Transarterial Chemoembolization with Miriplatin plus Epirubicin in Patients with Hepatocellular Carcinoma

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Abstract. *Aim: We aimed to evaluate the therapeutic efficacy of transcatheter arterial chemoembolization (TACE) using miriplatin plus epirubicin in unresectable hepatocellular carcinoma (HCC). Patients and Methods: The efficacy of TACE was evaluated by dynamic computed tomography (CT) or magnetic resonance imaging (MRI) three months after the procedure according to the Response Evaluation Criteria in Cancer Study Group of Japan. Adverse events (AEs), including clinical symptoms, hematological toxicities and blood chemistry toxicities, were assessed using Common Terminology Criteria Version 4.0. Results: Thirty patients with HCC received TACE with miriplatin (miriplatin group) and 29 patients received TACE with miriplatin plus epirubicin (miriplatin-plus-epirubicin group). AEs, such as anorexia and neutropenia, were observed more frequently in the miriplatin-plus-epirubicin group than in the miriplatin group (p=0.028 and 0.014, respectively). However, there was no significant difference in the incidence of these AEs (grade 3/4) between groups. The objective response rate (ORR), including the complete response (CR) and partial response (PR), was 76.7% in the miriplatin group and 58.6% in the miriplatin-plus-epirubicin group (p=0.224). The median time to progression (TTP) in the miriplatin group and the miriplatin-plus-epirubicin group was 8.2 and 6.1 months, respectively (p=0.123). Conclusion: Although TACE with miriplatin plus epirubicin was safe and tolerable, no additional anti-tumor effects were observed compared to TACE with miriplatin. Further analysis is required to refine the efficacy of TACE using miriplatin plus epirubicin.*

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality worldwide (1, 2). As HCC is one of the major hypervascular tumors, transcatheter arterial chemoembolization (TACE) and transarterial embolization (TAE) have been widely applied for unresectable HCC (3-5). Anticancer agents, such as doxorubicin, epirubicin, mitomycin and cisplatin, have been used in TACE (6-8). Recently, miriplatin (Miripla®), a new hydrophobic platinum-based anticancer agent, was developed for intra-arterial treatment and launched for transarterial infusion for HCC in Japan (9). Miriplatin is usually used as a suspension with an oily contrast agent (Lipiodol®), which gradually releases an active platinum substrate from lipiodol on HCC tissues. It has been reported that TACE with miriplatin displays similar anti-tumor effects to that of cisplatin (10). Additionally, miriplatin has a few adverse events (AEs) compared with cisplatin (11). However, a problem has been pointed-out with the viscosity of the miriplatin/lipiodol suspension that often causes insufficient drug delivery into small tumor vessels and results in reduced anti-tumor effects (12). To resolve this problem, some practical measures, such as warming (13, 14) and emulsifying the drug into a water-soluble contrast agent (15), have been tested successfully with strengthening of the anti-tumor effects.

It has been reported that TACE using epirubicin showed superior local control rates than miriplatin (16). However, whether the combined use of epirubicin and miriplatin augments the anti-tumor effects compared to the use of miriplatin alone remains to be elucidated. In the present study, we evaluated the safety and efficacy of TACE with miriplatin plus epirubicin.

Patients and Methods

Patients and tumors. The medical records of patients receiving TACE with miriplatin (Miripla®; Dainippon Sumitomo Pharma, Osaka, Japan) alone or with miriplatin and epirubicin from June 2012 to October 2013 in Chiba University Hospital were collected. Patients were selected according to the following criteria: (i) diagnosed with HCC in accordance with the treatment guidelines of

the American Association for the Study of Liver Diseases, (ii) classified as Child-Pugh A or B, (iii) performed dynamic computed tomography (CT) or magnetic resonance imaging (MRI) within 1 month before TACE, (iv) no vascular invasion, (v) no extrahepatic metastasis, (vi) having at least one lesion more than 10 mm in diameter confirmed by CT or MRI at baseline and (vii) no history of TACE with miriplatin or epirubicin. All the patients provided a written-informed consent before TACE. This study has been approved in clinical trials of the Chiba University Hospital.

TACE procedure. All patients received pre-medication with intravenous dexamethasone and granisetron. The femoral artery was catheterized under local anesthesia and a 4- or 5-Fr Shepherd Hook catheter was inserted. All patients underwent angiography of the superior mesenteric artery and celiac artery, which was performed to confirm the location of HCC. We performed superselective TACE using a 2- or 2.5-Fr microcatheter to detect the feeding artery to obtain a complete occlusion of the nourishing arteries. Miriplatin was suspended in lipiodol (Lipiodol®; Guerbet, Tokyo, Japan) and its concentration was adjusted to 20 mg/ml according to the package insert. For the miriplatin group, the adjusted miriplatin/lipiodol suspension was emulsified with an equal volume of a water-soluble contrast agent (Omnipaque; Daiichi Sankyo, Tokyo, Japan). For the miriplatin plus epirubicin group, the adjusted miriplatin/lipiodol suspension was emulsified with an equal volume of epirubicin/omnipaque solution (epirubicin, 10 mg/dl). The final concentration of miriplatin and epirubicin was 10 mg/ml and 5 mg/ml, respectively. The emulsification of these solutions was performed by stirring them 20 times using a three-way cock and two pairs of 10 ml syringes immediately before their administration into the feeding arteries. The maximum dose of miriplatin was limited to 120 mg in both groups. Next, the complete embolization of the feeding arteries was performed using 1 mm gelatin cubes after the administration of anticancer agent(s).

Adverse events. Treatment-related toxicity was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Clinical symptoms (fever, anorexia, nausea and abdominal pain), hematological toxicities (leukopenia, neutropenia, anemia and thrombocytopenia) and blood chemistry toxicities (an increase in serum aspartate aminotransferase, alanine aminotransferase, total bilirubin and creatinine levels and a decrease in albumin level) were evaluated.

Treatment efficacy evaluation. The treatment effect of TACE was evaluated by dynamic CT or MRI performed within three months after the procedure according to the Response Evaluation Criteria in Cancer of the Liver. The treatment effect per patient was evaluated as follows: progressive disease (PD); total tumor size enlarged by more than 25%, partial response (PR); overall tumor-necrosis effect or overall tumor size reduction rate of 50%-100%, complete remission (CR); complete tumor disappearance or 100% tumor necrosis, stable disease (SD) not classified as PD, PR or CR. Dynamic CT or MRI follow-up was performed every 3-4 months. Time to progression (TTP) of each patient was determined based on the dynamic CT or MRI images. TTP was defined as the time between the day when TACE was performed and the day when the patient was judged as PD.

Statistical analysis. All analyses were carried out using the JMP software (version 10; SAS Institute, Cary, NC, USA). The patients, tumor characteristics, AEs and treatment effects were analyzed by the chi-square test or the unpaired *t*-test. The median time to the first follow-up by dynamic CT or MRI was assessed by the unpaired *t*-test. The TTP per tumor was estimated using the Kaplan-Meier method and comparisons were made using the log-rank test. All *p*-values less than 0.05 were considered statistically significant.

Results

Characteristics of patients and tumors. Out of 112 patients who underwent TACE using miriplatin alone or miriplatin plus epirubicin at our Institute, 59 patients were included in this study (Figure 1). In total, 53 patients were excluded, out of whom 10 were classified as Child-Pugh C, 11 had macroscopic vascular invasion, 15 had extrahepatic metastasis, 11 received TACE with partial splenic embolization and 6 received balloon-occluded TACE. Finally, 30 patients were selected for the miriplatin group and 29 for the miriplatin plus epirubicin group. The median time to first follow-up by dynamic CT or MRI was 2.9 months in the miriplatin group and 3.1 months in the miriplatin-plus-epirubicin group (p=0.647).

There was no significant difference between the two groups with respect to median age, Eastern Cooperative Oncology Group-Performance Status, the Child-Pugh score, the etiology of chronic liver damage, Barcelona Clinic Liver Cancer (BCLC) stage, tumor node metastasis (TNM) staging proposed by the Liver Study Group of Japan, the number of previous TACE, median serum alpha-fetoprotein level, median serum des-gamma carboxy prothrombin level, the median of the number of tumor and the median of maximal tumor size (Table I). The median (range) doses of miriplatin was 65 mg (range=15-120 mg) in the miriplatin group and 49 mg (range=12-110 mg) in the miriplatin plus epirubicin group (p=0.070).

Adverse events. Clinical symptoms, such as fever, anorexia, nausea and abdominal pain, were frequently observed in both groups (Table II). Among them, anorexia was observed more frequently in the miriplatin-plus-epirubicin group than in the miriplatin group (p=0.028). In addition, neutropenia was observed more frequently in the miriplatin-plus-epirubicin group than those in the miriplatin group (p=0.014). However, there was no significant difference in the incidence of AEs (grade 3/4) between groups. No significant difference existed between groups in terms of elevation of liver enzymes and creatinine levels. All AEs were temporary and reversible in both groups. No patients died within a month after TACE.

Treatment efficacy. Next, the treatment effects were evaluated three months after TACE by follow-up dynamic CT or MRI (Table III). There was no difference in both groups for whole treatment effects (p=0.609). In the miriplatin group, 18

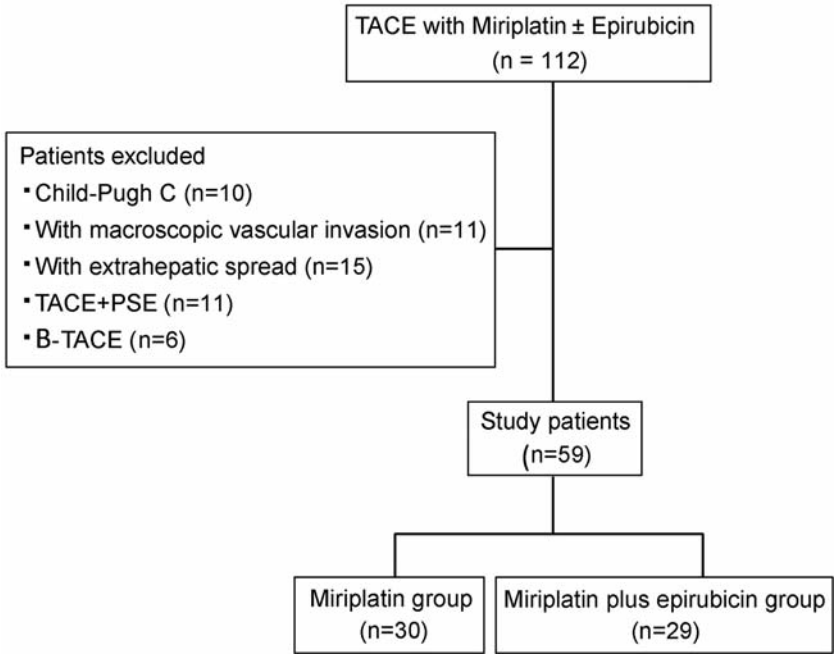

Figure 1. *Summary of patients selected for this study. TACE, Transcatheter arterial chemoembolization; PSE, partial splenic embolization; B-TACE, balloon-occluded transarterial chemoembolization.*

(60.0%) and 5 patients (16.7%) achieved CR and PR, respectively. In the miriplatin-plus-epirubicin group, 11 (37.9%) and 6 patients (20.7%) achieved CR and PR, respectively. The response rate (CR+PR) in the miriplatin group and the miriplatin plus epirubicin group was 76.7% and 58.6%, respectively (p=0.224). Although the patients in the miriplatin-plus-epirubicin group showed a lower progression-free rate than those in the miriplatin group (p=0.123), no significant difference existed (Figure 2). The median TTP in the miriplatin plus epirubicin group and in the miriplatin group was 8.2 and 6.1 months, respectively.

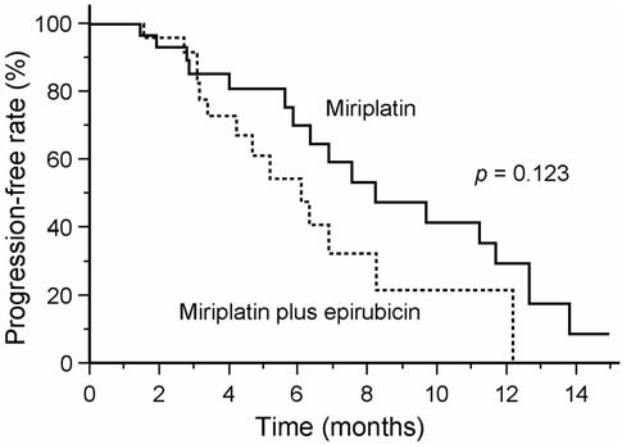

Figure 2. *Time to progression per patient in the miriplatin group and the miriplatin-plus-epirubicin group.*

Discussion

It has been reported that multi-agent chemotherapy often enhances anti-tumor effects and contributes to the prolongation of survival in a wide range of cancers (17, 18). Consistent with these findings, TACE with epirubicin plus mitomycin C was shown to exhibit stronger anti-tumor effects in HCC compared to TACE with miriplatin (19). Epirubicin is a hydrophilic, fast-acting anthracycline that induces vascular damage. On the other hand, miriplatin is a hydrophobic, slow-acting drug that exerts less damage to the hepatic arteries in TACE (20). Therefore, we assumed that the combined use of these drugs induces synergistic anti-cancer effects against HCC. Therefore, we conducted a retrospective analysis to examine the safety and efficacy of TACE with the combined use of miriplatin and epirubicin.

First, we analyzed the frequency of AEs between the miriplatin group and the miriplatin-plus-epirubicin group. Because of pre-medication with intravenous dexamethasone, clinical symptoms, such as fever, anorexia, nausea and

Table I. *Characteristics of patients and tumors*.

	Miriplatin (n=30)	Miriplatin plus epirubicin (n=29)	*p*-Value
Gender: Male/Female	17/13	20/9	0.479**
Median age (range)	72 (50-92)	72 (54-85)	0.573*
ECOG-PS 0/1/2	17/12/1	22/7/0	0.230**
Child-Pugh A/B	23/7	17/12	0.228**
Etiology HBV/HCV/other	2/21/7	7/17/5	0.172**
TNM stage per Liver Study Group of Japan I/II/III	1/13/16	3/18/8	0.108**
Number of previous TACE 0/1/2/≥3	24/4/0/2	22/5/2/0	0.242**
Median (range) AFP (ng/mL)	22 (3-328,500)	20 (3-41,250)	0.776*
Median (range) DCP (mAU/mL)	81 (9-58,721)	62 (6-73,160)	0.728*
Median (range) number of tumors per patient	4 (1-15)	3 (1-15)	0.100*
Median (range) maximal tumor size per patient (mm)	28 (7-180)	34 (9-220)	0.246*
Median (range) doses of miriplatin (mg)	65 (12-120)	49 (12-110)	0.070*
Median (range) doses of epirubicin (mg)	-	21 (5-62)	-

ECOG-PS; Eastern Cooperative Oncology Group-performance status; BCLC, Barcelona Clinic Liver Cancer; TMN, tumor node metastasis; TACE, transcatheter arterial chemoembolization; AFP, alfa-fetoprotein; DCP, des-gamma carboxy prothrombin. *Unpaired *t*-test, **χ^2 test.

Table II. *Adverse events*.

	Miriplatin (n=30)		Miriplatin plus epirubicin (n=29)		*p*-Value*	
	Any	G3/4	Any	G3/4	Any	G3/4
Fever	9 (30.0%)	0 (0%)	5 (17.2%)	0 (0%)	0.398	–
Anorexia	0 (0%)	0 (0%)	6 (20.7%)	0 (0%)	0.028	–
Nausea	0 (0%)	0 (0%)	1 (3.5%)	0 (0%)	0.986	–
Abdominal pain	6 (20.0%)	0 (0%)	3 (10.3%)	0 (0%)	0.503	–
Leukopenia	14 (52.4%)	0 (0%)	19 (65.5%)	4 (13.3%)	0.232	0.112
Neutropenia	3 (10.0%)	0 (0%)	12 (41.4%)	3 (10.0%)	0.014	0.224
Anemia	30 (100%)	1 (3.3%)	27 (93.1%)	5 (16.7%)	0.457	0.181
Thrombocytopenia	24 (80.0%)	3 (10.0%)	28 (96.6%)	6 (20.0%)	0.118	0.436
Increased AST level	29 (96.7%)	7 (23.3%)	29 (100%)	11 (37.9%)	0.321	0.350
Increased ALT level	26 (86.7%)	4 (13.3%)	24 (82.8%)	6 (20.7%)	0.956	0.685
Increased T-bil level	17 (56.7%)	3 (10.0%)	17 (58.6%)	0 (0%)	0.879	0.248
Increased creatinine level	3 (10.0%)	0 (0%)	9 (30.0%)	0 (0%)	0.092	–
Hypoalbuminemia	30 (100%)	0 (0%)	29 (100%)	0 (0%)	–	–

G, Grade; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-bil, total bilirubin. *χ^2 test.

abdominal pain, were less frequently found compared to previous reports (21, 22). The frequency of fever and abdominal pain was higher in the miriplatin group than in the miriplatin-plus-epirubicin group. In contrast, the frequency of anorexia was higher in the miriplatin-plus-epirubicin group than in the miriplatin group. In addition, hematological toxicities, such as neutropenia and thrombocytopenia, were observed more frequently in the miriplatin-plus-epirubicin group than in the miriplatin group. Although the mean dose of epirubicin used in TACE was 7-10 mg in previous reports, the dose in our study was 21 mg (range=5-62 mg) (21, 22). Taking into consideration myelosuppression associated with epirubicin (23), the dose escalation of epirubicin might result in frequent hematological toxicities.

Next, we examined the therapeutic efficacy between the miriplatin and the miriplatin-plus-epirubicin group. It was reported that TACE with miriplatin plus epirubicin shows superior anti-tumor effects and improved TTP compared with miriplatin alone (21, 22). However, the present study showed no additional anti-tumor effects of epirubicin on miriplatin in terms of treatment efficacy and TTP. Of importance, the dose of miriplatin per patient in the miriplatin-plus-epirubicin group was lower than that in the miriplatin group, although there was no significant difference between the two groups. It is possible that a lower miriplatin dose in the miriplatin-plus-epirubicin group resulted in inferior anti-tumor effects and shorter TTP than those in the epirubicin group. Of interest, the

Table III. *Therapeutic effects*

	Miriplatin (n=30)	Miriplatin plus epirubicin (n=29)
CR	18 (60.0%)	11 (37.9%)
PR	5 (16.7%)	6 (20.7%)
SD	3 (10.0%)	2 (6.9%)
PD	3 (10.0%)	7 (24.1%)
NE	1 (3.3%)	3 (10.3%)

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

addition of epirubicin to the cisplatin/lipiodol suspension accelerates the release of active platinum compounds (24). Given that both cisplatin and miriplatin are platinum agents, another possibility would be that early release of active platinum compounds led to insufficient anti-tumor effects in the miriplatin-plus-epirubicin group.

There exist certain limitations to this study. First, the number of cases included in the study was relatively small and the observation period was rather short. Second, this is a retrospective study conducted in a single institute. Further analyses in a larger number of patients would be necessary to clarify the therapeutic advantages of combination therapy using miriplatin and epirubicin.

In conclusion, TACE with miriplatin plus epirubicin seems to be tolerable. The therapeutic advantage for the additional use of epirubicin with miriplatin in TACE appears equivocal.

Conflicts of Interest

Osamu Yokosuka received grant support (Scholarship contribution) from Dainippon Sumitomo Pharma Co, Ltd (Osaka, Japan). The remaining authors disclose no conflicts.

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