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Effects of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma Using a Combination of Platinum Agents (Cisplatin plus Miriplatin): A Retrospective Comparison with Cisplatin Monotherapy

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Abstract

Background: Miriplatin is a slow-release, lipophilic platinum complex, developed to produce a superior antitumor effect for hepatocellular carcinoma (HCC). However, the miriplatin suspension is highly viscous and can form an embolism in the hepatic artery, which can result in insufficient antitumor effect. Thus, reducing the viscosity of the suspension compound by combining it with the less-viscous cisplatin suspension might reduce or even prevent vessel embolism, while providing the quick-release effects of cisplatin. **Purpose:** To compare the outcomes of therapy using miriplatin plus cisplatin and cisplatin monotherapy in transcatheter arterial chemoembolization (TACE) for HCC. **Methods:** We retrospectively evaluated a total of 87 patients with Barcelona Clinic Liver Cancer (BCLC) stage A or B HCC who received conventional TACE using a combination of platinum agents (cisplatin and miriplatin) (n = 50) or cisplatin alone (n = 37) for the first time from September 2006 to December 2012. Short term therapeutic effect was measured by dynamic computed tomography 1 - 3 months after TACE, in reference to the modified Response Evaluation Criteria in Solid Tumors. Treatment-related adverse effects were graded by the National Cancer Institute Common Termi-

nology Criteria (ver. 4.0). 1-, 3-, and 5-year survival rates were calculated. Subgroup analyses were performed by Child-Pugh classification and BCLC criteria. **Results:** Median duration of follow-up was 35 months (range 7 - 90). Median overall survival was 38 months. Patients who had combination therapy had better 1-, 3-, and 5-year survival rates: 100%, 56.7%, and 26.2%, respectively, compared to monotherapy: 100%, 42.1%, and 9.0%, respectively ($p = 0.034$). No serious complication or treatment-related mortality was observed in both groups. **Conclusion:** TACE using miriplatin plus cisplatin was related to a prolonged survival, with comparable adverse effects of TACE using cisplatin alone.

Keywords

Hepatocellular Carcinoma, Transcatheter Arterial Chemoembolization, Miriplatin, Cisplatin

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignant diseases globally [1]. In Japan, more than 30,000 people die from HCC each year [2]. Curative therapies, including surgical resection, liver transplantation, and percutaneous tumor ablation, are applicable in only 30% - 40% of patients with HCC. For those patients ineligible for curative therapy, transcatheter arterial chemoembolization (TACE) is an effective palliative treatment [3]-[9]. According to the 2013 guidelines for therapy of HCC by the Japan Society of Hepatology, TACE is recommended for two or three tumors larger than 3 cm in diameter and for 4 or more tumors [10]. Moreover, the Barcelona Clinic Liver Cancer (BCLC) group recommends TACE for 2 or 3 tumors larger than 3 cm in diameter and for 4 or more tumors in patients with Child-Pugh A or B class [11]. Although many chemotherapeutic agents (e.g., epirubicin, mitomycin C, doxorubicin, and cisplatin) are used in the treatment of HCC, a consensus on the optimal regimen for first- or second-line chemotherapeutic agents for TACE has not been reached [4] [12] [13] [14] [15]. Miriplatin (cis-[((1R,2R)-1,2-cyclohexanediamine-N,N') bis(myristato)]-platinum (II) monohydrate; Dainippon Sumitomo Pharma Co., Ltd, Osaka, Japan) is a lipophilic cisplatin derivative that can be suspended in lipiodol, a lipid lymphographic agent that is also used with the above-mentioned therapeutic agents [16] [17] [18]. Conversely, fine-powder cisplatin (IA-call; Nippon Kayaku Co., Ltd. Tokyo, Japan) is a powdered preparation of cisplatin with a mean particle diameter of 25 μm. Because cisplatin is hydrophilic and its suspension is unstable in lipiodol, cisplatin is released from the suspension more rapidly than miriplatin is.

Some previous studies have reported that miriplatin is effective against HCC [19] [20]. Moreover, the addition of embolizing agents to the miriplatin-lipiodol suspension has resulted in a higher objective response in patients with HCC

[21]. Additionally, TACE with warmed miriplatin has been found to be more effective than TACE with room-temperature miriplatin for the treatment of HCC [22]. However, a number of groups have reported that the response rate of TACE with miriplatin is only 50% - 60% [21] [23] [24] [25] and that treatment results are not improved relative to other chemotherapeutic agents [5] [6] [26]. Recent studies have reported a response rate of TACE with cisplatin of 60% - 80% [27] [28] [29].

We conducted a single-center retrospective cohort study to investigate the hypothesis that TACE using miriplatin and cisplatin/lipiodol suspension can improve the anti-tumor effects in patients with HCC compared to TACE using cisplatin/lipiodol suspension. In addition, we evaluated the incidence of adverse events.

2. Materials and Methods

2.1. Patients

This was a retrospective cohort study. Patients with HCC were recruited this study if they met the following inclusion criteria: age 20 to 85 years; at least one typical HCC finding on digital-subtraction angiography; pathologically and/or clinically diagnosed HCC; other treatment was not found to be effective or suitable for their condition according to the Japanese therapeutic guidelines for HCC; Stage A or B in BCLC criteria; performance status for the Eastern Cooperative Oncology Group was 0 - 2; adequate hepatic function (Child-Pugh class A or B, total bilirubin ≤ 3.0 mg/dl; albumin ≥ 2.0 g/dl); adequate hematological function (neutrophils ≥ 1500/mm^3, platelets ≥ 40,000/mm^3, hemoglobin ≥ 7.0 g/dl); and sufficient renal function (creatinine clearance ≥ 50 ml/min adjusted for 1.73 m^2 of body surface area).

The medical records of 313 consecutive Japanese adult patients with HCC were reviewed in accordance with a TACE study protocol from September 2006 to December 2012 at Southern-Tohoku General Hospital. Of these patients, we enrolled 87 patients who received miriplatin plus cisplatin [the double-platinum (DP)-TACE group)] or cisplatin alone [the cisplatin (CDDP)-TACE group] for the first time.

This study was approved by our institutional review board and was conducted in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all the patients before TACE.

2.2. HCC

Based on computed tomography (CT), or magnetic resonance imaging and digital-subtraction angiography findings, nodules were radiologically diagnosed as HCC if they showed typical enhancement pattern of HCC (*i.e.*, substantial enhancement in the arterial phase and washout with a corona-like peripheral enhancement during the portal or equilibrium phase) or characteristics similar to coexisting nodules previously diagnosed as HCC.

3. Treatment

All TACE procedures were performed super selectively. A4 or 5-Fr Shepherd Hook catheter (FansaIV or Angiomaster; Terumo Clinical Supply, Gifu, Japan) was inserted via femoral artery. Portography through the superior mesenteric artery and celiac artery was performed to reconfirm the site of HCC. Next, as a superselective one-step method, a <2.0-Fr microcatheter (Carnelian® PIXIE ER; Tokai Medical Products, Aichi, Japan; Sniper 2 μ7; Terumo Clinical Supply, Gifu, Japan) was advanced into the subsegmental artery via femoral artery, and the miriplatin-cisplatin/lipiodol suspension or cisplatin/lipiodol suspension was administrated slowly under careful fluoroscopic guidance. The miriplatin-cisplatin/lipiodol suspension contained 60 mg of miriplatin, 50 mg of cisplatin, and 6 mL of lipiodol. The cisplatin suspension contained 100 mg of cisplatin and 10 mL of lipiodol. The dosages were determined according to tumor size, treatment area, and patient liver function. Subsequently, the feeding arteries to HCC were embolized with 1-mm gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan). If extrahepatic collateral arteries were present, TACE was performed through these collateral arteries. Large tumors (e.g., those of >10 cm in diameter) were treated by a single TACE, with the embolization performed using a larger number of gelatin particles than that for smaller tumors. Post-procedural unenhanced C-arm CT images were obtained to check for lipiodol accumulation in the tumors.

To avoid renal damage before and after injection of the chemotherapeutic agents, appropriate preload replacement was done by intravenous infusion of 500 - 2000 mL.

4. Evaluation of the Antitumor Efficacy

The primary endpoint is the response rate that is the proportion of complete response (CR) and partial response (PR). The evaluation was performed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [30]; CR was defined as the disappearance of any arterial enhancement in the tumors or 100% necrosis of all the tumors, PR was defined as a>30% reduction and/or necrosis in the sum of diameters of viable target lesions, progressive disease (PD) was defined as a >20% enlargement in the sum of viable target lesions and/or the appearance of new lesions, and stable disease (SD) was considered as any disease that did not qualify for classification as CR, PR, or PD. The size of the lesions were measured by contrast-enhanced CT or magnetic resonance imaging at one to three months after TACE, based on changes in the maximum diameter of viable target lesions, which had been observed as arterially enhanced areas. For six patients with an allergy to the iodine compound, magnetic resonance imaging was used to assess the effect on the tumor.

Forty-three and 30 patients in the DP-TACE and CDDP-TACE groups, respectively, were treated with additional TACE, performed using the same drugs as in the initial TACE. The indication for the additional TACE was the appearance

of new lesions, residual tumor, and recurrence of the local tumor. Nine and 9 patients in the DP-TACE and CDDP-TACE groups, respectively, were treated with sorafenib after TACE failure.

4.1. Toxicity Evaluation

Adverse effects were assessed by the National Cancer Institute Common Terminology Criteria (ver. 4.0). We evaluated complete blood cell count, clinical biochemistry, and symptoms (*i.e.*, fever, appetite loss, abdominal pain) within 14 days before treatment (pre), at 3 - 7 days and 1 month after TACE,

4.2. Statistical Analysis

IBM SPSS software program (IBM Corp., Armonk NY, USA) was used to perform all the statistical analyzes. Fisher's exact test or Kruskal-Wallis exact test was used to compare categorical variables and the Mann-Whitney *U*-test was used to compare median values of continuous variables. Death was calculated using the Kaplan-Meier method and was compared using the log-rank test. Survival duration was measured from the time of recruitment until either death or the date of the last follow-up visit for patients who remained alive. A P-value of <0.05 by a two-tailed test were considered statistically significant.

5. Results

5.1. Patient Characteristics

Table 1 shows the patients' baseline characteristics. Among 87 patients with HCC, 50 (57.5%) and 37 patients (42.5%) received miriplatin plus cisplatin from January 2010 to December 2012 or cisplatin alone from September 2006 to February 2010, respectively. There were no significant differences in the gender, age, etiology, laboratory data, Child-Pugh class, or follow up period between the DP-TACE group and CDDP-TACE group.

Tumor profiles and treatment history are summarized in Table 2. There were no significant differences in the tumor size, tumor multiplicity, number of tumors, BCLC Stage, or history of TACE.

Table 1. Base-line characteristics of the patients according to the treatment group.

	CDDP-TACE group	DP-TACE group	P-value
Demographic data			
No. of patients	37	50	
Sex (male/female)	22/15	34/22	0.499
Age, years	73 (52 - 84)	72 (41 - 85)	0.908
Etiology, HBV/HCV/other	4/30/3	5/36/9	0.317
Laboratory data			
Albumin, g/dL	3.6 (2.5 - 4.6)	3.6 (2.2 - 4.7)	0.609
Serumaspartate aminotransferase, IU/L	49 (20 - 161)	46 (17 - 157)	0.534

Continued

Serum alanine aminotransferase, IU/L	41 (7 - 152)	39 (9 - 137)	0.857
Total bilirubin, mg/dL	0.78 (0.25 - 2.22)	0.82 (0.29 - 2.15)	0.864
Platelet count, $\times 10^4$/mL	9.4 (4.0 - 24.7)	10.0 (4.0 - 18.7)	0.952
Prothrombin activity, %	75 (38 - 105)	80 (58 - 111)	0.293
AFP, μg/L	26.5 (1.2 - 17255)	21.8 (1.5 - 3840)	0.847
DCP, AU/L	106.0 (12 - 5235)	118.5 (15 - 39676)	0.305
Child-Pugh class, A/B	25/12	35/15	0.819
Follow-up period, months	34 (7 - 75)	37.5 (15 - 90)	0.226

Continuous variables presented as median and range. Abbreviations: CDDP-TACE: cisplatin transcatheter arterial chemoembolization; DP-TACE: double-platinum transcatheter arterial chemoembolization; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin.

Table 2. Tumor profiles and treatment history of the patients who underwent TACE with miriplatin plus cisplatin or cisplatin alone.

	Total	CDDP-TACE	DP-TACE	P-value
No. of patients	87	37	50	
Tumor size, mm	24 (6 - 123)	25 (6 - 123)	23 (7 - 93)	0.514
Tumor multiplicity (Single/Multiple)	30/57	14/23	16/34	0.367
No. of tumors	2 (1 - 4)	2 (1 - 4)	2 (1 - 4)	0.278
BCLC Stage (A/B)	41/46	21/16	20/30	0.092
History of TACE	51 (58.6%)	21 (56.8%)	30 (60.0%)	0.466

Continuous variables presented as median and range. Abbreviations: CDDP-TACE: cisplatin transcatheter arterial chemoembolization; DP-TACE: double-platinum transcatheter arterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer.

5.2. Short Term Treatment Effects

There was no significant difference between DP-TACE group and CDDP-TACE group for median intervals to the date of CT or MRI from the date of TACE (64 days vs. 70 days; P = 0.175).

Of the 87 treated patients, 39 (44.8%) experienced CR; 24 patients (27.6%), PR; 15 patients (17.2%), SD; and 9 patients (10.3%), PD (Table 2). Overall, 72.4% of patients achieved an objective response (CR plus PR).

In the DP-TACE group, there were 25 CRs (50.0%), 17 PRs (34.0%), 5 SDs (10.0%), and 3 PDs (6.0%). In the CDDP-TACE group, there were 14 CRs (37.8%), 7 PRs (18.9%), 10 SDs (27.0%), and 6 PDs (16.2%). The percentage of patients with either CR or PR was significantly different between the DP-TACE and CDDP-TACE groups (84.0% vs. 56.8%; P = 0.007).

5.3. Survival

Thirty-four and 33 patients assigned to the DP-TACE and CDDP-TACE groups died respectively. Hepatic insufficiency due to worsening of the HCC was the cause of death in 22 and 16 patients in the DP-TACE and CDDP-TACE groups,

respectively. Additionally, progression of hepatic insufficiency without remarkable progression of the HCC was the cause of death in 10 and 12 patients in the DP-TACE and CDDP-TACE groups, respectively. In seven cases, other diseases became the cause of death. The median follow-up period was 35 months (range: 7 - 90 months).

The overall survival rate was significantly better in the DP-TACE group than the CDDP-TACE group (P = 0.037; Figure 1). The 1-year survival values were 100% in the DP-TACE group and 100% in the CDDP-TACE group, whereas the 3-year survival values were 60.8% and 47.2% in the DP-TACE and CDDP-TACE groups, respectively. The 5-year survival values were 27.0% in the DP-TACE group and 9.4% in the CDDP-TACE group. Median survival time was 42 months in the DP-TACE group and 34 months in the CDDP-TACE group.

The overall survival rate was not significantly difference in the BCLC stage A and B (P = 0.288, Figure 2). Median survival time was 52 months in the BCLC stage A group and 36 months in the BCLC stage B group. The overall survival rate was not significantly difference in the Child-Pugh classification A and B (P = 0.768, Figure 3). The overall survival rate was 38 months in the Child-Pugh A group and 38 months in the Child-Pugh B group.

5.4. Toxicity

Table 3 shows the major adverse events. Hematological toxicity was relatively mild and temporal in both groups, although 1 patient (1.4%) developed grade 4 thrombocytopenia in the DP-TACE group. Meanwhile, hyperbilirubinemia, elevations in serum liver enzymes, fever, appetite loss, and abdominal pain occurred

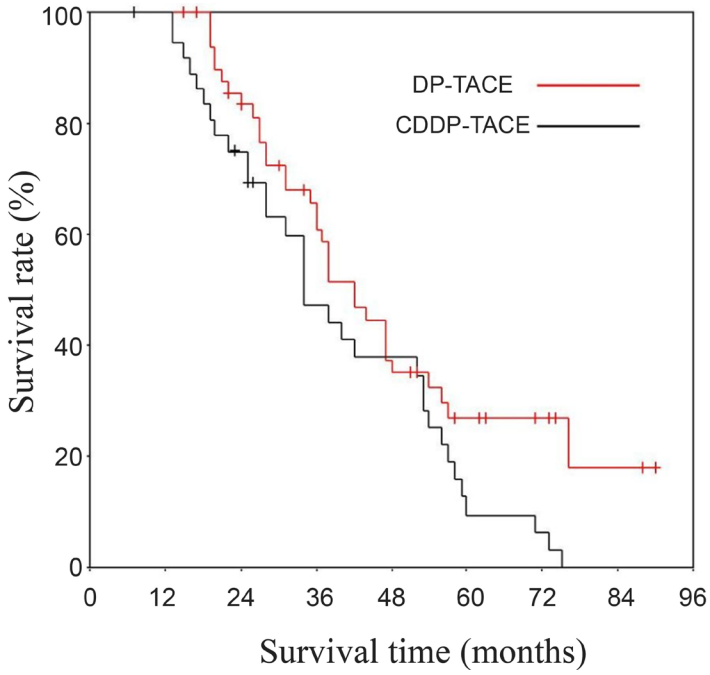

Figure 1. Kaplan-Meier Estimates of Survival in 37 patients who received CPPD-TACE and 50 patients who received DP-TACE (P = 0.037 by the Log-Rank test).

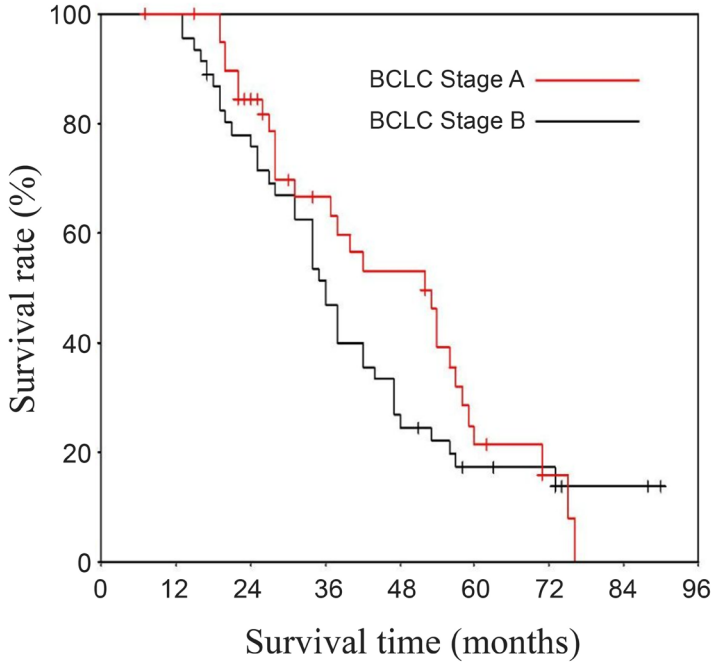

Figure 2. Kaplan-Meier Estimates of Survival in 41 patients who are BCLC stage A and 46 patients who are BCLC stage B (P = 0.288 by the Log-Rank test).

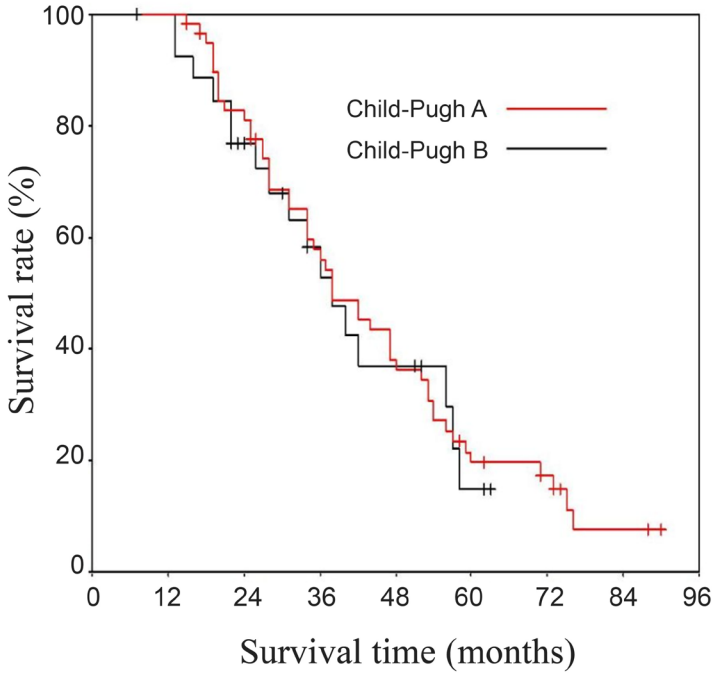

Figure 3. Kaplan-Meier Estimates of Survival in 60 patients who are Child-Pugh classification A and 27 patients who are Child-Pugh B (P = 0.768 by the Log-Rank test).

as major non-hematological toxicities in both groups. The elevation in the serum liver enzymes observed in both groups improved within 2 weeks. Vascular complications in the hepatic artery (*i.e.*, dissection and acute thrombosis) were not observed in the patients. No other severe complication or treatment-related

Table 3. Adverse effects.

	CDDP-TACE				DP-TACE				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	P-value
Decrease in white blood cell count	7 (18.9%)	1 (2.7%)	1	0	2 (4.0%)	3 (6.0%)	1 (2.0%)	0	0.191
Anemia	28 (75.7%)	3 (8.1%)	0	0	26 (52.0%)	10 (20.0%)	1 (2.0%)	0	0.114
Decrease in platelet count	15 (40.5%)	14 (37.8%)	5 (13.5%)	0	22 (44.0)	10 (20.0%)	10 (20.0%)	1 (2.0%)	0.301
Increase in aspartate aminotransferase	17 (45.9%)	11 (29.7%)	8 (21.6%)	0	24 (48.0%)	11 (22.0%)	12 (24.0%)	0	0.761
Increase in alanine aminotransferase	16 (43.2%)	6 (16.2%)	10 (27.0%)	0	31 (62.0%)	10 (20.0%)	0	0	<0.001
Total bilirubin	9 (24.3%)	8 (21.6%)	0	0	16 (32.0%)	7 (14.0%)	1 (2.0%)	0	0.390
Fever	24 (64.9%)	0	0	0	27 (54.0%)	0	0	0	0.381
Appetite loss	17 (45.9%)	0	0	0	19 (38.0%)	0	0	0	0.513
Abdominal pain	19 (51.4%)	0	0	0	25 (50.0%)	0	0	0	0.901

Abbreviations: CDDP-TACE: cisplatin transcatheter arterial chemoembolization; DP-TACE: double-platinum transcatheter arterial chemoembolization.

mortality was observed in either group.

6. Discussion

We retrospectively studied the safety and efficacy of combination therapy using miriplatin plus cisplatin as compared to cisplatin monotherapy in TACE for HCC. This study identified TACE using miriplatin plus cisplatin was associated with a prolonged survival compared to TACE using cisplatin alone.

TACE is widely performed in patients with HCC who are not eligible for curative therapy. Several intra-arterial chemotherapy regimens using adriamycin, fluorouracil, fluorodeoxyuridine, mitomycin C, cisplatin, epirubicin, mitoxantrone, and miriplatin administered alone or in combination have been reported as treatments for HCC [12] [27] [31]. Although some regimens have shown a high response rate, the most effective regimen remains unclear [9] [12] [15].

However, a previous retrospective study that evaluated the safety and efficacy of TACE with miriplatin plus epirubicin reported that local tumor control rates were better with TACE using miriplatin plus epirubicin than TACE using miriplatin [32] [33].

Cisplatin is hydrophilic and barely soluble in lipiodol. Therefore, only a small volume of cisplatin remains in the tumor for a long time. Systemic adverse effects such as nausea, vomiting, and renal dysfunction was caused because most of the agent is released into the bloodstream in the systemic circulation in a short time. Miriplatin has been developed as a lipophilic platinum complex in order to increase the anti-tumor effect for HCC and reduce toxicity than cisplatin [19]. Miriplatin suspension is a stable and colloidal emulsion that is deposited within HCCs and gradually releases active derivatives of miriplatin within

the tumors. Unlike cisplatin, miriplatin is not an active agent against HCC, but miriplatin has greater stability and longer sustained release of active platinum compounds that bind to nuclear DNA in comparison with cisplatin-lipiodol [18]. A previous *in vitro* study reported that only 5.9% of the total platinum was released into the surrounding parenchyma at 28 days after infusion of a miriplatin-lipiodol suspension into artery [34]. The duration of maximum plasma concentration ranged from 18 to 37 days for miriplatin, and only from 10 to 60 minutes for cisplatin [17] [20] [35]. However, the miriplatin suspension is highly viscous and forms an embolism in the vessel when it is administered into the hepatic artery. Hence, a sufficient amount may not reach the peripheral tumor vessels. Therefore, the possibility of early washout is present, which could result in an insufficient antitumor effect. Two methods of lowering the viscosity of a miriplatin suspension are warming the miriplatin suspension [22] or creating an oil-in-water emulsion [36]. However, the efficacy of TACE with a miriplatin suspension relative to that of TACE with a miriplatin emulsion remains controversial [37] [38].

Various modifications such as dilution by mixing with a water-soluble contrast agent and administration after heating have been devised for ensuring that the miriplatin suspension reaches the peripheral tumor vessels. Meanwhile, a previous study has reported that 20% of cisplatin in a cisplatin-lipiodol suspension is released within 24 hours, whereas 50% of cisplatin in a cisplatin-epirubicin-lipiodol suspension is released within 24 hours [31]; this implies that cisplatin is released from lipiodol at different rates when administered alone or in combination with other drugs. Further, although the viscosity of a cisplatin-lipiodol suspension is not different from that of lipiodol alone, a miriplatin-lipiodol suspension has been reported to be slightly more viscous than lipiodol alone [37]. During TACE with a double-platinum suspension, half of the normal concentration of miriplatin is used (10 mg/ml) for preparing the cisplatin-miriplatin suspension. Therefore, a lower-than-normal level of viscosity is expected. We considered that a sufficient antitumor effect could be achieved with a solution at a viscosity that allows the drug to reach the peripheral tumor vessels. That is, an antitumor effect would occur through the combination of the slow-release nature of miriplatin with the concentration-dependent nature of CDDP. Based on these considerations, we hypothesized that combination therapy with cisplatin and miriplatin would result in prompt damage to HCC tumors and longstanding antitumor effects in the TACE of HCC. In addition, Kishimoto *et al.* reported no cross-resistance between cisplatin and miriplatin [39]. Moreover, Seko *et al.* reported that the viscosity of miriplatin/lipiodol suspension decreases with increasing temperature and that warmed miriplatin is associated with an objective response [22]. Therefore, in future studies, we should also compare DP-TACE with miriplatin TACE.

The treatment-related adverse effects of using miriplatin and cisplatin in combination, were mild and acceptable in this study. Overall incidence rates for

adverse events were not significantly different between TACE using miriplatin and cisplatin and TACE using cisplatin alone. Moreover, the incidence rates of severe adverse events categorized as grade 3 or 4 for TACE with the combination therapy were comparable to those for TACE with cisplatin alone. This study had several limitations. This study was a retrospective and the patients were not randomized with respect to DP-TACE or CDDP-TACE. The study was conducted with a small sample size and at a single institution.

7. Conclusion

In conclusion, TACE with miriplatin plus cisplatin for unresectable HCC showed higher objective response rates and longer survival period with comparable adverse effects as compared to TACE with cisplatin alone under conditions of matched patient profiles, tumor characteristics, and treatment procedures. Subsequently, for further improvement of therapeutic results, we believe a future direction is the evaluation of TACE with warmed miriplatin [22] and cisplatin or balloon-occluded TACE [40] using miriplatin plus cisplatin.

Conflicts of Interest

There are no conflicts of interest to declare.

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