Initial Safety and Outcomes of Miriplatin plus Low-dose Epirubicin for Transarterial Chemoembolisation of Hepatocellular Carcinoma

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Abstract. *Aim: To evaluate the initial safety and efficacy of combination therapy using miriplatin plus low-dose epirubicin for transarterial chemoembolisation (TACE) of unresectable hepatocellular carcinoma (HCC). Patients and Methods: Patients who underwent TACE using miriplatin plus epirubicin (n=48) and control patients who underwent TACE using miriplatin-alone (n=51) were included in this study. Results: The objective response rate in the miriplatin plus epirubicin group (91%) was significantly higher than that in the miriplatin group (74%, p=0.024). Concomitant use of miriplatin and epirubicin was an independent factor associated with higher objective response rate (hazard ratio=0.18; p=0.012). Overall incidence adverse events was not significantly different between the miriplatin plus epirubicin group (50%) and the miriplatin group (49%, p=0.575). Conclusion: TACE using miriplatin plus low-dose epirubicin was associated with an increased objective response rate and comparable adverse effects compared to TACE using miriplatin-alone.*

Miriplatin (Miripla; Dainippon Sumitomo Pharma, Osaka, Japan) is a new platinum-based anticancer agent specifically designed for the intra-arterial treatment of hepatocellular carcinoma (HCC) (1). Unlike other hydrophilic anticancer agents, miriplatin possesses myristates as lipophilic side chains that facilitate the easy preparation of a miriplatin–lipiodol suspension without the need for emulsification (2). Following intra-arterial administration, the miriplatin–lipiodol suspension initially accumulates in the target tumour, and continuous antitumor effects caused by gradual release of active platinum compounds are expected (2-4). In an early phase II trial, 56% of the patients treated with miriplatin *via* transarterial chemoinfusion therapy were shown to achieve complete response without major adverse events (5). In a randomised late phase II study, miriplatin suspension demonstrated a therapeutic efficacy similar to that of zinostatin stimalamer suspension, and caused less hepatic vascular injury than the latter (6). Furthermore, miriplatin is reported to be associated with fewer adverse events than cisplatin (7). These clinical studies suggested that miriplatin is a promising alternative to conventional hydrophilic anticancer agents such as epirubicin and cisplatin for treating unresectable HCC.

However, more recent studies have reported that transarterial chemoembolisation (TACE) of HCC using miriplatin–lipiodol suspension resulted in inferior local tumour control compared to epirubicin–lipiodol emulsion (8, 9). These studies have proposed several hypotheses, *e.g.* the poor local tumour control using miriplatin was possibly caused by early recanalization and unintentional proximal occlusion of the tumour feeder, and by excessively slow release of the active platinum compound (8, 9). Concomitant use of vascular-toxic hydrophilic anticancer agents such as epirubicin with miriplatin is theoretically expected to increase vascular toxicity and prevent early recanalization, reduce chemotherapeutic viscosity and prevent proximal occlusion, and enable rapid release of the hydrophilic anticancer agent. However, the safety and efficacy of miriplatin plus epirubicin combination therapy in TACE of unresectable HCC has not yet been investigated.

The present study was designed to evaluate the initial safety and efficacy of concomitant use of miriplatin and low-dose epirubicin (Farmorubicin; Pfizer Japan, Tokyo, Japan) emulsified with lipiodol and contrast medium, in TACE of unresectable HCC, compared to the use of miriplatin-lipiodol suspension-alone as a control.

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Patients and Methods

Patients. This study included 48 patients who underwent TACE using miriplatin plus low-dose epirubicin between July 2011 and April 2012, as well as 51 comparative patients who underwent TACE using miriplatin-alone between June 2010 and July 2011 at Nissay Hospital. Each patient was required to meet the following criteria: histopathologically- or clinically-diagnosed HCC, no indication for surgical resection, a Child-Pugh classification of A or B, a total serum bilirubin level of <3 mg/dl, no portal venous thrombus in the main trunk, and an interval of at least four weeks after the cessation of any previous anticancer therapy. The diagnosis of HCC was confirmed from previous imaging findings, as well as by the elevated levels of serum tumour markers. Viable lesions were considered as evidence from abnormal early enhancement with washout in the delayed phase of each imaging modality. A serum α-fetoprotein level of ≥20 ng/ml and/or a serum des-carboxy-prothrombin level of ≥40 mAU/ml were considered as positive tumour markers. The sizes and numbers of tumours were determined from cone-beam computed tomographic (CT) images obtained during each TACE session. The TNM stage was classified according to the tumour staging system, as revised by the Liver Cancer Study Group of Japan (10).

This study protocol was approved by our Institutional Review Board, and all patients gave fully informed written consent prior to TACE using miriplatin plus epirubicin as well as gelatin particles.

Drug preparation. Miriplatin–lipiodol suspension was prepared by dissolving 70 mg of miriplatin in 4 to 5 ml of lipiodol (Lipiodol Ultrafluid; Terumo, Tokyo, Japan), while the miriplatin–lipiodol emulsion with epirubicin was prepared by mixing 4 to 5 ml of miriplatin–lipiodol suspension, containing 70 mg of miriplatin, with 1 ml of iopamidol (Iopamiron 370; Bayer Schering Pharma, Osaka, Japan) containing 10 mg of epirubicin. The emulsification process was carried out manually by pumping the chemotherapeutic mixture with two syringes connected with a three-way stopcock. The maximum dose for a single TACE session was limited to 140 mg for miriplatin and 20 mg for epirubicin. The actual dose was determined on the basis of the size and number of target tumours and the liver function of the patient.

Transarterial chemoembolisation. All TACE procedures were performed using the same angiographic system (Innova 3100; GE Healthcare, Waukesha, WI, USA) by the same two interventional radiologists, who have more than 10 years' experience in hepatic vascular interventions. Firstly, an appropriate microcatheter was coaxially inserted through a 4-F catheter *via* the femoral artery and placed into the tumour feeder. Secondly, a cone-beam CT image was obtained by injecting iopamidol from the microcatheter to confirm whether the target tumour was actually located within the treatment area. After the locations of the tumours were confirmed, each hepatic area containing the target tumours was embolised with porous gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan), following infusion with the appropriate concentration of chemotherapeutic agents. Administration of the drugs and gelatin particles was terminated when the tumour vessels were completely filled with the drugs and the tumour stain disappeared on angiographic imaging.

Treatment evaluation. The therapeutic efficacy of TACE was evaluated on the basis of the change in the maximum diameter of the viable portion of the target lesions observed on triphasic contrast-enhanced CT images acquired one month after therapy. Recurrence was evaluated by evidence of abnormal early enhancement in arterial phase images from contrast-enhanced CT. The response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (11). The response categories were complete response (CR, disappearance of any intratumoral arterial enhancement), partial response (PR, at least a 30% decrease in the sum of the diameters of viable lesions), stable disease (SD, any cases that do not qualify for the other three categories), and progressive disease (PD, at least a 20% increase in the sum of the diameters of viable lesions). Objective response was defined as the sum of the cases categorised as CR and PR. The areas of lesions where lipiodol uptake was observed were considered as necrotic tissue.

Toxicity evaluation. Treatment-related adverse events were assessed according to the National Cancer Institute Common Terminology Criteria (version 4.0). Adverse events were evaluated as the maximum change in the grade within the four weeks after therapy. The assessment factors included fever; anorexia; pain; nausea; vomiting; fatigue; increased levels of aspartate aminotranferase, alanine aminotransferase, serum amylase, total bilirubin, and creatinine; hypoalbuminaemia; leucopaenia; neutropaenia; lymphopaenia; eosinophilia; anaemia; and thrombocytopenia.

Statistical analyses. We statistically compared the patient profiles, tumour characteristics, and treatment procedures between the miriplatin plus epirubicin group and the miriplatin group by using the Mann-Whitney *U*-test or the unpaired *t*-test. The treatment response and adverse events between the two groups were compared using the Mann-Whitney *U*-test. Factors affecting objective response were assessed by multivariate and univariate analyses. All variables with $p<0.2$ in univariate analysis were subjected to multivariate logistic regression analysis. All tests were two-sided, and factors were considered statistically significant at $p<0.05$.

Results

The patients' profiles, tumour characteristics, and treatment procedures for the miriplatin plus epirubicin group and the miriplatin group are summarised in Table I. The serum α-fetoprotein level was significantly higher in the former group than in the latter group ($p=0.026$). No significant differences were found between the other factors investigated in the two study groups.

The therapeutic efficacies of both treatment protocols are listed in Table II. CR was obtained in 28 (58%) and 22 (43%) patients in the miriplatin plus epirubicin group and the miriplatin group, respectively. No significant differences were found between the CR rates of the two groups ($p=0.133$). Objective response was obtained in 44 (91%) and 38 (74%) patients in the miriplatin plus epirubicin group and the miriplatin group, respectively. The objective response rate was significantly higher in the miriplatin plus epirubicin group than in the miriplatin group ($p=0.024$).

Univariate analysis showed that recurrent HCC ($p=0.031$) and lobar or whole-liver chemoembolisation ($p=0.004$) were factors significantly associated with a low objective response

Table I. *Baseline patient profiles, tumour characteristics, and treatment procedures.*

	Miriplatin+epirubicin (n=48)	Miriplatin (n=51)	*p*-Value
Gender (female/male)	20/28	21/30	0.964
Age (years)	72 [47-83]	73 [45-83]	0.872
Hepatitis (B/C/other)	8/32/8	10/34/7	0.617
Child-Pugh class (A/B)	39/9	37/14	0.310
TMN stage (I/II/III/IV)*	14/22/11/1	8/27/14/2	0.166
Treatment history (primary/recurrence)	13/35	19/32	0.283
Maximum tumour size (mm)	20 [5-71]	19 [10-100]	0.953
Serum AFP level (ng/ml)	24.5 [3-11555]	19 [3-3557]	0.026
Treatment area (subsegment/segment/lobe/whole liver)	20/13/11/4	14/19/14/4	0.297
Number of treated tumours (1/2/3/4/≥5)	22/6/4/2/14	19/10/5/4/13	0.715
Lipiodol dose (ml)	4 [1-10]	4 [1-10]	0.674
Miriplatin dose (mg)	70 [17.5-140]	70 [20-140]	0.814
Epirubicin dose (mg)	10 [2.5-20]	–	–

Data in brackets denote the data range for the median value provided. AFP, α-Fetoprotein.*Based on the revised TNM staging system of the Liver Cancer Study Group of Japan (10).

rate. The concomitant use of miriplatin and epirubicin (p=0.030) was associated with a high objective response rate. In the multivariate logistic regression analysis, concomitant use of miriplatin and epirubicin was an independent factor associated with a high objective response rate (hazard ratio=0.18; p=0.012). A lower objective response rate was associated with recurrent HCC (hazard ratio=11.6; p=0.025) and lobar or whole-liver chemoembolisation (hazard ratio=4.7; p=0.012; Table III).

Treatment-related adverse events are shown in Table IV. The overall incidence rates of adverse events were 50% (435 events) and 49% (450 events) for the miriplatin plus epirubicin group and the miriplatin group, respectively. No significant differences were found in the overall incidence rate of adverse events between the two groups (p=0.575). Of all adverse events, anaemia (p=0.019) and fatigue (p=0.025) were significantly more and less frequent, respectively, in the miriplatin plus epirubicin group. The incidence rates of severe adverse events (grade 3 or 4) were 7.4% (64 events) and 7.7% (71 events) for the miriplatin plus epirubicin group and the miriplatin group, respectively. No significant differences in the overall incidence rates of severe adverse events were found between the two groups (p=0.794). Of all severe adverse events, thrombocytopenia (p=0.049) was significantly less frequent in the miriplatin plus epirubicin group, while no significant difference was found in the incidence rates of other severe adverse events.

Table II. *Therapeutic efficacy of chemoembolisation of hepatocellular carcinoma.*

	Miriplatin + epirubicin (n=48)	Miriplatin (n=51)
CR	28 (58%)	22 (43%)
PR	16 (33%)	16 (31%)
SD	2 (4%)	9 (18%)
PD	2 (4%)	4 (8%)

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Discussion

In the present study, TACE using miriplatin plus low-dose epirubicin achieved a significantly higher objective response rate than did TACE with miriplatin-alone. The objective response rate from a single session of lipiodol-TACE using miriplatin for HCC was reported to be 57% to 58% (12, 13), relatively lower than that (74%) observed in our study. Compared with the previously reported cases, more patients in this study were treated with segmental or more distal chemoembolisation (64% *vs*. 18%), and this is an independent factor affecting the higher objective response rate in this study. Recently, a multicenter survey on therapeutic efficacy and adverse events in miriplatin therapy was conducted by the Study Group on New Liver Cancer Therapies (14). According to this survey in 425 patients, TACE using miriplatin achieved a treatment effect of -3 or -4 in 47% of the cases in which target lesions were reduced by over 50% in size. Surprisingly, the objective response rate for miriplatin plus epirubicin therapy observed in the current study (91%) was considerably higher than that for miriplatin therapy reported in our study or in previous studies.

Table III. *Univariate and multivariate analyses of factors affecting objective response to chemoembolisation.*

	Univariate		Multivariate	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Treatment history (primary *vs*. recurrence)	9.7 (1.2-76.9)	0.031	11.6 (1.3-100.3)	0.025
Treatment area (subsegment/segment *vs*. lobe/whole liver)	5.0 (1.6-15.1)	0.004	4.7 (1.4-16.0)	0.012
Administered drug (miriplatin *vs*. miriplatin + epirubicin)	0.26 (0.07–0.88)	0.030	0.18 (0.04-0.69)	0.012

Table IV. *Adverse events observed after chemoembolisation.*

	Miriplatin + epirubicin (n=48)		Miriplatin (n=51)		*p*-value	
	Overall (%) Gr (1/2/3/4)	Gr 3/4 (%)	Overall (%) Gr (1/2/3/4)	Gr 3/4 (%)	Overall	Gr 3/4
Fever	62 (28/2/0/0)	0	52 (24/3/0/0)	0	0.434	–
Anorexia	47 (20/3/0/0)	0	39 (14/6/0/0)	0	0.122	–
Pain	58 (14/14/0/0)	0	52 (19/7/1/0)	2	0.307	0.342
Nausea	43 (18/3/0/0)	0	54 (26/2/0/0)	0	0.362	–
Vomiting	35 (14/3/0/0)	0	33 (15/2/0/0)	0	0.777	–
Fatigue	35 (14/3/0/0)	0	56 (21/8/0/0)	0	0.025*	–
AST increase	93 (18/3/22/2)	50	94 (21/7/18/2)	39	0.521	0.284
ALT increase	93 (15/10/18/2)	20	88 (19/6/16/4)	39	0.477	0.808
Amylase increase	16 (5/1/2/0)	4	17 (6/1/2/0)	4	0.915	0.959
Hypoalbuminaemia	62 (22/8/0/0)	0	54 (12/15/1/0)	2	0.773	0.342
Bilirubin increase	50 (10/12/2/0)	4	66 (17/11/6/0)	11	0.150	0.170
Creatinine increase	31 (10/4/0/1)	2	21 (8/3/0/0)	0	0.492	0.312
Leukopaenia	12 (3/2/1/0)	2	7 (4/0/0/0)	0	0.402	0.312
Neutropaenia	10 (3/2/0/0)	0	5 (3/0/0/0)	0	0.389	–
Lymphopaenia	97 (19/15/12/1)	27	90 (10/20/14/2)	31	0.487	0.644
Eosinophilia	20 (10/0/0/0)	0	23 (11/1/0/0)	0	0.715	–
Anaemia	83 (34/5/1/0)	2	60 (27/3/1/0)	2	0.019*	0.977
Thrombocytopaenia	50 (17/7/0/0)	0	60 (18/9/4/0)	8	0.145	0.049*

Numbers in parentheses denote the number of cases categorised as each grade according to the National Cancer Institute Common Terminology Criteria (version 4.0). Gr, Grade; AST, aspartate aminotranferase; ALT, alanine aminotransferase.

One reason for this improvement in objective response when using miriplatin plus epirubicin combination therapy could be the increased vascular damage caused by epirubicin. Okusaka *et al*. (5) reported that the intra-arterial administration of miriplatin causes less vascular damage than does zinostatin stimalamer. Repeated use of miriplatin in the same hepatic area is clinically feasible without inducing major vascular occlusion or arterioportal shunting. However, because some vascular damage may prevent early recanalization of tumour vessels and feeders, using miriplatin alone for TACE may result in earlier restoration of blood supply to the tumours and earlier washout of the lipiodol from the tumour site. In contrast, TACE performed with an anthracycline anticancer agent, such as epirubicin or doxorubicin, has been reported to induce a high incidence of vascular damage and occlusion of the hepatic artery (15, 16). The addition of low-dose epirubicin may induce certain vascular injuries, thereby preventing early recanalization of the tumour vessels.

The viscosity of the miriplatin–lipiodol suspension may be higher than that of the miriplatin–lipiodol emulsion. We found that droplets of the miriplatin–lipiodol emulsion delivered to the tumour were generally much smaller than those of the miriplatin–lipiodol suspension. The lower viscosity and smaller size of the chemotherapeutic droplets of the emulsion may have prevented the unintentional early occlusion of narrow tumour feeders before lipiodol could completely accumulate in the entire tumour.

Another reason for a higher objective response with TACE using miriplatin plus epirubicin may be the fast release of active anticancer components from the tumour site. Miriplatin exerts its antitumor effect only when active platinum is released from the lipophilic chemical complex. In a previous study on rat hepatic tumours, only 6% of the total platinum was reported to be released into the surrounding parenchyma at 28 days after intra-arterial chemoinfusion of miriplatin–lipiodol suspension (2). The maximum plasma concentration time ranged from 18 to 37 days for the miriplatin study, which was much longer than the 10 to 60 min observed in the study using the water-soluble platinum anticancer agent cisplatin (5, 17). Because epirubicin is a hydrophilic anticancer agent, epirubicin added to the miriplatin–lipiodol emulsion may be transiently deposited in the target tumour, following which it is rapidly released into the bloodstream, thereby exerting a prompt antitumor effect just after therapy. Conversely, miriplatin retained in the target tumour may later exert antitumor activity by gradual release of the active platinum complex. Consequently, combined use of miriplatin and epirubicin may result in complementary and long-standing antitumor effects in the TACE of HCC.

The treatment-related toxicity of using miriplatin and low-dose epirubicin in combination, was generally mild and acceptable in this study. The overall incidence rates of adverse events using miriplatin plus epirubicin were comparable to those using miriplatin-alone. The major toxicities caused by this combination therapy were liver dysfunction and lymphopaenia, but the toxicity profile of this treatment was similar to that of miriplatin-alone. All clinical toxicities such as nausea, pain, or fever observed in the miriplatin plus epirubicin group were limited to grade 2, which was compatible with the results from the miriplatin group and previous studies as well (11, 12, 14, 18). The incidence rates of severe adverse events categorised as grade 3 or 4 for the miriplatin plus epirubicin group were also comparable to those for the miriplatin group. Acute renal failure was observed in one patient (2%) who received the miriplatin plus epirubicin combination treatment. The incidence rate of increased creatinine levels at grade 3 or 4 was reported to be 1.8% in miriplatin-TACE (14). This renal toxicity may have been induced by the administered contrast medium used for the TACE procedure, but the potential influence of the epirubicin added to the miriplatin suspension cannot be excluded.

This study has certain limitations. Firstly, the study was a retrospective comparative analysis rather than a randomised controlled trial. Patients were grouped according to the date that the initial therapy was performed; therefore, selection bias may be included. The improvement in objective response may also be partly the result of a newly-developed catheter or the improved embolisation technique of the operators. Secondly, there was no histological confirmation of HCCs. All study lesions were diagnosed as HCC on the basis of imaging findings and elevated serum levels of tumour markers. Therefore, tumours other than HCC may have been unintentionally included in the study. Thirdly, the observation period was relatively short. For this reason, we were unable to determine long-term safety and outcomes resulting from the use of miriplatin plus epirubicin. Finally, our sample size was fairly small, which limited the number of patients available for subgroup analyses.

In conclusion, the lipiodol-based TACE of unresectable HCC using an emulsion of miriplatin plus epirubicin resulted in higher objective response rates with comparable adverse events, compared to the use of a suspension of miriplatin-alone, under conditions of matched patients' profiles, tumour characteristics, and treatment procedures. Multivariate analysis demonstrated that the combined use of miriplatin and epirubicin was an independent factor associated with a higher objective response rate that presented a hazard ratio of 0.12 when compared to the use of miriplatin-alone.

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