ORIGINAL ARTICLE

Gut and Liver, Vol. 7, No. 5, September 2013, pp. 576-584

What Is the Most Effective Drug Delivery System for Cisplatin during the Treatment of Hepatic Tumors with Single-Session Transcatheter Chemotherapy? A Pilot Study

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Background/Aims: The aim of this study was to determine the pharmacodynamics of cisplatin following three different treatment procedures for intrahepatic arterial infusion therapy for hepatocellular carcinoma (HCC). **Methods:** We divided 13 HCC patients into the following three groups: group A, lone injection of cisplatin (n=3); group B, combined injection of cisplatin and lipiodol, with embolization using small gelatin cubes (GCs) (n=5); and group C, injection of suspended lipiodol with cisplatin powder, with embolization using small GCs (n=5). In each group, the free cisplatin concentration in the hepatic vein was measured at 0, 5, 10, and 30 minutes. **Results:** The mean free cisplatin concentrations were as follows. For group A, the mean was 48.58 μg/mL at 0 minute, 7.31 μg/mL at 5 minutes, 5.70 μg/mL at 10 minutes, and 7.15 μg/mL at 30 minutes. For the same time points, for group B, the concentrations were 8.66, 4.23, 3.22, and 1.65 μg/mL, respectively, and for group C, the concentrations were 4.81, 2.61, 2.52, and 1.75 μg/mL, respectively. The mean area under the curve $(AUC)_{0\text{-infinity}}$ for the free cisplatin concentration was 7.80 in group A, 2.48 in group B, and 2.27 in group C. The $AUC_{0\text{-infinity}}$ for the free cisplatin concentration gradually decreased, from group A to group C. **Conclusions:** These results indicate that the combination of lipiodol and small GCs may be useful for delaying cisplatin drainage from the liver. **(Gut Liver 2013;7:576-584)**

Key Words: Cisplatin; Attention; Carcinoma, hepatocellular; Drug delivery

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common neoplasms in Africa and in Asia, including Japan. It was established recently that more than 80% of cases with HCC have liver cirrhosis, and therefore a routine check-up for cirrhotic patients using ultrasound (US) usually detects small HCCs. However, due to the association between cirrhosis and tumor multiplicity, surgical resection is performed in only 20% of cases or less.[1,2] Transcatheter arterial chemoembolization (TACE) has been reported to be an effective palliative treatment for patients with unresectable HCC.[3-10] Although repeated TACE is one of the most potent therapies for unresectable HCC, resistance to this therapy often results after repeated therapy, with the long-term survival rates achieved after 3 years not being sufficiently high.

Platinum analogues are effective against many malignant tumors, and in recent years have been used in the treatment of HCC. For example, there are numerous reports that cisplatin is effective for advanced HCC and that combination therapy of cisplatin and lipiodol may be especially effective.[11-18]

Our group has reported previously that the rate of complete or partial response in cases of epirubicin TACE-resistant patients was significantly higher in patients treated with a platinum-analogue used TACE compared with a single hepatic arterial injection (HAI) without embolization.[19]

It is thought that the measurement of cisplatin concentration in samples collected from the hepatic veins after intrahepatic infusion is a useful method for determining differences in the curative effect of different treatment methods for cisplatin.

However, to our knowledge, there is no information on cisplatin concentration in the hepatic vein following different treatment methods. The aims of this study were therefore to measure total (protein-bound and unbound) and free (protein unbound)-cisplatin concentration in the hepatic vein and to carry out a pharmacokinetic analysis on the three kinds of drug delivery

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Received on September 21, 2012. Revised on January 7, 2013. Accepted on January 31, 2013. Published online on August 14, 2013.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2013.7.5.576

methods.

MATERIALS AND METHODS

1. Study population and ethical considerations

From 2007 to 2008, we carried out a prospective study on total and free cisplatin concentration in samples collected from the hepatic and peripheral veins during transcatheter arterial cisplatin chemotherapy in 13 patients with HCC. All the patients were considered to have an unresectable HCC at the time of diagnosis. Before treatment with the platinum analogue, all the patients underwent an evaluation consisting of a medical history, physical examination, measurement of tumor size, performance status, chest radiograph, liver imaging (computed tomography [CT], US, and digital subtraction angiography [DSA]), complete blood count, and blood chemistry. The diagnosis of HCC was established on the basis of the findings of the US, CT, and DSA.

A total of 13 patients were enrolled in the study using the following inclusion criteria: 1) typical hypervascular HCC observed in all imaging modalities; 2) Child-Pugh A or B classification; 3) performance status of 0 to 1; 4) adequate liver function with a bilirubin level ≤5 mg/dL; 5) sufficient hematopoietic function with a platelet count of >25,000 mm^3 and leukocyte count >2,000 mm^3; 6) an expected survival time of at least 3 months.

At first, if the patients had advanced portal vein invasion (tumor thrombus reaching the main trunks of the portal vein) or a severe arterioportal shunt, they were treated using only transcatheter arterial infusion of cisplatin (group A). The remaining patients were informed of the two other methods for administering cisplastin and the appropriate method was then chosen. One group received a combined injection of cisplatin and lipiodol, with embolization in small gelatin cubes (GCs) (group B), while the other group received an injection of suspended lipiodol with cisplatin powder, with embolization in small-GCs (group C). As a result, three patients were assigned to group A, five to group B, and five to group C (Fig. 1). The clinical background, laboratory data, and tumor characteristics of the patients are summarized in Tables 1 and 2.

The physicians in charge explained the purpose and method of this clinical trial to each patient, who provided their informed consent prior to participation.

The study was approved by Institutional Review Board of our hospital.

2. Details of treatment procedures

Hydration of the patients was performed through a peripheral line. The femoral artery was catheterized under local anesthesia, and a catheter then inserted superselectively into the hepatic artery that supplied the target tumor, followed by injection of cisplatin (IA-call; Nippon Kayaku, Tokyo, Japan) with or without lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet, Aulnay-sous-Bois, France) and 1-mm GCs (Gelpart; Nippon Kayaku). The dose of cisplatin was 100 mg/body administered over 20 minutes under careful fluoroscopic guidance.

In group A, only cisplatin was administered using transcatheter arterial infusion; in group B, cisplatin and lipiodol were first divided into six to eight parts and injected mutually, followed

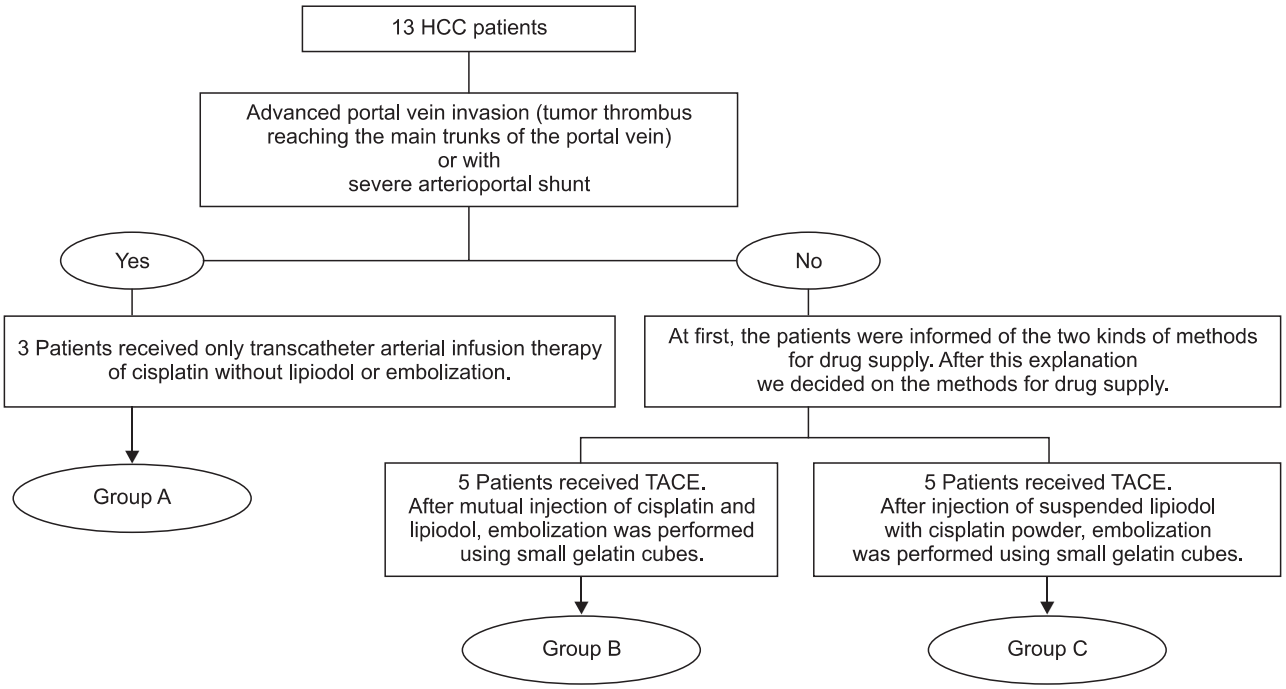

Fig. 1. Distribution of patients receiving cisplatin by three different administration procedures.
HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

Table 1. Demographic and Laboratory Data for 13 Patients with Unresectable Hepatocellular Carcinoma Who Underwent Blood Sampling from the Hepatic and Peripheral Veins for the Measurement of the Cisplatin Concentration after Transcatheter Arterial Chemotherapy Using Cisplatin

Parameter	Group A (n=3)	Group B (n=5)	Group C (n=5)
Patient characteristics			
Gender, male:female	2:1	4:1	5:0
Age, yr*	58 (46-73)	67 (57-87)	69 (63-77)
Backgrounds of liver disease			
Hepatitis B surface antigen positive	2	1	1
Anti-HCV antibody positive	1	4	4
Both negative	0	0	0
Liver function status			
Child-Pugh classification, A/B	2/1	5/0	5/0
Laboratory data			
Albumin, g/dL*	3.4 (2.8-3.7)	3.1 (2.9-4.0)	3.7 (3.2-3.9)
Bilirubin, mg/dL*	0.6 (0.4-1.8)	0.7 (0.5-1.4)	1.0 (0.5-1.1)
Prothrombin time, %*	94.7 (72.6-100.3)	86.8 (72.2-97.3)	82.1 (63.0-89.5)
AFP, μg/L*	55.9 (31.7-114,560.0)	1,664.0 (38.9-98,200.0)	116.0 (6.8-3,702.0)
DCP, AU/L*	3,065.0 (2,139.0-12,391.0)	141.5 (32.0-137,420.0)	98.5 (14.0-190.0)

*Data are presented as median (range).
HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-γ carboxyprothrombin.

Table 2. Profiles of 13 Patients with Unresectable Hepatocellular Carcinoma Who Underwent Blood Sampling from the Hepatic and Peripheral Veins for the Measurement of the Cisplatin Concentration after Transcatheter Arterial Chemotherapy Using Cisplatin

Profiles of liver cancer	Group A (n=3)	Group B (n=5)	Group C (n=5)
Tumor size, median (range), mm	139 (79-187)	65 (16-140)	26 (5-76)
Intrahepatic multiplicity			
Solitary	0	0	1
Multiple, localized to one segment	0	0	0
Multiple, localized to one lobe	0	2	0
Multiple, extended to both lobes	3	3	4
Portal vein invasion, no/yes	1/2	3/2	4/1

by embolization using 1-mm GCs; and in group C embolization was performed using 1-mm GCs after injection of suspended lipiodol with cisplatin powder. In patients treated with lipiodol, its volume ranged from 2.0 to 5.0 mL, with the dose being determined according to tumor size and degree of liver dysfunction.

3. Method of drug and pharmacokinetic analyses

A pharmacokinetic study of cisplatin was performed after transcatheter arterial chemotherapy on day 1. After administration of cisplatin, blood samples were collected from the hepatic and peripheral veins. Total and free platinum concentration was measured in each sample, with the detailed pharmacokinetic study being performed only on the hepatic vein samples. The time the arterial infusion finished represented the observation starting point (0 minute), with blood samples collected at 5, 10, and 30 minutes. A sample was also collected from a peripheral vein 120 minutes after the completion of cisplatin infusion (Fig. 2). The blood samples were collected into heparinized syringes for measurement of plasma ultrafilterable platinum levels. Each sample was centrifuged at 3,000 rpm for 10 minutes and the plasma then placed in an ultrafiltration kit (Contrifree, MMPS-3; Amicon Inc., Tokyo, Japan), followed by centrifugation at 1,700×*g* for 20 minutes. This plasma ultrafiltrate was frozen immediately and stored at <-20°C. Platinum concentrations were analyzed using flameless atomic absorption spectrophotometry using a Hitachi polarized Zeeman atomic absorption spectrometer (Model Z-8000 with graphite furnace, temperature controller and autosampler; Hitachi Factor, Tokyo, Japan). The sample volumes were 10 μL. The oven was programmed using the following steps: 1) drying, 40 seconds at 80°C to 100°C; 2) drying, 50 seconds at 100°C to 130°C; 3) drying, 15 seconds at 130°C to 600°C; 4) charring, 15 seconds at 1,800°C; 5) atomization, 10 seconds at 3,000°C; 6) cleaning, 3 seconds at 3,000°C.

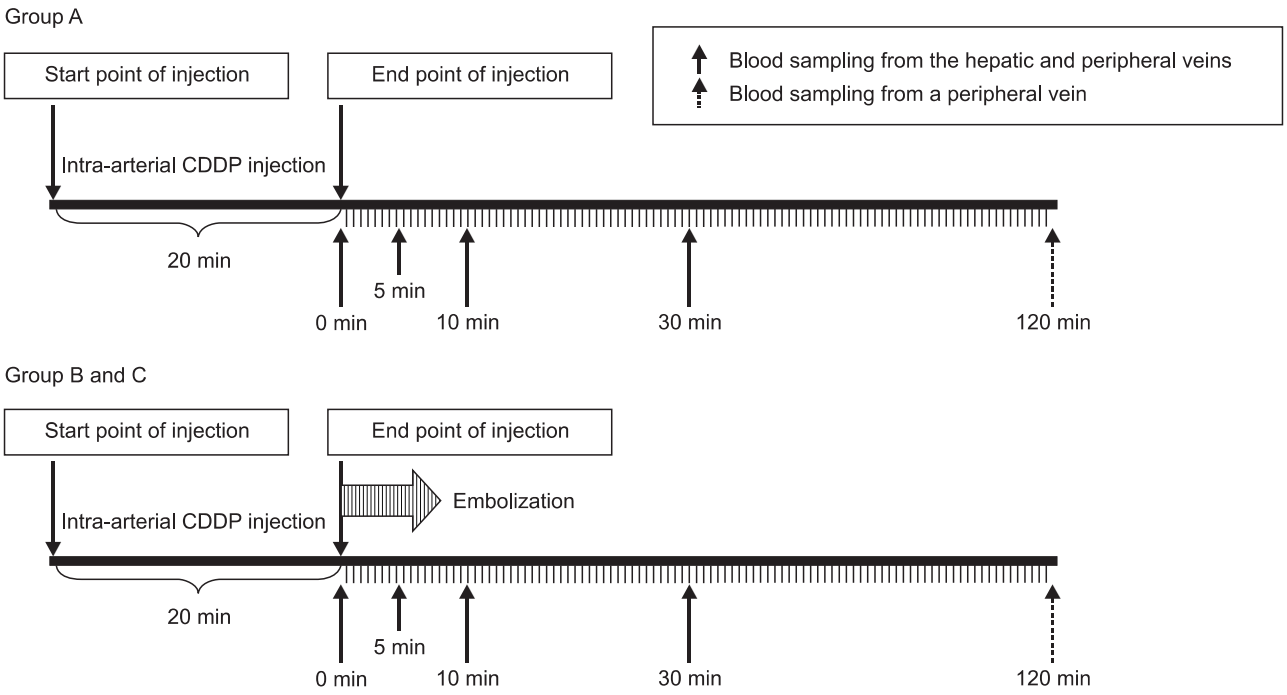

Fig. 2. Study protocol of cisplatin injection and blood sampling.
CDDP, cisplatin.

The absorbance of the samples was then measured at 265.9 nm. Standardization was performed using cisplatin saline solutions up to 1 μg/mL, with a detection limit of 10 ng/mL. Using this ultrafiltration kit almost all protein-bound cisplatin was eliminated and only free cisplatin (protein-unbound) could be measured. The measurement of cisplatin was carried out by NAC Co., Ltd., Tokyo, Japan. The AUC of total and free-cisplatin was calculated by the Automated Pharmacokinetic Analysis System computer program.[20]

4. Toxicity evaluation

Treatment-related toxicity was assessed using the National Cancer Institute Common Terminology Criteria version 4.0. The following toxicity evaluations were made within the 2 week period before treatment was started, and 3 to 7 days (three times during this period) and 2 weeks after treatment was started: hematological (leukocyte and thrombocyte counts) and clinical chemistry assessments (serum aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], total bilirubin, and serum creatine).

RESULTS

1. Total and free-cisplatin concentration in hepatic vein samples following each treatment procedure

The mean±SD total and free-cisplatin concentrations in hepatic vein samples were 68.08±30.30 and 48.58±41.56 μg/mL at 0 minute, 8.18±0.92 and 7.31±1.46 μg/mL at 5 minutes, 6.48±1.95 and 5.70±1.65 μg/mL at 10 minutes, and 9.46±8.59 and 7.15±7.12 μg/mL at 30 minutes in patients in group A; 10.35±4.89 and 8.66±5.36 μg/mL at 0 minute, 5.35±1.04 and 4.23±1.39 μg/mL at 5 minutes, 5.23±1.79 and 3.22±0.91 μg/mL at 10 minutes, and 3.36±0.67 and 1.65±0.33 μg/mL at 30 minutes in patients in group B; and 5.54±5.21 and 4.81±4.95 μg/mL at 0 minute, 3.30±1.28 and 2.61±1.19 μg/mL at 5 minutes, 3.75±1.97 and 2.52±1.13 μg/mL at 10 minutes, and 2.55±1.37 and 1.75±1.05 μg/mL at 30 minutes in patients in group C (Fig. 3).

With the exception of the 30 minutes time point, free-cisplatin concentration and the mean concentration of total and free-cisplatin were higher in the order of group A, B, and C at each measurement point.

2. Total and free-cisplatin concentration from a peripheral vein following each treatment procedure

Mean±SD total and free-cisplatin concentration of samples collected from a peripheral vein were 12.35±3.01 and 11.94±2.67 μg/mL at 0 minute, 6.75±1.00 and 5.87±0.35 μg/mL at 5 minutes, 5.54±1.01 and 4.92±0.61 μg/mL at 10 minutes, 3.91±1.40 and 2.69±0.68 μg/mL at 30 minutes, and 1.59±0.76 and 0.66±0.23 μg/mL at 120 minutes in patients in group A; 5.54±1.47 and 3.80±0.68 μg/mL at 0 minute, 4.31±0.55 and 3.04±0.51 μg/mL at 5 minutes, 4.33±1.08 and 2.65±0.45 μg/mL at 10 minutes, 3.34±0.76 and 1.66±0.17 μg/mL at 30 minutes, and 2.48±0.54 and 0.39±0.15 μg/mL at 120 minutes in patients in group B; and 2.30±0.88 and 1.70±0.95 μg/mL at 0 minutes, 2.49±0.68 and 1.93±0.58 μg/mL at 5 minutes, 2.21±0.93 and 1.58±0.51 μg/mL at 10 minutes, 1.85±0.77 and 1.07±0.40 μg/

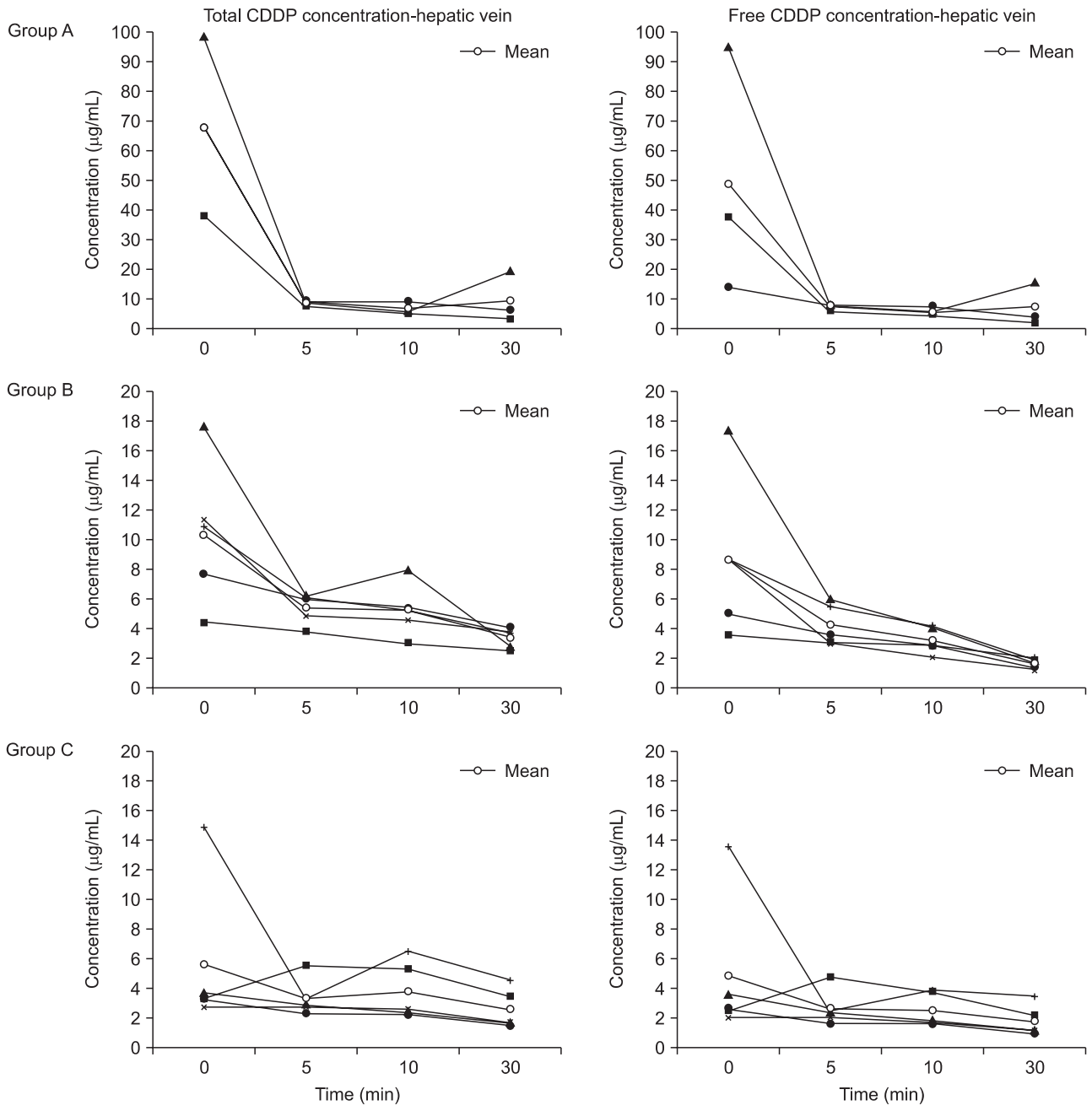

Fig. 3. Total and free cisplatin concentrations in samples collected from the hepatic vein after injection.
CDDP, cisplatin.

mL at 30 minutes, and 1.37±0.75 and 0.46±0.47 μg/mL at 120 minutes in patients in group C (Fig. 4).

The mean concentrations of total and free-CDDP were higher in the order of group A, B, and C at each measurement point, with the exception of the 120 time point.

3. Pharmacokinetic analysis of total cisplatin concentration in samples from the hepatic vein, following each treatment procedure

The pharmacokinetic analysis showed mean±SD maximum concentration (Cmax) of cisplatin in hepatic vein samples was 68.08±30.30 μg/mL in group A, 10.35±4.89 μg/mL in group B, and 5.99±5.06 μg/mL in group C.

Mean±SD $AUC_{0\text{-last}}$ was 6.43±2.70 μg/mL in group A, 2.52±0.65 μg/mL in group B, and 1.71±0.87 μg/mL in group C, while mean±SD $AUC_{0\text{-infinity}}$ was 11.84±6.16 μg/mL in group A, 5.93±2.00 μg/mL in group B, and 3.77±1.73 μg/mL in group C. The mean Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-infinity}}$ of total and free-cisplatin concentration were all higher in the order of group A, B, and C at each measurement point. The mean±SD of terminal half-life ($t_{1/2}Z$) was 0.53±0.17 hours in group A, 0.68±0.33 hours in group B, and 0.59±0.13 hours in group C (Table 3).

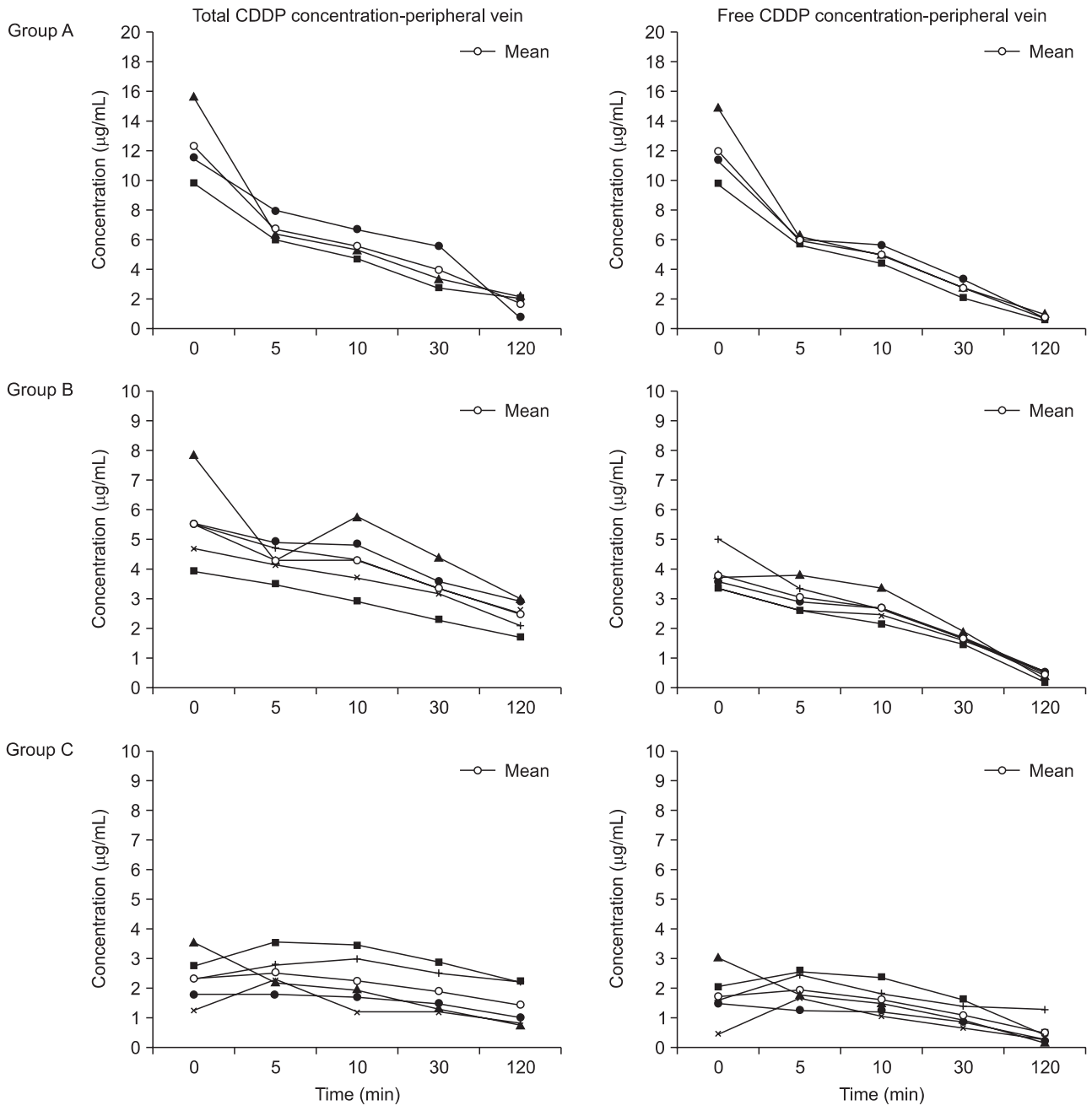

Fig. 4. Total and free cisplatin concentrations in samples collected from the peripheral vein after injection.
CDDP, cisplatin.

4. Pharmacokinetic analysis of free cisplatin concentration in samples from the hepatic vein following each treatment procedure

Pharmacokinetic analysis of free cisplatin in hepatic vein samples showed mean±SD Cmax was 48.58±41.56 μg/mL in group A, 8.66±5.36 μg/mL in group B, and 5.27±4.77 μg/mL in group C; $AUC_{0\text{-last}}$ was 5.01±2.81 μg/mL in group A, 1.66±0.51 μg/mL in group B, and 1.24±0.61 μg/mL in group C, and $AUC_{0\text{-infinity}}$ was 7.80±4.96 μg/mL in group A, 2.48±0.53 μg/mL in group B, and 2.27±1.10 μg/mL in group C. The means of Cmax, $AUC^{0\text{-last}}$, and $AUC_{0\text{-infinity}}$ for total and free cisplatin concentration was higher in the order of group A, B, and C at each measurement point. The mean±SD $t_{1/2}Z$ was 0.36±0.05 hours in group A, 0.35±0.10 hours in group B, and 0.45±0.06 hours in group C (Table 4).

5. Toxic effects

In this study, grade 4 side effects were not observed, although the following grade 3 events were observed: decreased hemo-

Table 3. Pharmacokinetic Parameters of Total Cisplatin

Parameter	Group A (n=3)	Group B (n=5)	Group C (n=5)
Hepatic vein			
Cmax, μg/mL*	68.08±30.30	10.35±4.89	5.99±5.06
$t_{1/2}Z$, hr†	0.53±0.17	0.68±0.33	0.59±0.13
$AUC_{0\text{-last}}$, μg/hr/mL‡	6.43±2.70	2.52±0.65	1.71±0.87
$AUC_{0\text{-infinity}}$, μg/hr/mL§	11.84±6.16	5.93±2.00	3.77±1.73

Data are presented as mean±SD.
*Cmax, maximum concentration (units, μg equation of cisplatin/mL); †$t_{1/2}Z$, terminal half-life (units, hour); ‡$AUC_{0\text{-last}}$, area under the curve from zero to the last measurable time point (units, μg equation of cisplatin/hr/mL); and §$AUC_{0\text{-infinity}}$, area under the curve from zero to infinity (units, μg equation of cisplatin/hr/mL).

Table 4. Pharmacokinetic Parameters of Free Cisplatin

	Group A (n=3)	Group B (n=5)	Group C (n=5)
Hepatic vein			
Cmax, μg/mL*	48.58±41.56	8.66±5.36	5.27±4.77
$t_{1/2}Z$, hr†	0.36±0.05	0.35±0.10	0.45±0.06
$AUC_{0\text{-last}}$, μg/hr/mL‡	5.01±2.81	1.66±0.51	1.24±0.61
$AUC_{0\text{-infinity}}$, μg/hr/mL§	7.80±4.96	2.48±0.53	2.27±1.10

Data are presented as mean±SD.
*Cmax, maximum concentration (units, μg equation of cisplatin/mL); †$t_{1/2}Z$, terminal half-life (units, hour); ‡$AUC_{0\text{-last}}$, area under the curve from zero to the last measurable time point (units, μg equation of cisplatin/hr/mL); and §$AUC_{0\text{-infinity}}$, area under the curve from zero to infinity (units, μg equation of cisplatin/hr/mL).

globin level in one patient (8%), decreased platelet counts in one patient (8%), increased AST in five patients (38%), increased ALT in two patients (15%), and increased bilirubin level in two patients (15%). All these abnormalities resolved within two weeks. In this study group, no other serious complications or treatment-related deaths were observed after administration of cisplatin.

DISCUSSION

Cisplatin is one of the effective carcinostatic agents for HCC. When HCC is treated using transcatheter chemotherapy we usually use a combination of lipiodol and carcinostatics. TACE is now established as a method for administering chemotherapy in cases of HCC. Lipiodol has the characteristic of accumulating in a tumor vessel of HCC, and therefore carcinostatics are usually used in combination with lipiodol when performing TACE. It has been reported that water in an oil type emulsion is useful for steady accumulation and sustained release of carcinostatics.[21,22] However, cisplatin was prepared conventionally for use in intravenous drips using dosage increases in small steps, making preparation of the suspended injection with lipiodol difficult.

Until recently, mutual injections of cisplatin and lipiodol were used as one of the methods for administrating cisplatin in HCC patients. This method was reported previously as "sandwich therapy."[13] Now, "IA-call" which is a preparation of fine cisplatin powder, has been developed for use as an intrahepatic artery injection, with the fine powder being added easily to lipiodol to make a suspension.

In the present study we measured the concentration of total and free-cisplatin in hepatic vein and peripheral vein samples, and determined whether the treatment procedure influenced delay of drug delivery. Our data showed both total and free-cisplatin concentration increased in the order of group A, B, and C. These results may indirectly indicate that cisplatin was slowly released from liver tissue and decreased in the order of group A, B, and C. Regarding these results, we interpreted that lipiodol mainly affected the slow elution of cisplatin, and GCs augmented drug retention in the liver and tumor tissues by a temporary shut off of arterial blood flow. However, in this study, we could not directly investigate cisplatin concentrations in liver and tumor tissues. Although, one recent animal experimental study reported that suspended lipiodol with cisplatin powder mostly retained the cisplatin concentration as compared to other treatment methods (HAI and combined use of GCs without lipiodol) in VX-2 tumor tissues of rabbits.[23] Thus, we will need additional studies on human liver and tumor tissues. At this time, in order to retain cisplatin in liver tissue for a long duration, it was useful that the methods for administering cisplatin, lipiodol, and embolization also affected cisplatin concentration in liver and tumor tissue, and in the case of HCC patients treated with cisplatin, the use of TACE using Lipiodol and small-GCs provided additional benefits based on this study and previously reported experimental study results.[23] In recent years, we have used third-generation platinum compounds that do not have cross-resistance to cisplatin. Repeated use of cisplatin often causes drug resistance and allergic reactions such as anaphylaxis. The risk of allergic reactions increases from the third session of TACE with cisplatin,[24] and therefore, miriplatin can be considered as a second-line chemoembolization agent in patients who exhibit hypersensitivity or resistance to cisplatin. On the other hand, the development of drug-eluting microspheres (DEMs) provides a new treatment method for drug delivery.

Preclinical and clinical studies on TACE using DEM have demonstrated greater and longer retention times of drug within tumors and a lower systemic concentration compared with conventional TACE using lipiodol.[25-27]

To date, two types of microspheres capable of being loaded with a drug are commercially available: superabsorbent polymer microspheres (HepaSphere; Merit Medical Systems, Salt Lake City, UT, USA) and polyvinyl alcohol-based microspheres (DC

Bead; Biocompatibles, Farnham, UK). HepaSphere has a reservoir effect after loading with some chemotherapeutic agents, with two *in vitro* studies confirming that it efficiently loads and elutes doxorubicin, irinotecan, and cisplatin.[28,29]

In accordance with our previous report,[19] Seki and Hori[30] reported it was useful to switch anticancer therapy from epirubicin to cisplatin for treatment of HCC that had become refractory to TACE using epirubicin-loaded microspheres.

We therefore consider that it is necessary for future studies to carry out additional investigations on DEM.

Finally, this study had several limitations. First, the study sample size was too small and we could not examine liver and tumor tissues. In addition, tumor characteristics were different for each treatment method. Therefore, tumor characteristics (i.e., portal vein invasion, severe arterioportal) may have greatly affected the cisplatin concentrations in the hepatic and peripheral veins in group A. Regarding this point, we intend to investigate the same study protocol for patients with similar tumor characteristics in the future. Second, we only investigated useful drug delivery methods under single session transcatheter therapy. Therefore, we did not investigate continuous hepatic arterial infusional chemotherapy (i.e., combined use of cisplatin and 5-fluorouracil [5-FU]).

Primarily in Asian countries, many patients in group A are selected for continuous hepatic arterial infusional chemotherapy if they have adequate liver function. Therefore, additional studies will be needed under continuous hepatic arterial infusional chemotherapy with or without lipiodol. Also, we usually use epirubicin for first line treatment of HCC by TACE in Japan. Therefore, it is difficult to compare the actual efficacy of each anticancer drug (i.e., mitomycin-C, 5-FU) at the same level. Thus, we will need a prospective study to investigate this.

In conclusion, combined use of lipiodol and small-GCs clearly reduced the $AUC_{0\text{-infinity}}$ of total and free cisplatin concentrations in samples collected from the hepatic vein. In other words, free cisplatin concentrations in the liver were retained to a greater extent in the patient group administered lipiodol and small-GCs together. We consider that these results strongly support the combined use of embolization for treatment of HCC without advanced portal vein invasion or with severe arterioportal shunt that uses cisplatin at the time of injection into the hepatic artery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

The present work was supported, in part, by grants-in-aid from the Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labour and Welfare.

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