the tumor response was a predictive factor of survival. TACE might prolong the survival of patients with cirrhosis,

HCC, and TIPS, since repeated TACE could significantly prolong survival in HCC with portal invasion (24, 27), or at least serve as a bridge to liver transplantation. The safety assessment of repeated TACE in this study might promote further research on its survival benefit in patients with TIPS.

In addition to the limitations of a retrospective study design and a small sample size, the present study also lacks a control group of patients without TIPS shunt. However, since the main purpose of this study was to analyze the safety of multiple TACE sessions; the divergence of tumor progression in the control group might have influenced our conclusion. Thus, the patient's reserved liver function was individually compared to evaluate the safety of repeated TACE procedures.

In conclusion, the study results indicate that repeated TACE is safe in selected patients with TIPS. However, future studies are required to determine whether this treatment is beneficial in patients with TIPS.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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