Clinical Utility of Transarterial Infusion Chemotherapy Using Cisplatin-lipiodol Emulsion for Unresectable Hepatocellular Carcinoma

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Abstract. *Background: We evaluated the clinical efficacy of transarterial infusion chemotherapy using a cisplatin-lipiodol emulsion for unresectable hepatocellular carcinoma (HCC). Patients and Methods: Fifty-seven patients with advanced HCC, with no indications for surgical resection or local ablative therapy, such as percutaneous ethanol injection and radiofrequency ablation, were enrolled in this retrospective study. Results: Twelve patients were treated with cisplatin-alone at a dose of 65 mg/m^2 by infusion into the artery. Forty-two patients were treated with the same dose of cisplatin suspended in 1-10 ml of lipiodol (C/LPD). Cumulative survival rates in the cisplatin-treated group were 46.2% at one year, and 18.5% at two years, whereas these in the C/LPD group were 81.6% and 44.4%, respectively, with a significant difference between the two groups ($p<0.01$). In the cisplatin-treated group (n=13), no (0%) patients had a complete response (CR), two (15%) a partial response (PR), three (23%) no change (NC), and eight (62%) progressive disease (PD). In the C/LPD group (n=44), four (9%) patients had CR, 16 (35%) PR, 12 (26%) NC, and 12 (26%) PD. CR and PR were seen in 15% of the cisplatin-treated group and in 44% of the C/LPD group. C/LPD was significantly more effective than cisplatin-alone ($p=0.039$). Some patients showed tumor response to C/LPD after intra-arterial infusion of low-dose 5-fluorouracil. Conclusion: C/LPD produced superior effects compared to cisplatin-alone for unresectable HCC, causing no major side-effects, and increasing the survival rate.*

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Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, and its incidence is increasing in various regions, including Asia. Current options for the treatment of HCC mainly consist of surgical resection, orthotropic liver transplantation, transcatheter arterial embolization (TACE), and percutaneous ablation therapy (1-3). Recent surveillance strategies and advances in imaging have made early-diagnosis possible. However, there are no established therapies for advanced HCC despite recent developments in therapeutic approaches. TACE with anticancer agents and embolic substances has generally been the used treatment for advanced HCC. Chemoembolization is another treatment option, in which embolization agents may be administered together with lipiodol (LPD) during intra-arterial chemotherapy. Doxorubicin, mitomycin, and cisplatin are commonly used for chemoembolization. In some studies (1-4), arterial embolization produced partial responses in 15%-55% of patients. However, embolization is contraindicated in patients with severe liver dysfunction and portal vein thrombosis.

Consequently, in order to achieve higher therapeutic efficacy than that obtained with intravenous administration of anticancer agents, hepatic arterial infusion therapy, in which anticancer agents-alone are infused into the hepatic artery without any embolic substances, is preferred for advanced HCC with tumor thrombi in the portal vein or multiple metastases. Continuous intra-arterial chemotherapy is a treatment in which a drug is infused into an artery supplying a tumor, in order to obtain high concentrations of anticancer agents at the target site in the liver (5, 6). The response rate reaches as high as 46%, according to the nation-wide survey conducted by the Liver Cancer Study

Group of Japan (LCSGJ) (1). Furthermore, the overall survival of responders is superior to that of other patient groups. This technique requires the establishment of a subcutaneously implanted reservoir port; therefore, it is not performed in Western countries (1). Recently, a fine-powder formulation of cisplatin has been developed, making possible the preparation of aqueous solutions of high concentration. The response rate to hepatic arterial infusion of these high-concentration solutions has not been high. Therefore, we speculated that cisplatin would accumulate in liver tumors at higher concentrations if it were mixed with lipiodol, after which the cisplatin-lipiodol (C/LPD) emulsion would be injected *via* the hepatic artery. This treatment would facilitate cisplatin retention in the tumor. Lipiodol can be used as a carrier of antitumor drugs in order to enhance the efficacy of the anticancer agent, without the expectation of producing embolization (7-15).

In this study, we compared the effects of transarterial infusion chemotherapy using C/LPD with the use of cisplatin-alone in patients with unresectable advanced HCC.

Patients and Methods

Patients. From November 2004 to March 2009, 57 patients with advanced HCC with tumor thrombi in the portal vein or in which the tumor had spread throughout the liver, who were not candidates for surgical resection or local ablative therapy such as percutaneous ethanol injection and radiofrequency ablation, were enrolled in this retrospective study at the Department of Gastroenterology, Mie University Hospital.

Patients with HCC were considered eligible for the study if they possessed all of the following characteristics: Eastern Cooperative Oncology Group performance status of 0-1; Child–Pugh classification A or B; maintenance of adequate bone marrow, kidney, and cardiac functions; satisfaction of the clinical laboratory test criteria (white blood cell counts ≥3,000/mm^3, platelet count ≥5×10^4/mm^3, hemoglobin concentration ≥9.5 g/dl, serum creatinine value ≤the upper limit of normal range, blood urea nitrogen ≤25 mg/l, and prothrombin activity ≥50%); and predicted survival time ≥3 months.

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of our hospital, and written informed consent was obtained from all participating patients.

Transarterial infusion chemotherapy. Transarterial infusion chemotherapy was performed through the femoral artery under local anesthesia using the Seldinger method. Angiography of the celiac trunk and superior mesenteric artery was performed to visualize the arterial vascularization of the liver and to evaluate portal vein patency.

A catheter was introduced into the hepatic artery under angiographic guidance. The drug administered was a formulation of 65 mg/m^2 fine-powder cisplatin (IA-call® 100 mg/vial; Nipponkayaku, Tokyo, Japan) suspended in 1-10 ml of lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet, Aulnay-sous-Bois, France) non-ionic contrast medium (C/LPD). The volume of the lipiodol was determined according to the tumor size and the liver function.

Table I. *Characteristics and laboratory data of 57 patients with advanced hepatocellular carcinoma who underwent transcather arterial chemotherapy using cisplatin powder. Data are median (range) or frequencies.*

Variable	N=57
Age, years §	68.5 (37-81)
Gender, male/female	49/8
Etiology, HBV/HCV/other	8/39/10
Child-Pugh classification, A/B	36/21
Laboratory data	
Total bilirubin (mg/dl)	0.8 (0.2-4.6)
Albumin (g/dl)	3.35 (2.4-4.6)
Prothrombin time (%)	80.3 (52.7-122)
Platelet count (×10^4/μl)	10.4 (5.3-35.6)
Stage, III:IVa:IVb	31/18/8
Tumor thrombus, present/absent	19/38
CLIP score	2.72±1.03
AFP (ng/ml)	114 (3-697300)
DCP (mAU/l)	207 (10-142500)
Therapy, cisplatin alone/C/LPD	13/44

HBV, Hepatitis B virus; HCV, hepatitis C virus; CLIP, Cancer of the Liver Italian Program; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; C/LDP, cisplatin with lipiodol.

Most patients were treated by arterial infusion chemotherapy in principle, but lipiodol was not used for all patients, particularly not for those with severe liver failure. In those patients, cisplatin-alone was completely dissolved in 70 ml physiological saline and heated to 50˚C to obtain a final cisplatin concentration of 1.43 mg/ml. The drug was administered at a dose of 65 mg/m^2, by infusion into the artery at a rate of 2 ml/min. Dosage was based on tumor size, and injection was discontinued based on the full accumulation of iodized oil in the tumor vessels and the degree of visualization of the portal vein during injection on fluoroscopy. The accumulation of iodized oil in the tumor was evaluated by computed tomography-hepatic angiography (CTHA) scan; if accumulation in the tumor was poor, other vessels were tested; when a vessel was identified as a feeding vessel, C/LPD was added to the infusion. In cases where the tumor progression was by diffuse infiltration, C/LPD was injected into the right hepatic artery, left hepatic artery, or proper hepatic artery.

To prevent kidney damage, adequate hydration was ensured before and after drug administration by an intravenous drip infusion of 3000 ml/day of an infusion solution. Because of the potentially high incidence of nausea and vomiting, a 5-hydroxvtryptamine antagonist was administered prophylactically, and treatment of symptoms associated with the underlying chronic liver disease, such as digestive system dyspepsia, was permitted.

Response and toxicity evaluation. Before treatment, a complete medical history was taken, together with performance of a physical examination. Laboratory data were obtained, including a complete blood count and chemistry and coagulation parameters. For all patients, a complete blood count and chemical parameters were measured before treatment and at 1, 3, and 7 days, and at 1 month after treatment. The antitumor effect was evaluated by dynamic CT, which was performed 4 weeks after treatment. In addition, the serum alpha-fetoprotein (AFP) and protein-induced by vitamin K

Table II. *Characteristics of patients. Data are reported as means±SD or frequencies.*

Variables	Cisplatin	C/LPD	*p*-Value
No. of patients	13	44	
Age, year	58.1±11.1	68.9±8.3	0.0003
Gender, male/female	11/2	38/6	0.9882
Etiology, HBV/HCV/others	4/9/0	4/30/10	0.7616
Child-Pugh class, A/B	6/7	30/14	0.1885
Child-pugh score	6.5±1.1	5.9±1.0	0.0500
Total bilirubin (mg/dL)	1.37±1.2	0.96±0.5	0.0734
Albumin (g/dL)	3.19±0.6	3.45±0.5	0.151
Prothrombin time (%)	77.6±10.6	81.3±14.7	0.3965
Platelet count ($\times 10^4$/L)	14.2±7.5	10.7±5.6	0.0701
Stage, III:IVa:IVb	6/4/3	25/14/5	0.7671
Tumor thrombus, present/absent	7/6	31/13	0.3068
CLIP score	2.92±0.8	2.41±1.0	0.1132
AFP (median ng/ml)	651 (3-62490)	90 (4.6-697300)	0.7075
DCP (median mAU/L)	479 (10-142500)	144 (10-60800)	0.1865

C/LPD, Cisplatin with lipiodol; HBV, hepatitis B virus; HCV, hepatitis C virus; CLIP, Cancer of the Liver Italian Program; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

absence/antagonist-II/des-γ-carboxy prothrombin (DCP) values were measured as references to determine therapeutic efficacy. The area of lipiodol accumulation and the area of hypoattenuation without contrast enhancement in the early-phase of dynamic CT were evaluated as the area of tumor necrosis. The response was assessed as follows: complete response (CR), complete disappearance or 100% necrosis of all tumors with no evidence of new lesions; partial response (PR), more than 50% reduction and/or more than 50% necrosis of all measurable lesions with no evidence of new lesions; progressive disease (PD), more than 25% enlargement of all measurable lesions or appearance of new lesions; no change (NC), disease not qualifying for classification as CR, PR, or PD.

Low-dose chemotherapy of cisplatin and 5-fluorouracil via implanted fusion port. For some patients with advanced HCC, arterial infusion of cisplatin (10 mg/h on days 1 to 5), together with subsequent 5-fluorouracil (5-FU) (250 mg/5 h on days 1 to 5) every 4 to 6 weeks, through a subcutaneously implanted infusion port (LFP) was also performed. This treatment was essentially continued until disappearance or severe progression of the tumors.

Patients treated with both C/LPD and LFP therapy were further divided into two groups: patients receiving C/LPD, followed by LFP (n=6), and patients receiving LFP followed by C/LPD (n=6).

Statistical analysis. Data were statistically analyzed on July 1, 2009. The un-paired Student's *t*-test was used to compare averages between groups, and the chi-square test and Fisher's exact probability test were used to compare independence. Overall survival rates were computed using Kaplan–Meier estimates and the Kaplan–Meier method. Analyses were performed using the StatView statistics package (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics. The study group consisted of 49 men and 8 women ranging in age from 37 to 81 years (median, 69 years). Tests were positive for hepatitis C virus in 39 patients and for hepatitis B virus in 8 patients. Thirty-six patients were classified as having Child-Pugh class A (63%) disease and 21 as Child class B disease (37%). The median total bilirubin level was 0.8 mg/dl, and the median serum albumin level was 3.35 g/dl. Tumor staging was defined based on the tumor node metastasis staging system of the Liver Cancer Study Group of Japan (LCSGJ), as stage III (one of the three intrahepatic conditions) n=31 (54%), and stage IV [stage Iva (none of the three intrahepatic conditions, with no distant metastases or any intrahepatic condition with lymph node metastases); stage IVb (any intrahepatic condition with distant metastases)], n=26 (46%).

Table II shows a comparison of the baseline data before therapy began between patients treated with transarterial infusion chemotherapy using the fine-powder formulation of cisplatin-alone and the patients receiving the combination of cisplatin powder-lipiodol (C/LPD). There were 13 (23%) out of the 57 study patients who received cisplatin-alone, and 34 (77%) who received C/LPD. No statistically significant differences were seen between the two groups with respect to gender, etiology, albumin, clinical stage, tumor thrombosis, Cancer of the Liver Italian Program (CLIP) score, Child-Pugh class, platelet count, serum total bilirubin, alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP), and prothrombin time (PT) levels. The age of the C/LPD group was significantly greater than the that of the cisplatin group ($p<0.01$).

Survival rates. The overall survival curve is shown in Figure 1. In the cisplatin-treated group, the median follow-up period was 11.0 months (range, 4.0 to 19.0 months). In this group,

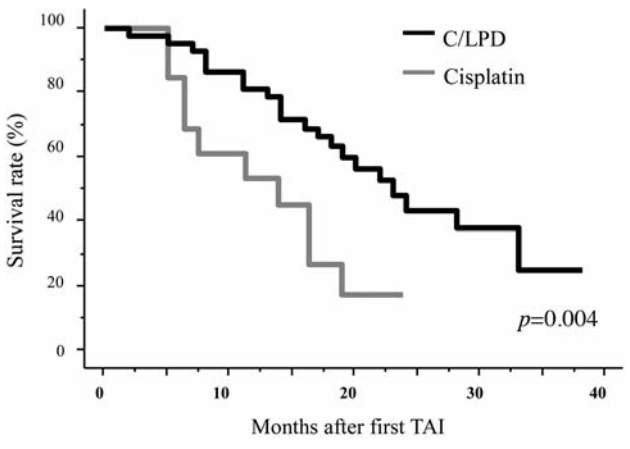

Figure 1. *Cumulative survival rate according to therapy. C/LPD: Cisplatin with lipiodol.*

Table III. *Therapeutic responses according to therapy.*

Responses	Total (%)	Cisplatin (%)	C/LPD (%)
CR	4 (7%)	0 (0%)	4 (9%)
PR	18 (32%)	2 (15%)	16 (35%)
SD	15 (26%)	3 (23%)	12 (26%)
PD	20 (35%)	8 (62%)	12 (26%)

C/LPD, Cisplatin with lipiodol; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table IV. *Univariate analysis for efficacy of cisplatin therapy. Data are reported as means±SD or frequencies.*

Variables	CR/PR	SD/PD	*p*-Value
No. of patients	22	35	
Age, year	70.4±9.4	64.1±9.6	0.0178
Gender, male/female	18/4	31/4	0.4749
Child-pugh score	5.7±1.0	6.3±1.1	0.1262
Total bilirubin (mg/l)	0.93±0.4	1.13±0.9	0.3277
Albumin (g/dl)	3.6±0.5	3.23±0.6	0.0131
Prothrombin time (%)	82.9±14.7	78.5±13.3	0.2494
Platelet count ($\times 10^4$/l)	10.6±4.2	11.8±7.3	0.4751
Tumor thrombus, present/absent	6/16	13/22	0.3974
TAE, with/without	10/12	20/15	0.4411
Lipiodol, with/without	20/2	24/11	0.0397
AFP≥400/<400 (ng/ml)	7/15	17/18	0.1639
DCP≥200/<200 (mAU/l)	10/12	18/17	0.9999
Number of therapies	3.78±1.9	2.29±1.5	0.0031

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; TAE, transarterial embolization; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyl prothrombin.

the cumulative survival rates were 46.2% and 18.5% at one and two years, respectively, whereas in the CD/LPD group, the cumulative survival rates were 81.6% and 44.4%, respectively, with significant differences between the two groups ($p<0.01$). In the C/LPD group, the median follow-up period was 18.1 months (range, 4.1 to 38.0 months).

Therapeutic tumor responses. The tumor responses are shown in Table III. CR and PR were seen in 15% of the cisplatin-treated group, and in 44% of the C/LPD group. C/LPD was significantly more effective than was cisplatin-alone ($p=0.039$).

Evaluation based on the serum levels of tumor markers revealed that among the 26 patients with elevated serum AFP values (AFP>100 ng/ml) before treatment, 14 (54%) showed a decrease in AFP levels subsequent to treatment. With respect to serum DCP, among the 24 patients with elevated serum values of DCP (>40 mAU/l) before treatment, 16 (67%) showed a decreased level after treatment.

To determine the effect of background factors on therapeutic efficacy, monovariate analyses were conducted with respect to age, gender, Child-Pugh score, total bilirubin levels, albumin levels, prothrombin time, platelet count, presence or absence of tumor thrombus, positive or negative history of previous treatment with TACE, with or without lipiodol, and tumor markers (Table IV). Univariate analysis showed significant curative effects in the patients with higher age and higher albumin levels, in patients who received C/LPD, and in patients who underwent a greater number of treatments.

Adverse effects with C/LPD. The incidence of adverse effects and their severity was as follows. Abdominal pain, nausea, vomiting, fever, and anorexia were observed in 75%, 50%, 50%, 45%, and 38% of patients who received C/LPD, respectively. The number of days before the appearance of the symptoms was one for all symptoms, and the number of days until recovery was five. However, these symptoms were transient, and recovery occurred within five days at the most. With regard to clinical laboratory parameters, leukopenia, neutropenia, thrombocytopenia, and elevation of serum aspartate aminotransferase (AST) occurred in ≥40% of the patients. Severe thrombocytopenia occurred in 12.5% of patients. The maximum severity of thrombocytopenia occurred on the third day after treatment. These toxic levels returned to their initial levels within one week after treatment (Figure 2). Liver dysfunction (Child-Pugh score) returned to the initial level within four weeks after the peak in all patients except two, whose score did not attain to the initial level during this follow-up period (Figure 3). Severe renal insufficiency and other serious complications were not

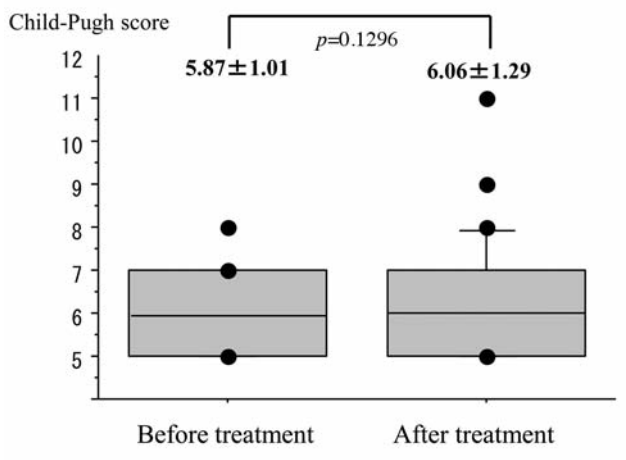

Figure 2. *Child-Pugh score before and after C/LPD therapy.*

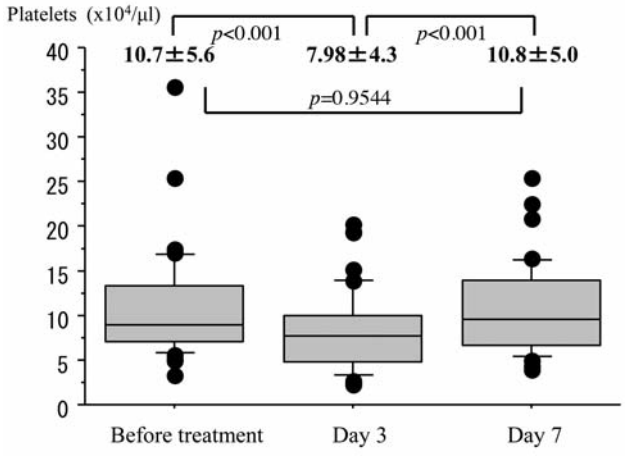

Figure 3. *Platelet counts before and after C/LPD therapy.*

Table V. *Characteristics of patients who changed therapy.*

Variables	C/LPD→LFP	LFP→C/LPD	*p*-Value
No. of patients	6	6	
Age, years §	61.2±13.2	63.5±11.5	0.7508
Gender, male/female	5/1	5/1	
Etiology, HBV/HCV/others	1/4/1	1/4/1	
Child-Pugh class, A/B	4/2	4/2	
Child-Pugh score §	5.5±0.8	6.2±1.5	0.3575
Total bilirubin (mg/dL) §	0.77±0.3	0.84±0.5	0.7709
Albumin (g/dL) §	3.32±0.8	3.60±0.7	0.5103
Prothrombin time (%) §	86.7±18.9	81.6±27.8	0.7363
Platelet count ($\times 10^4$/L) §	16.9±11.1	9.8±4.6	0.1804
Stage, III:IV	5/1	4/2	0.505
Tumor thrombus, present/absent	4/2	5/1	0.505
AFP (median ng/ml)	116 (5.4-73190)	329 (3-10455)	0.3632
DCP (median mAU/L)	4251 (22-60800)	638 (11-24900)	0.4968

LFP, Low-dose 5-fluorouracil with cisplatin.

observed. Injection of C/LPD suspension into the catheter on the second transarterial infusion chemotherapy resulted in anaphylactic shock in one patient, but this patient also subsequently improved within 24 h in two patients.

Comparison between low-dose cisplatin and 5-FU chemotherapy via implanted fusion port. We previously reported the utility of LFP for advanced HCC, such as cases with portal vein tumor thrombi or cases of multiple HCC. However, there were no clear criteria for selecting treatment with either arterial infusion of C/LPD therapy or LFP, the choice was left to the patients. In addition, comparison of the two treatments was difficult because of differences in the respective patients' hepatic and tumor backgrounds. We therefore investigated the characteristics of both therapies by investigating cases in which both therapies were performed in the same patient. The subjects were six patients who were changed from C/LPD to LFP, and six patients who were changed from LFP to C/LPD. No significant differences were seen in the patients' backgrounds (Table V).

Interestingly, among the patients in whom the LFP was administered but no beneficial effect was obtained, beneficial effects including CR were seen in two patients after changing from LFP to C/LPD (Table VI). However, no beneficial effects were seen among the patients who were changed from C/LPD to LFP (Table VII). With regard to the period during which the condition was controlled, there were cases in which the tumor could be controlled for long periods of 10 and 35 months with stable disease (SD) among the LFP patients. During the long-term course, there were

Table VI. *Response and outcome of patients who changed to LFP from C/LPD treatment.*

No	Age/gender	C/LPD		Time-to-progression (months)	Reason for the change	LFP		Time-to-progression (months)
		Freq.	Response			Freq.	Response	
1	63/M	3	PD	-	Angiostenosis	1	PD	-
2	69/F	1	PD	-	Tumor progression	25	SD	35
3	68/M	2	SD	3	Tumor progression	12	SD	10
4	72/M	3	PD	-	Tumor progression	6	PD	-
5	55/M	5	SD	3	Angiostenosis	5	SD	5
6	66/M	4	PR	3	Angiostenosis	4	PD	-

Table VII. *Response and outcome of patients who changed to C/LPD from LFP treatment.*

No	Age/gender	LFP		Time-to-progression (months)	Reason for the change	C/LPD		Time-to-progression (months)
		Freq.	Response			Freq.	Response	
1	62/F	2	PD	-	Infection	2	PD	-
2	69/M	2	PD	-	Tumor progression	10	CR	8
3	78/M	12	SD	10	Obstruction	5	PR	6
4	71/M	3	SD	3	Tumor progression	3	SD	6
5	46/M	3	SD	3	Infection	7	CR	8
6	54/M	4	PD	-	Infection	1	PD	-

patients treated with C/LPD in whom the hepatic artery narrowed with repetition and continuing treatment became difficult, while in the patients treated with LFP, cases of reservoir infection or occlusion were seen.

Discussion

Our study results have shown that arterial infusion chemotherapy using a fine-powder formulation of cisplatin in suspension with lipiodol exerts a favorable effect on advanced HCC and prolongs survival. The efficacy of C/LPD was far superior to that of cisplatin-alone, with response rates of 44% *vs*. 15% with the cumulative survival rates of our study subjects, at 1 and 2 years, of 81.6% *vs*. 46.2% at 1 year and 44.4% *vs*. 18.5% at 2 years.

Yoshikawa *et al*. (13) reported clinical results from a phase II study of hepatic arterial infusion of the fine-powder formulation of cisplatin. The response rate was 33.8%; the 1-year survival rate was 67.5% and the 2-year survival rate was 50.8%.

Some reports have demonstrated good clinical effects of lipiodolization using cisplatin against advanced HCC and the superiority of its clinical results compared with doxorubicin. Maeda *et al*. (9) reported on an overall response rate of 59.4% (142/239 cases) to lipiodolization using a method they developed to suspend cisplatin in lipiodol. Okusaka *et al*. (11) reported a CR rate of 56.3% (9/16 cases) in response to lipiodolization using SM-11355 (a lipophilic platinum derivative). Yamashita *et al*. (15) reported an overall response rate of lipiodolization using cisplatin powder of 57.1% (20/35 cases) and a CR rate of 45.7% (16/35 cases); these results are comparable to our results. Kawaoka *et al*. (14) reported that the OS rates of the 107 patients enrolled in their study who received C/LPD were 86% at 1 year, 40% at 3 years, 20% at 5 years, and 16% at 7 years. Ono *et al*. (4) reported survival rates of patients with unresectable HCC of 30% at 3 years with C/LPD compared with 14% at 3 years with doxorubicin. Kamada *et al*. (8) also reported that the survival rate was significantly better for the C/LPD-treated group than for the doxorubicin/LPD group. Therefore, the antitumor effect of the cisplatin-lipiodol suspension would appear to be due, not only to the effect of the anticancer drug, but also to the maintenance of a high concentration of cisplatin in the lesion for a long time.

In the present retrospective investigation, arterial infusion therapy was performed in: cases of advanced (inoperable)

HCC with clear tumor embolism within vessels; cases of diffuse-type HCC, cases with severe, multiple metastasis in the liver in which TACE was ineffective or it was predicted to be clearly ineffective; and cases in which there were multiple recurrences throughout the liver. In cases of multiple metastases in diffuse or aggregate HCC in particular, the growth pattern was such that it was difficult to obtain an effect with hepatic arterial embolization. In addition, when there were foci in both lobes, it was necessary to treat the entire liver. In cases of portal vein tumor thrombus or arterial-portal venous shunt, there was a possibility that normal embolization would cause hepatic failure, and arterial infusion therapy was thought to be well-indicated.

Considering the difficulty with embolization therapy for such highly advanced cancer, comparatively good results have been achieved with C/LPD. It is thought to be difficult to obtain a significant treatment effect or prolonged survival outcome in groups treated with cisplatin alone.

Cisplatin is mainly excreted by the kidneys. The side-effects of cisplatin are anaphylaxis, nephrotoxicity, neurotoxicity, and hematological toxicity (16-18). With regard to the safety of cisplatin in HCC, following its intravenous administration (80 mg/m^2) to 28 patients with HCC, Okada *et al*. (17) reported the occurrence of nausea or vomiting in 57.1%, leukopenia in 42.9%, thrombocytopenia in 60.7%, anemia in 39.3%, elevation of serum AST in 14.3%, elevation of serum alanine transaminase (ALT) in 14.3%, elevation of total serum bilirubin in 25%, and elevation of serum creatinine in 25% of cases. Yoshikawa *et al*. (13) observed non-hematological toxicities (anorexia, vomiting, fever, general fatigue) in more than 30% of patients who were intra-arterially injected with fine-powder cisplatin, and severe adverse events (grade 3 or higher) including anorexia (22.5%), vomiting (6.3%), and abdominal pain (1.3%). In addition, Yoshikawa *et al*. (13) reported grade 3 or higher thrombocytopenia (2.5%), neutropenia (13%), anemia (1.3%), AST/ALT elevation (11.3%), total bilirubin elevation (3.8%), and creatinine elevation (2.5%). Special caution must be exercised in relation to aggravation of liver damage following hepatic arterial infusion of cisplatin.

Yamashita *et al*. (15) reported that with respect to severe toxicity in their phase II study of lipiodolization using cisplatin powder, there was only one case of grade 3 thrombocytopenia (2.9%). Monitoring during C/LPD injection is therefore warranted, and injection should be stopped at the first sign of symptoms.

We investigated the occurrence of adverse effects after C/LPD arterial infusion, and found trends especially related to hepatic reserve or changes in platelets. No significant exacerbation of hepatic reserve was seen after treatment. There was a transient decrease in platelets after treatment, but the platelets recovered to the pre-treatment level in approximately one week.

Many institutions in Japan attempt reservoir hepatic infusion therapy, including LFP, in which 5-FU, as the effector, and low-dose cisplatin, as the modulator, are concurrently administered from the reservoir, and 5-FU arterial infusion chemotherapy is combined with interferon. There are no direct comparisons in the literature between LFP and C/LPD arterial infusion therapy; a simple comparison of the two treatments cannot be made. In this study, we investigated the utility of C/LPD in 12 patients who received both LFP and C/LPD therapy. There were patients in whom C/LPD was effective even when LFP had not been effective. This would seem to make attempting C/LPD therapy of greater value.

There are no clear criteria in selecting either of these therapies, and it is important to consider the indications individually. With the emergence of molecularly-targeted drugs, treatment for advanced liver cancer has been changing in recent years. It will be necessary to investigate therapeutic systems, including molecularly-targeted drugs, in the future. At present, however, C/LPD therapy may be considered an effective treatment modality with which comparatively good efficacy can be expected, even for advanced liver cancer.

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