A retrospective comparative study of epirubicin–lipiodol emulsion and cisplatin–lipiodol suspension for use with transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma

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Transcatheter arterial chemoembolization (TACE) is widely used to treat unresectable hepatocellular carcinoma (HCC). Recently, a fine-powder formulation of cisplatin (DDP-H) was developed in Japan. We aimed to compare clinical outcomes after TACE using epirubicin or DDP-H in patients with HCC. We evaluated 202 patients who were treated with TACE alone, using either epirubicin–lipiodol emulsion or DDP-H–lipiodol suspension. Of these, epirubicin and DDP-H treatment groups comprised 106 and 96 patients, respectively. The median follow-up time was 32 months (range: 1–45 months). The progression-free survival rate in the DDP-H–lipiodol group was significantly higher than in the epirubicin–lipiodol group (log-rank test, $P=0.0164$). Moreover, the DDP-H–lipiodol group showed significantly better overall survival than the epirubicin–lipiodol group (log-rank test: $P=0.0052$). The overall survival rate at 1, 2, and 3 years was 88.5, 71.8 and 62.4%, respectively, for the DDP-H–lipiodol group and 83.0, 57.9 and 36.5%, respectively, in the epirubicin–lipiodol group. In a multivariate analysis, the independent factors affecting overall survival were drug (epirubicin vs. DDP-H; hazard ratio 0.44, $P=0.0001$), clinical stage (I/II vs. III/IV; hazard ratio 1.93, $P=0.0026$), and Child–Pugh score (A vs. B/C; hazard ratio 3.15, $P<0.0001$). TACE using a gelatin sponge and lipiodol with DDP-H showed better progression-free survival and overall survival rates than TACE with the epirubicin–lipiodol emulsion in patients with HCC. The improvement of overall survival in patients with HCC receiving this treatment warrants further investigation as a randomized control trial. *Anti-Cancer Drugs* 22:277–282 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Transcatheter arterial chemoembolization (TACE) is a common treatment for advanced hepatocellular carcinoma (HCC) [1,2]. TACE generally involves the injection of a mixture of anticancer agent and lipiodol (Lipiodol Ultra-Fluide, Laboratoire Guerbet, Aulnay-sous-Bois, France) into the segmental or subsegmental arteries of the liver [3]. Commonly used anticancer agents for HCC include doxorubicin, epirubicin, mitomycin C, cisplatin, and fluorouracil. Few reports, however, have been published on the selection of the anticancer agents for this method [4–9].

In Japan, epirubicin has been frequently used with lipiodol for TACE in HCC. In contrast, the use of cisplatin for TACE has been minimal because the standard concentration of cisplatin solution in Japan (0.5 mg/ml) cannot be dispensed with an appropriate dose of lipiodol. A fine-powder formulation of cisplatin (DDP-H; IA-call, Nippon Kayaku, Tokyo, Japan) with a particle size of 20–30 μm was developed in July 2004, facilitating the preparation of a high-concentration aqueous solution [10]. Moreover, unlike conventional preparations, DDP-H is readily miscible when mixed with lipiodol and therefore, is easy to use for TACE. We compared the effectiveness and tolerability of TACE using epirubicin or DDP-H in this single-institution retrospective study.

Methods

Patients

We evaluated 202 patients who were retrospectively identified in terms of the 12-month follow-up and 436 patients who had been treated with TACE for advanced HCC at Narumi hospital from July 2004 and December 2006. All patients met the following criteria: (i) HCC was confirmed histologically or clinically by diagnostic imaging, (ii) no treatment experience of TACE, and no indication of surgical resection or local ablation therapy such as radiofrequency ablation therapy, (iii) hypervascular tumors showing enhancement during angiography, (iv) Eastern Cooperative Oncology Group performance status 0–2, (v) no tumor thrombus in the main trunk of the portal vein, (vi) no prominent arteriovenous shunt or arterioportal shunt, (vii) no lingering effect of earlier therapy (at least a 6-week interval should follow the

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cessation of the other therapy), (viii) no evidence of active heart or renal diseases meeting the contraindications for epirubicin and cisplatin therapy, respectively, and (xi) total serum bilirubin less than 3 mg/dl.

The exclusion criteria were clinically evident congestive heart failure, serious cardiac arrhythmia, active clinically serious infections, seizure disorder requiring medication, history of organ allograft, history of serious hypersensitivity to drugs and contrast medium, and, in women, pregnancy or lactation. All patients gave fully written informed consent before the performing TACE, computed tomographic scan (CT) during hepatic arteriography, and CT scan during arterial portography using the Seldinger method by the transfemoral arterial approach. Of these patients, 202 completed the treatment schedule for the evaluation of statistics.

Four interventional radiologists at Narumi Hospital with abundant TACE experience chose the anticancer agents depending on their professional judgment, taking factors such as cardiac toxicity, nephrotoxicity, and allergic reaction into account in their selection. Consequently, 106 patients were treated with epirubicin, and 96 patients were treated with DDP-H.

The study protocol was approved by the Ethics Committee of Narumi Hospital. The study complied with the provisions of the Declaration of Helsinki and local laws and regulations.

Treatment

We performed TACE using the conventional epirubicin–lipiodol emulsion (EPI/Lip) or the DDP-H–Lipiodol suspension (DDP-H/Lip). We used gelatin sponge particles (Gelpart; Nippon Kayaku, Tokyo, Japan) as the embolization agent for all patients.

DDP-H/Lip was prepared by mixing 100 mg of cisplatin powder (IA-call) into 5–10 ml of lipiodol. The EPI/Lip emulsion was prepared by dissolving 30–50 mg of epirubicin in 1–2 ml of a contrast medium, before mixing with 3–10 ml lipiodol. The dosage of lipiodol and the anticancer agents was adjusted depending on the tumor size, number of tumors, degree of liver impairment, and renal function. However, a maximum dose limit was fixed at 15 ml.

To prevent renal damage, we ensured that the patients were adequately hydrated before and after DDP-H/Lip treatment by administering 1000–2000 ml of an electrolyte infusion through an intravenous drip. In addition, 5-HT_3 antagonist and dexamethasone were given to all patients prophylactically to prevent nausea and emesis.

All patients were tested with ultrasound, CT scan and/or magnetic resonance imaging after 1 month and every 3 months thereafter. TACE procedures were repeated when a relapse was detected in the treated lesions and/or if new hepatic lesions emerged. These patients received additional TACE using the same agent during the follow-up period. TACE was repeated until complete regression of the tumor was achieved, or until the patient could no longer be treated by extra TACE.

Treatment effect and toxicity evaluation

The efficacy of TACE was evaluated by CT scanning 1 month after the initial treatment. When lipiodol perfusion was seen in more than 90% of the tumor, the efficacy was considered 'complete'; and in less than 90% of the tumor, it was considered 'non-complete'. Grading for lipiodol retention was based on quantitative measurement of the tumor diameter, based on the assumption that the portion of tumor retaining lipiodol was a necrotic tissue [5]. Treatment-related toxicity was assessed using the National Cancer Institute Common Terminology Criteria version 3.0.

Statistical analysis

The differences in the clinical background of the patients between the DDP-H/Lip group and EPI/Lip group were assessed by either the Wilcoxon rank-sum test or Fisher's exact test. The median follow-up time was calculated by the reverse Kaplan–Meier method [11]. Progression-free survival (PFS) was estimated from the date when the therapy was started to the date on which tumor progression was documented or the date of patient death. Overall survival (OS) was estimated from the date when the therapy was started to the date of patient death. Both parameters were assessed by the Kaplan–Meier method, and the differences between the two treatment groups were analyzed by the log-rank test and the generalized Wilcoxon test. Sex, age, drug, Child–Pugh, and clinical stage adopted by the Liver Cancer Study Group of Japan were then subjected to univariate and multivariate analysis using the Cox proportional hazards model. Statistical significance was noted if the P value was 0.05 or less. All analyses were carried out using the Statistical Analysis System (ver. 8.02, SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

The characteristics of the 202 patients in the two groups were summarized (Table 1). We enrolled 135 male and 67 female patients, ranging in age from 47 to 86 years (median, 71 years). Tumor staging was defined based on the tumor node metastasis staging system of the Liver Cancer Study Group of Japan: stage I [fulfilling three intrahepatic conditions: solitary, less than or equal to 2 cm, no vessel invasion; $n = 24$ (11.9%)], stage II [two of the three intrahepatic conditions; $n = 66$ (32.7%)], stage III [one of the three intrahepatic conditions; $n = 36$ (17.8%)], stage IV A [none of the three intrahepatic conditions, with no distant metastases or any intrahepatic conditions with lymph node metastases; $n = 69$ (34.2%)], and stage IV B [any intrahepatic condition with distant

Table 1 Patient characteristics

Arm	EPI/Lip ($n=106$)	DDP-H/Lip ($n=96$)	P value
Age [median (range)]	71 years (50–86)	70 years (47–84)	0.1906[c]
Sex, *n* (%)			
Male	71 (67.0%)	64 (66.7%)	1.0000[d]
Female	35 (33.0%)	32 (33.3%)	
Child–Pugh class, *n* (%)			
A	44 (41.5%)	24 (25.0%)	0.0042[c]
B	62 (58.5%)	67 (69.8%)	
C	0 (0.0%)	5 (5.2%)	
Etiology, *n* (%)			
HBV	5 (4.7%)	7 (7.3%)	0.5984[d]
HCV	97 (91.5%)	82 (85.4%)	
B&C	1 (0.9%)	2 (2.1%)	
NBNC	3 (2.8%)	5 (5.2%)	
Stage[a], *n* (%)			
I	10 (9.4%)	14 (14.6%)	0.1139[c]
II	41 (38.7%)	25 (26.0%)	
III	23 (21.7%)	13 (13.5%)	
IVA	32 (30.2%)	37 (38.5%)	
IVB	0 (0.0%)	7 (7.3%)	
Initial treatment evaluation[b], *n* (%)			
Complete	83 (78.3%)	69 (71.9%)	0.3291[d]
Not complete	23	27	

B&C, concurrent infection with both hepatitis B and C viruses; DDP-H/Lip, fine-powder cisplatin–Lipiodol; EPI/Lip, epirubicin–Lipiodol; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, neither hepatitis B nor C.
[a]Staging system of the Liver Cancer Study Group of Japan.
[b]One month after treatment, we regarded Lipiodol accumulation in tumor as being a necrotic area.
[c]Wilcoxon rank sum test.
[d]Fisher's exact test.

metastases; $n=7$ (3.5%)] [12]. For the assessment of differences in the characteristics of the patients, the patients were divided into two groups based on each characteristic. A significant difference was found between the DDP-H/Lip and EPI/Lip groups in the Child–Pugh classification of chronic liver disease. More patients of the poor Child–Pugh classification were enrolled in the DDP-H/Lip group than in the EPI/Lip group ($P=0.0042$). There were no significant differences between the two groups in any other characteristics.

Progression-free survival

The median follow-up time was 32 months (range: 1–45 months). In all patients receiving TACE, 1-, 2-, and 3-year PFS rates were 29.9, 12.9, and 6.8%, respectively. In the DDP-H/Lip group, the PFS rates at 1, 2, and 3 years were 32.2, 18.8, and 15.7%, respectively. In contrast, the corresponding values in the EPI/Lip group were 27.7, 7.7, and 1.5%, respectively. The PFS rates in the DDP-H/Lip group were significantly higher than those in the EPI/Lip group (log-rank test: $P=0.0164$, generalized Wilcoxon test: $P=0.0315$) (Fig. 1).

Overall survival

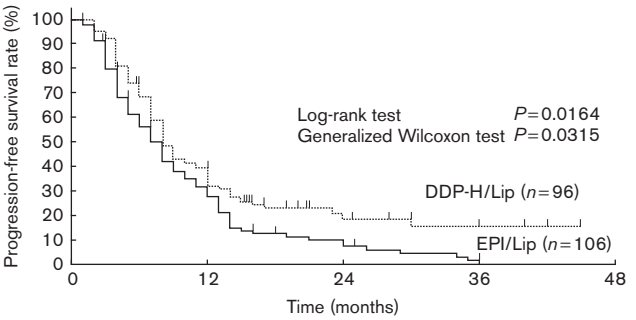
The OS rates at 1, 2, and 3 years of all patients who underwent TACE were 85.6, 64.2, and 46.4%, respectively. The OS rate at 1, 2, and 3 years was 88.5, 71.8, and 62.4%, respectively, for the DDP-H/Lip group and 83.0, 57.9, and 36.5%, respectively, in the EPI/Lip group. The DDP-H/Lip group showed significantly better OS than the EPI/Lip group (log-rank test: $P=0.0052$, generalized Wilcoxon test: $P=0.0073$) (Fig. 2).

In univariate analysis, the significant factors affecting OS were drugs, clinical stage, and Child–Pugh score. This was confirmed in a multivariate analysis, in which the independent factors affecting OS were also drugs [epirubicin vs. DDP-H; hazard ratio 0.44; 95% confidence interval (CI) 0.29–0.67; $P=0.0001$], clinical stage (I/II vs. III/IV; hazard ratio 1.93; 95% CI: 1.26–2.95; $P=0.0026$), and Child–Pugh score (A vs. B/C; hazard ratio 3.15; 95% CI: 1.92–5.17; $P<0.0001$) (Table 2).

Adverse events

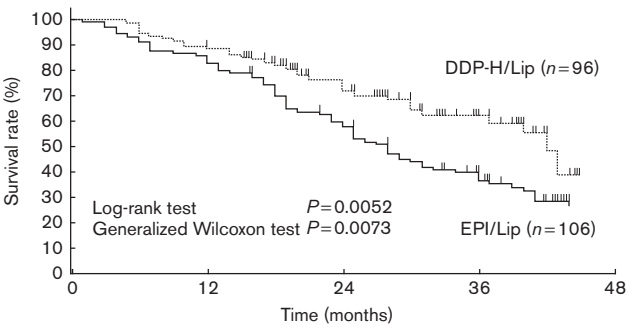
Nausea, fever, abdominal pain, and elevation of serum transaminase levels were observed in most patients in both groups, but these symptoms were mild and transient.

Fig. 1



Comparison of the progression-free survival (PFS) rate between the DDP-H–lipiodol suspension (DDP-H/Lip) group and the epirubicin–lipiodol emulsion (EPI/Lip) group. The PFS rate was significantly higher in the DDP-H/Lip group than in the EPI/Lip group (log-rank test: $P=0.0164$, generalized Wilcoxon test: $P=0.0315$).

Fig. 2



Comparison of the overall survival rate between the DDP-H–lipiodol suspension (DDP-H/Lip) group and epirubicin–lipiodol emulsion (EPI/Lip) group. Overall survival was significantly higher in the DDP-H/Lip group than in the EPI/Lip group (log-rank test: $P=0.0052$, generalized Wilcoxon test: $P=0.0073$).

Table 2 Significant prognostic factors determined by multivariate analysis with the Cox proportional hazards model

	Univariate		Multivariate		
	Log-rank test (*P* value)	Generalized Wilcoxon test (*P* value)	Hazard ratio	95% confidence interval	*P* value
Sex (male vs. female)	0.3666	0.5394	1.16	0.76–1.77	0.5059
Age (<70 vs. ≥70)	0.4910	0.9604	1.03	0.69–1.53	0.8935
Drug (EPI vs. DDP-H)	0.0052	0.0073	0.44	0.29–0.67	0.0001
Stage (I/II vs. III/IV)	0.0009	<0.0001	1.93	1.26–2.95	0.0026
Child–Pugh (A vs. B/C)	<0.0001	<0.0001	3.15	1.92–5.17	<0.0001

DDP-H, fine-powder cisplatin; EPI, epirubicin.

In the DDP-H/Lip group, grade 3 thrombocytopenia (one patient) and hypersensitivity reactions (two patients) were observed. All these cases had recovered within 1 month. No other serious complications or treatment-related deaths were observed in either group.

Discussion

TACE has been widely used for the treatment for unresectable HCC. However, the most suitable anticancer drug for TACE has yet to be established by well-designed randomized control studies [1,2]. The most commonly used TACE treatment for HCC is an emulsion of lipiodol and an anthracycline anticancer agent (doxorubicin or epirubicin), together with a gelatin sponge, but frequent recurrence of tumors occurs with these treatments [13,14]. With regard to the efficacy of doxorubicin and epirubicin anticancer agents, which have been commonly used as conventional chemotherapy with lipiodol for HCC, a randomized controlled comparative study between these two agents did not show any statistically significant differences in either the necrotic rate or the survival rate [6].

Cisplatin is an effective anticancer agent used for the treatment of various malignancies [15]. The antitumor activity of cisplatin is closely associated with the serum concentration of the drug [16] and thus, it can be enhanced by increasing the dose. The response rate to hepatic arterial infusion (HAI) of an aqueous solution of high-concentration cisplatin (65 mg/m^2) without lipiodol was 33.8% in a phase II multicenter clinical trial in Japan [10]. Lipiodol acts as an embolic material and as a selective carrier of anticancer agents, which are then gradually released [17]. Although the mechanism of topical accumulation of lipiodol in the tumor is not yet precisely understood, this agent is used as a targeting drug delivery system to achieve long-lasting accumulation in the tumor cell. Consequently, TACE with lipiodol would be expected to augment antitumor efficacy without severe side effects. Earlier studies have reported that injection of TACE using cisplatin and lipiodol can be safely administered to patients with high-risk HCC and main portal vein occlusion [18,19]. In addition, these studies reported that combining HAI with TACE may promote longer survival of patients with HCC and main portal vein occlusion.

Ono *et al.* [4] reported that TACE using a suspension of cisplatin powder in lipiodol was more effective in treating unresectable HCC than using an emulsion of doxorubicin and lipiodol. Other investigators have also frequently reported the favorable results obtained with TACE using a suspension of cisplatin powder and lipiodol in patients with HCC [5,8]. Conversely, Pelletier *et al.* [20] reported that TACE with cisplatin sometimes causes severe complications such as acute hepatic failure. Furthermore, the treatment did not yield any significant improvements in the survival rate. The use of cisplatin powder for this therapy is further complicated by the characteristics of the drug formulation: cisplatin powder must be custom formulated in individual institutions [21]. Therefore, only those institutions whose pharmacies can properly formulate cisplatin could offer TACE with cisplatin.

A fine-powder formulation of cisplatin, known as DDP-H, for intra-arterial infusion has been available for HCC treatment since 2004 in Japan. Dispensing of cisplatin powder improved with the development of DDP-H, which has now replaced cisplatin powder. TACE using DDP-H became widespread in Japanese institutions because DDP-H/Lip for TACE in patients with HCC was expected to yield better therapeutic outcomes. Morimoto *et al.* [22] investigated the pharmacological advantages of TACE using DDP-H for hypervascular hepatic tumors in animal experiments, and reported that the tumor concentration of the platinum agent in the DDP-H/Lip TACE group was about 14 times higher than that in a group receiving DDP-H aqueous solution by HAI. In addition, they also found that plasma concentrations of the platinum agent at 5 and 10 min from the start of infusion were lower in the DDP-H/Lip group than those in the DDP-H–HAI group. Another study published the results of a phase I/II study of DDP-H for TACE using lipiodol and gelatin sponge particles in HCC patients [23]. The recommended dose (65 mg/m^2 of DDP-H for TACE) was well tolerated in patients with unresectable HCC. The response rate in 19 patients who received the recommended dose was 21% (as measured using Response Evaluation Criteria In Solid Tumors criteria). However, if lipiodol accumulation lesions were excluded from tumor size on the basis of their being nonviable or necrotic, response rate increased to 74%. Grade 3 or higher nonhematological toxicity occurred in 44% (aspartate

aminotransferase/alanine aminotransferase elevation), whereas grade 3 or higher hematological toxicity occurred in 8% of patients (thrombocytopenia). Kawaoka *et al.* [24,25] reported that repeated (three or more times) chemoembolization with cisplatin and lipiodol suspension tended to cause hypersensitivity reactions. Therefore, given the risk of a hypersensitivity reaction, care should be taken in treating patients with chronic cisplatin/Lip infusions. Kasai *et al.* [26] reported that the analysis of the results in the entire study population showed that the objective response rate in the DDP-H group was significantly higher than that in the doxorubicin group. Moreover, although there was no significant difference in the OS between the two groups, this could be explained by the fact that TACE with doxorubicin cannot be repeated as required because of the high incidence of adverse effects with doxorubicin such as leucopenia, severe vascular changes and occlusion of the hepatic artery [4,27,28]. They concluded that anthracyclines such as doxorubicin may be relatively less effective against HCC because of the high expression level of P-glycoprotein in HCC tumors, causing high levels of active efflux of antitumor agents such as anthracyclines or vinca alkaloids from these cells [29]. A similar comparison of the survival rates of patients receiving TACE using either DDP-H/Lip or EPI/Lip has not yet been performed. Therefore, we compared the outcome of TACE using DDP-H/Lip or an emulsion of lipiodol with epirubicin. To ensure that patient characteristics, such as sex, age, Primary Tumor, Regional Lymph Nodes, Distant Metastasis classification, and Child–Pugh score did not influence our results, we used multivariate analysis for the comparison of the efficacy between the dosing regimens. The analysis identified the anticancer agents used for TACE as one of the most important prognostic factors. TACE using gelatin sponge and lipiodol with DDP-H showed better PFS and OS rates than TACE with the EPI/Lip emulsion in patients with HCC. These results warrant further evaluation in advanced HCC that had been treated earlier. Therefore, we are currently conducting a multicenter randomized phase II/III trial comparing DDP-H/Lip TACE with a conventional regimen such as EPI/Lip (ACE 500 study; UMIN000001384).

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