Feasibility Study of Transcatheter Arterial Chemoembolization with Epirubicin Drug-eluting Beads for Hepatocellular Carcinoma in Japanese Patients

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Abstract

Purpose: To evaluate the feasibility of drug-eluting bead (DEB)-transarterial chemoembolization (TACE) with 75 mg epirubicin for hepatocellular carcinoma (HCC) in Japanese patients with unresectable HCC prior to conducting a planned randomized controlled trial.

Materials and Methods: This study was conducted as a prospective multi-center feasibility study. Eligible patients had unresectable Barcelona Clinic Liver Cancer stage A or B HCC that was unsuitable for curative treatments, and all patients received TACE with 75 mg epirubicin-loaded DEB. Tumor response, as the primary endpoint, was assessed after 4 weeks by computed tomography or magnetic resonance imaging, based on the modified Response Evaluation Criteria in Solid Tumors. Adverse events after treatment were evaluated as the secondary endpoint, based on the Common Terminology Criteria for Adverse Events version 4.0.

Results: Between May and August 2014, 8 patients from two institutions were enrolled in this clinical study. There were no instances of complete response observed, partial response was obtained in 4 patients, and the overall response rate was 50%. No patients experienced grade 4 or higher adverse events. Grade 3 thrombocytopenia occurred in 1 patient. One patient experienced a grade 3 increase in aspartate aminotransferase, alanine aminotransferase, and bilirubin levels. All adverse events were well managed with conservative medical care. There were no procedure-related deaths.

Conclusions: DEB-TACE with 75 mg epirubicin was found to be feasible in Japanese patients, and it was deemed appropriate to proceed to a randomized controlled trial comparing DEB-TACE and conventional TACE.

Key words: Transcatheter Arterial Chemoembolization, Hepatocellular Carcinoma, Drug-eluting Beads
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Introduction

For unresectable hepatocellular carcinoma (HCC), transarterial chemoembolization (TACE) has become an established treatment with level I evidence derived from randomized controlled trials (RCTs) and meta-analyses [1-3]. Fundamental elements of TACE include administration of a chemotherapeutic agent to induce a local effect and administra-

tion of embolic materials to induce ischemic necrosis of the tumor cells; however, standardized techniques are lacking for each of the separate elements.

Conventional TACE (cTACE) consisting of administration of Lipiodol® (Guerbet LLC, Tokyo, Japan) and anthracycline agents, followed by embolization with gelatin sponge particles, has been a practical standard treatment in Asian countries [4]. Recently, the use of drug-eluting beads (DEB) with calibrated anthracycline drug-carrying microspheres (DC

Figure 1. Imaging findings from a 79-year-old woman with hepatocellular carcinoma. In arterial phase of dynamic CT, a hypervascular tumor was observed in segment 6 of liver.

Bead; Eisai Co., Ltd., Tokyo, Japan) was introduced as a novel method capable of sustained and tumor-selective drug delivery and permanent embolization [5]. DEB has gained wide acceptance and has been increasingly used as the first-line TACE procedure in Western countries [6]. Four multi-center international randomized trials comparing DEB-TACE and cTACE demonstrated equivalent efficacy results [7-10]. Thus, controversy remains regarding the selection of the embolic materials and the techniques for TACE. In accordance with the approval of DEB in Japan in 2014, the Japan Interventional Radiology in Oncology Study Group (JIVROSG) aimed to conduct a prospective, multi-center RCT comparing DEB-TACE and cTACE employing a standard technique in Asian countries. Given that there were no available clinical data regarding DEB-TACE in patients of Japanese ethnicity, and the available drug is different from that used in previous studies because epirubicin is the only approved anthracycline drug for hepatic arterial infusion in Japan, it was necessary to evaluate the feasibility of DEB-TACE in Japanese patients prior to the initiation of the principal RCT. The purpose of the present study was to evaluate the feasibility of DEB-TACE with 75 mg epirubicin for HCC in Japanese patients with unresectable HCC.

Materials and Methods

Study Design

This study was conducted as a prospective multi-center feasibility study.

Patient Eligibility

Eligible patients had unresectable Barcelona Clinic Liver Cancer (BCLC) stage A or B HCC that was unsuitable for curative treatments. Inclusion criteria were as follows: histologically or clinically diagnosed HCC excluding mixed

type histology; unsuitability as a candidate for hepatic resection, liver transplantation, or local ablative therapy; hypervascular tumor showing enhancement in the early phase on computed tomography (CT) or magnetic resonance (MR) imaging (**Fig. 1**); no tumor thrombosis in the first branch or main portal vein; Eastern Cooperative Oncology Group performance status of 0-2; Child-Pugh classification of A or B; adequate hematologic, hepatic, renal, and cardiac function (leukocytes $\geq 3,000/\text{mm}^3$, platelets $\geq 50,000/\text{mm}^3$, serum bilirubin $\leq 3.0 \text{ mg/dL}$); age ≥ 20 years. Exclusion criteria were as follows: prior biliary-enteric bypass or endoscopic transampullary stent placement or percutaneous biliary drainage; refractory ascites or pleural effusion; severe arterioportal or arteriovenous shunts in the liver; allergy to contrast medium; severe and active comorbidity such as heart disease or renal disease; hepatic encephalopathy or severe mental disorder; active gastrointestinal bleeding; active concomitant malignancy; pregnancy, lactation, or childbearing potential.

The present study was compatible with the Health Insurance Portability and Accountability Act and approved by the institutional review boards of the participating institutions. Informed consent was obtained from all patients.

DEB-TACE Procedure

One vial of 100 to 300 μm DEB was loaded with 75 mg epirubicin. Epirubicin was chosen based on its use in cTACE in Asian countries and the approval status of anthracycline drugs for hepatic arterial infusion in Japan. The dose of epirubicin was determined based on recent studies [11-13] in which the anthracycline doxorubicin was used at a dose of 50 mg. We set the dose of epirubicin at 75 mg, which is equivalent in potency to 50 mg of doxorubicin. Selective embolization using a microcatheter was performed according to the technical recommendations of Lencioni et al. [6]. DEB-TACE was performed as follows: (i) tumor en-

Figure 2. Angiography from the celiac trunk, a hypervascular tumor (arrow) was observed in right lobar of liver (A). The post-DEB-TACE angiography showed no tumor stain (B).

Table 1. Characteristics of Patients

Characteristics	No. Patient
Gender	
Male	6
Female	2
Age(y)	
Median(range)	69.5(46-79)
EGOG Performance Status	
0	7
1	1
Child-Pugh Classification	
A	6
B	2
Etiology	
Hepatitis C	2
Hepatitis B	4
Non B, Non C	2
BCLC	
A	3
B	5

ECOG: Eastern Cooperative Oncology Group,
BCLC: Barcelona Clinic Liver Cancer

hancement and the feeding artery were confirmed using abdominal angiography; (ii) a microcatheter was inserted into the feeding artery of the HCC, followed by the injection of the DEB; and (iii) the injection was continued until near stasis was observed in the artery directly feeding the tumor (**Fig. 2**). Concurrent use of embolic agents other than DEB was not allowed.

Study Design and Endpoints

This study was designed as a prospective, nonrandomized study in two cancer center hospitals. The primary endpoint was the tumor response rate at 4 weeks after the procedure. Contrast-enhanced CT or MR imaging was performed 4 weeks after DEB-TACE. The tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) [14]. The secondary endpoint

was the occurrence of any adverse event (AE). The severity of all AEs was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

Statistical Considerations

We defined the feasibility of epirubicin DEB-TACE as the attainment of a clinical response in 2 or more patients out of the 8 who were enrolled. We set the threshold response rate of the main trial at 50%. If a clinical response was observed in fewer than 2 of the 8 cases, the 95% confidence interval (CI) of the threshold response rate was below 50%. In that case, the method would not be considered feasible and the principal RCT would have to be reconsidered.

Results

Patient Characteristics

Between May and August 2014, 8 patients from two institutions were enrolled in this clinical study. The characteristics of the patients are shown in **Table 1**. In brief, out of 8 enrolled patients, the Child-Pugh classification was A in 6 patients (75.0%, 6/8), hepatitis etiology was hepatitis B virus in 3 patients (37.5%, 3/8), and BCLC stage was A in 3 (37.5%, 3/8) and B in 5 patients (62.5%, 5/8).

Tumor and Procedure Characteristics

The characteristics of the tumors and procedures are listed in **Table 2**. Median maximum viable tumor size was 24.2 mm (standard deviation [SD]: 18.8 mm). All patients had multiple tumors, and a bilobar distribution was observed in 6 patients (75.0%, 6/8). All procedures were technically successful with a median number of vials of DEB of 0.43 (SD: 0.26). The mean dose of epirubicin was 38.1 mg (SD: 19.7 mg).

Tumor Response

No instances of complete response were observed in any of the 8 patients, 4 patients showed a partial response (**Fig. 3**), 2 had stable disease, and 2 showed progressive disease. The overall response rate was 50% (95% CI: 22-79%).

Adverse Events

The AEs associated with the DEB-TACE procedure in the present study are listed in **Table 3**. There were no grade 4 or higher AEs. Grade 3 thrombocytopenia occurred in 1 patient. One patient experienced a grade 3 increase in aspartate aminotransferase, alanine aminotransferase, and bilirubin levels. All AEs were managed with medical treatments. There were no procedure-related deaths.

Discussion

DEB-TACE with 75 mg epirubicin was found to be feasible as treatment for unresectable HCC in the present study. Because the size of the cohort was small, the response rate

of 50% in this study cannot be precisely compared to the results from previous studies (**Table 4**); however, this rate is equivalent to the results of the PRECISION V study as reported by Lammer et al. Additionally, a 38.1 mg dose of epirubicin, which has a titer 1.5 times higher than that of doxorubicin (corresponding value: approximately 57 mg), was equivalent to that in previous studies in which doses of doxorubicin ranging from 55.1 to 57.8 mg were used. With regard to safety, no severe AEs were observed in the present study, consistent with the results of previous studies. Thus, it is deemed that a dose of 75 mg epirubicin per vial of DC Beads is acceptable in terms of safety and efficacy. The performance of DEB-TACE has increased in many institutions across the country following the approval of DC Beads in Japan in 2014. However, the dose of epirubicin has not been standardized, and doses vary across institutions. Therefore, the results presented here (75 mg epirubicin per vial) may provide a standard for the loading dose.

In the previous RCTs comparing cTACE with DEB-TACE in Western countries, cTACE techniques utilized various doses of chemotherapeutic agents (doxorubicin 56.9-223 mg), various embolic materials, and scheduled treatment timing. There has been no standardization of the technical procedure for cTACE. Accordingly, the authors determined that we needed to conduct a prospective, multi-center RCT comparing DEB-TACE and cTACE employing a standard technique in Asian countries. Asian cTACE consists of selective administration of the chemotherapeutic agents (approximately 40-60 mg of doxorubicin or epirubicin) mixed with Lipiodol into the feeding branch of the tumor followed by embolization with a gelatin sponge. The timing of the next treatment is unpredictable, depending on demands determined by the clinical and imaging findings of residual or recurrent tumors. The rationale of the safety and efficacy data of DEB-TACE has not been established in Japan. Data

Table 2. Characteristics of Tumor and Procedure

Maximum viable tumor size (mm)		
	Median (range)	24.2 (19.5-80)
No. of tumors		
	Single	0
	Multiple	8
Tumor distribution		
	Unilobar	2
	Bilobar	6
Technical success		8/8
No. of DEB vial		
	Median (range)	0.43 (0.25-1)
DEB: drug-eluting beads

Figure 3. CT at four weeks after DEB-TACE demonstrated disappearance of early enhancement in most of the tumor. Small enhanced area corresponding to viable hepatocellular carcinoma was seen in the cranial part of the tumor (arrow). This case was regarded as partial response.

Table 3. Adverse Events

AEs	Grade 1	Grade 2	Grade 3
Fatigue	1	2	0
Fever	2	0	0
Anorexia	1	1	0
Nausea	1	0	0
Vomiting	3	0	0
Alopecia	0	0	0
Platelets	0	2	1
WBC	0	1	0
AST	0	1	1
ALT	0	1	1
Bilirubin	0	1	1

WBC: white blood cell, ALT: alanine aminotransferase,
AST: aspartate aminotransferase.

Grading according to Common Terminology Criteria for Adverse Events, version 4.0

Table 4. Randomized Controlled Trials of Transcatheter Arterial Embolization

Author, Year	Study Design	Treatment	Drug	Mean dose of drug (mg)	No. Patient	Response Rate	Summary of AEs
Lammer, 2010 (PRECISION V)	Phase 2, RCT	conventional TACE	doxorubicin	223	108	44% (6M)	Alopecia Marrow suppression Mucositis
		DEB-TACE	doxorubicin	295	93	52% (6M)	Marrow suppression
Sacco, 2011	Phase 2, RCT	conventional TACE	doxorubicin	56.9	34	100% (1M)	Cholecystitis
		DEB-TACE	doxorubicin	55.1	33	100% (1M)	Liver failure
Van Malenstein, 2011	Phase 2, RCT	conventional TACE	doxorubicin	68 (m ²)	14	92% (6W)	Alopecia Leukopenia Liver dysfunction
		DEB-TACE	doxorubicin	65 (m ²)	16	77% (6W)	Infection Liver dysfunction Cholecystitis
Golfieri, 2014 (PRECISION Italia)	Phase 2, RCT	conventional TACE	epirubicin	47.2	86	89% (1M)	Post-procedural pain Infection Liver function worsening
		DEB-TACE	doxorubicin	57.8	88	90% (1M)	Fever Pain Cholecystitis

RCT: randomized control trial, TACE: transarterial chemoembolization, DEB: drug-eluting beads, AEs: adverse events

from the present study are preliminary; however, it is acceptable to affirm the feasibility of 75 mg epirubicin DEB-TACE in the Japanese population. Thus, based on the data from the present study, our study group has planned to conduct a prospective RCT comparing DEB-TACE and cTACE.

This study has several limitations. First, evaluation of the response was only conducted at one point (4 weeks after the treatment). This duration was determined based on the first evaluation point at approximately 1 month after TACE used in previous studies. Second, there may have been a lack of experience with the use of DEB because this study was conducted shortly after the approval of DEB in Japan. However, the use of a microcatheter in the present study was the same technique employed in cTACE in our daily clinical practice. Lectures as well as practical training regarding the best practices of embolization, including optimized preparation and embolization endpoints, were provided during a workshop prior to our first use of DEB.

In conclusion, DEB-TACE with 75 mg epirubicin was feasible in Japanese patients and it was deemed appropriate

to proceed to an RCT comparing DEB-TACE and cTACE.

This study has been presented at WCIO 2015.

Conflict of interest: There are no potential conflicts of interest with regard to this study.

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