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ORIGINAL RESEARCH

Effect of transarterial chemoembolization with miriplatin plus epirubicin on local control of hepatocellular carcinoma: a retrospective comparison with miriplatin monotherapy

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Naoko Hashimoto[1]
Jin Iwazawa[1]
Shoichi Ohue[2]
Takashi Mitani[1]

[1]Department of Radiology, Nissay Hospital, Nishiku, Osaka, Japan; [2]Department of Radiology, Komatsu Hospital, Neyagawa, Japan

Objective: We aimed to evaluate local tumor control after transarterial chemoembolization (TACE) for hepatocellular carcinoma using miriplatin and low-dose epirubicin combination therapy.

Methods: We retrospectively analyzed the records of patients who underwent TACE using miriplatin plus low-dose epirubicin (30 patients, 61 nodules, August 2011–March 2012) and control patients who underwent TACE using miriplatin alone (36 patients, 70 nodules, June 2010–July 2011). The local control rate was compared between the two groups using the Kaplan–Meier estimator and the log-rank test. Factors affecting local tumor recurrence were analyzed using multivariate logistic regression analysis. Treatment-related toxicity was evaluated using the Common Terminology Criteria for Adverse Events.

Results: The local control rates at 6 months and 1 year were 87% and 65% for the miriplatin plus low-dose epirubicin group, and 61% and 43% for the miriplatin group, respectively. Local tumor control rates were significantly better in the miriplatin plus low-dose epirubicin group than in the miriplatin group ($P = 0.038$). Multivariate analysis showed that the addition of epirubicin was an independent factor associated with better local tumor control (hazard ratio 0.2, $P = 0.001$). Overall incidence rates for adverse events were not significantly different between the two groups.

Conclusion: Additional usage of low-dose epirubicin for TACE using miriplatin improved local tumor control of hepatocellular carcinoma with adverse effects comparable to those observed with TACE using miriplatin alone.

Keywords: combination therapy, local recurrence, liver, embolization, comparative study

Introduction

Transarterial chemoembolization (TACE) is an effective treatment for patients with unresectable hepatocellular carcinoma (HCC).[1–3] Therapeutic efficacy depends on both sufficient accumulation of the chemotherapeutic agent at the target site and complete occlusion of tumor feeder vessels using the embolic material. Currently, different chemotherapeutic protocols are used for TACE in HCC, and determining which protocol is the most effective remains controversial.

Miriplatin (MPT; MIRIPLA®, Dainippon Sumitomo Pharma, Osaka, Japan), a third-generation platinum compound and anticancer drug, was first marketed in January 2010. Due to its high affinity for Lipiodol® (Lipiodol Ultrafluid, Terumo, Tokyo, Japan), once the MPT-Lipiodol suspension accumulates at the target tumor, it exerts a

Correspondence: Jin Iwazawa
Department of Radiology,
Nissay Hospital, 6-3-8 Itachibori,
Nishiku, Osaka 550-0012, Japan
Tel +816 6543 3581
Fax +816 6532 6482
Email jin.iwazawa@nissay-hp.or.jp

continuous antitumor effect through its gradual release from the tumor site. Furthermore, only mild systemic side effects are anticipated, as only trace amounts of the drug are expected to be released into systemic circulation.[4–8] MPT also has the advantage of causing few adverse effects such as vascular damage or renal disturbance.[9,10] However, local recurrence rates associated with TACE were reported to be higher when using MPT than when using epirubicin (EPI; Farmorubicin, Pfizer Japan, Tokyo, Japan) plus mitomycin or EPI alone.[11,12] The inferior local control associated with MPT can be attributed to its reduced ability to induce vascular damage, higher viscosity, and slower release from the tumor.[11,12] Concomitant use of vascular-toxic hydrophilic anticancer agents such as EPI is expected to enhance the therapeutic efficacy of MPT by compensating for these limitations.

This study was designed to assess whether combining MPT with low-dose EPI could increase the antitumor effect of MPT. In this regard, we retrospectively compared local tumor control rates between patients who had been treated with TACE using MPT plus low-dose EPI and those who had been treated with MPT alone.

Materials and methods

Patients

We enrolled 67 patients with unresectable HCC who underwent TACE using MPT with or without EPI between June 2010 and March 2012. Subjects were divided into two groups according to the anticancer drug(s) administered: 36 patients with 70 nodules were treated using MPT between June 2010 and July 2011 (MPT group), and 30 patients with 61 nodules were treated using MPT plus low-dose EPI between August 2011 and March 2012 (MPT + EPI group). Each patient was required to meet the following criteria: no previous treatment for the lesions under study, a total serum bilirubin level of <3 mg/dL, no portal venous thrombus in the main trunk, an interval of at least 4 weeks after the cessation of any previous anticancer therapy, and no more than five intrahepatic lesions. Subject nodules selected for treatment were enhanced in the arterial phase and washed out in the portal venous phase images of dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). The diagnosis of HCC was confirmed by preprocedural CT or MRI findings as well as by intraprocedural angiography and cone-beam CT imaging findings, according to the American Association for Study of Liver Disease guidelines.[13,14] Elevated levels of serum tumor markers were also considered for diagnosis. Tumor size was measured using cone-beam CT during TACE sessions. Comparative analysis was conducted for patient and tumor characteristics between the two groups. The TNM stage was classified according to the tumor staging system as revised by the Liver Cancer Study Group of Japan.[15] In this system, tumors are assigned a T factor according to the number and size of tumors and the location of invasion. A T1 classification refers to single tumors, ≤ 2 cm, and with no vascular or bile duct invasion. T2 tumors meet two of the above three criteria, T3 tumors meet one of these criteria, and T4 tumors do not meet any of the criteria.

The study protocol was approved by the Institutional Review Board of our hospital, and all patients provided informed written consent prior to TACE.

Drug preparation

The MPT preparation comprised 70 mg MPT suspended in 4 mL Lipiodol. For MPT plus low-dose EPI combination therapy, 10 mg EPI and 2 mL contrast agent (Iopamiron® 370; Bayer Schering Pharma, Osaka, Japan) were mixed with a suspension of 70 mg MPT and 4 mL Lipiodol. The upper limits set for MPT and EPI were 140 and 20 mg, respectively. Dosages were determined according to tumor size, treatment area, and patient liver function. All anticancer drugs were pumped 20 or more times in 5–10 mL doses with two syringes, using a three-way stopcock at room temperature.

Chemoembolization

All angiographic procedures were performed under a flat-panel detector cone-beam angiographic system (Innova® 3100; GE Healthcare, Waukesha, WI, USA) by two interventional radiologists, each with at least 10 years of experience. After inserting a 4-Fr catheter into the femoral artery, a 1.7–2.7-Fr microcatheter was advanced using the coaxial method into the tumor feeder vessel. The hepatic areas containing target tumors were subsequently infused with an appropriate dose of chemotherapeutic agents and embolized with 1–2 mm porous gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan) until the tumor vessels were completely filled. Post-procedural C-arm CT images were obtained to ensure that no viable tumors or additional tumor feeder vessels remained.

Treatment evaluation

On the seventh day after TACE, unenhanced CT using a 16-slice CT scanner (Somatom Sensation; Siemens Medical Solutions, Forchheim, Germany) was performed to assess the accumulation of Lipiodol at the tumor. Dynamic contrast-enhanced CT or MRI was performed every 1–3 months to assess local recurrence for each nodule

thereafter. Areas adjacent to the tumor that showed abnormal early enhancement with washout in the portal venous phase were considered to represent local recurrence. Newly appearing lesions at sites distant from the initially treated lesions were not considered local recurrence. The local tumor control rate was calculated from the date of TACE to the last date on which local recurrence was documented. The observation period was defined as the time from TACE to the last date on which local recurrence was documented or the last date on which the most recent CT/MR image was acquired.

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 4 weeks after therapy. The assessment factors included: fever; nausea; vomiting; pain; fatigue; increased levels of aspartate aminotransferase, alanine aminotransferase, serum amylase, total bilirubin, and creatinine; hypoalbuminemia; leukopenia; neutropenia; lymphopenia; eosinophilia; anemia; and thrombocytopenia.

Statistical analysis

We statistically compared the background profiles and adverse events between the two groups by using the Mann–Whitney *U*-test or the unpaired *t*-test. Local tumor control rates for the two groups of patients were compared using the Kaplan–Meier estimator with log-rank test. Factors affecting local tumor recurrence were assessed using multivariate and univariate analyses. Multivariate analysis was performed using the Cox proportional hazards model with a backward stepwise selection technique. All variables in univariate analysis were entered into multivariate analysis. All tests were two-sided, and difference levels of $P < 0.05$ were considered statistically significant.

Results

Among patient, tumor, and treatment background factors, significant differences were observed in the treatment area ($P = 0.021$). No significant differences were observed with respect to the other factors investigated (Table 1). The median follow-up duration was 279.5 days (range, 7–802 days) for the MPT group and 294 days (range, 6–498 days) for the MPT + EPI group.

The overall local recurrence rate was 64% (45/70 nodules) for the MPT group and 36% (22/61 nodules) for the MPT + EPI group. The local tumor control rate at 6 months and 1 year was 61% and 43% for the MPT group and 87% and 65% for the MPT + EPI group, respectively. As shown in Figure 1, local tumor control was significantly better in the MPT + EPI group than in the MPT group ($P = 0.038$).

Table 1 Patient, tumor, and treatment profiles

Factor	Anticancer drugs		*P*-value
	MPT	MPT + EPI	
Sex (male/female)	23/13	21/9	0.602
Age (years)[a]	74 (50–82)	73.5 (53–83)	0.796
HBS antigen (positive/negative)	5/31	4/26	0.948
HCV antibody (positive/negative)	26/10	21/9	0.843
Child-Pugh class (A/B/C)	25/10/1	23/6/1	0.544
TNM stage (I/II/III)[b]	12/18/6	11/14/5	0.838
Previous treatment (primary/recurrence)	14/22	11/19	0.854
Serum AFP level (ng/mL)[a]	24 (3–3,557)	17 (3–6,286)	0.786
Number of tumors (1/2/3/4/5)	18/9/3/5/1	15/6/3/5/1	0.856
Tumor size (mm)[a]	15 (3–52)	13 (3–60)	0.428
Treatment area (distal/subsegment/segment/lobe)	13/29/18/10	22/23/11/5	0.021
Lipiodol dose (mL)[a]	3.0 (0.5–10)	2.6 (0.8–8)	0.197
MPT dose (mg)[a]	53 (9–122)	47 (14–140)	0.138
EPI dose (mg)[a]	–	7 (2.0–20)	–

Notes: [a]Data in parenthesis denote the data range for the median value provided; [b]based on the revised TNM staging system of the Liver Cancer Study Group of Japan.[15]

Abbreviations: MPT, miriplatin; EPI, epirubicin; HBS, hepatitis B surface; HCV, hepatitis C virus; AFP, α-fetoprotein.

Univariate analysis revealed that hepatitis B surface antigen positivity ($P = 0.024$), hepatitis C virus antibody negativity ($P < 0.001$), a serum α-fetoprotein level <20 ng/mL ($P = 0.004$), and additional EPI usage ($P = 0.001$) were significant factors associated with better local tumor control (Table 2). In multivariate analysis, additional EPI usage was an independent factor associated with the increased local tumor control rate (hazard ratio, 0.2; $P = 0.001$). A low local tumor control rate was associated with hepatitis C virus antigen positivity (hazard ratio, 4.0; $P = 0.005$) (Table 3).

Treatment-related adverse events are shown in Table 4. No significant difference was found in the overall incidence rates for each adverse event investigated. The overall incidence rates of adverse events were 58% (213 events) and 60% (247 events) for the MPT + EPI and MPT groups, respectively. No significant differences were found in the overall incidence rate of adverse events between the two groups ($P = 0.633$). The incidence rates of severe adverse events (grade 3 or 4) were 4.4% (27 events) and 6.8% (42 events) in the MPT + EPI and MPT groups, respectively. No significant differences in the overall incidence rates of severe adverse events were found between the two groups ($P = 0.063$).

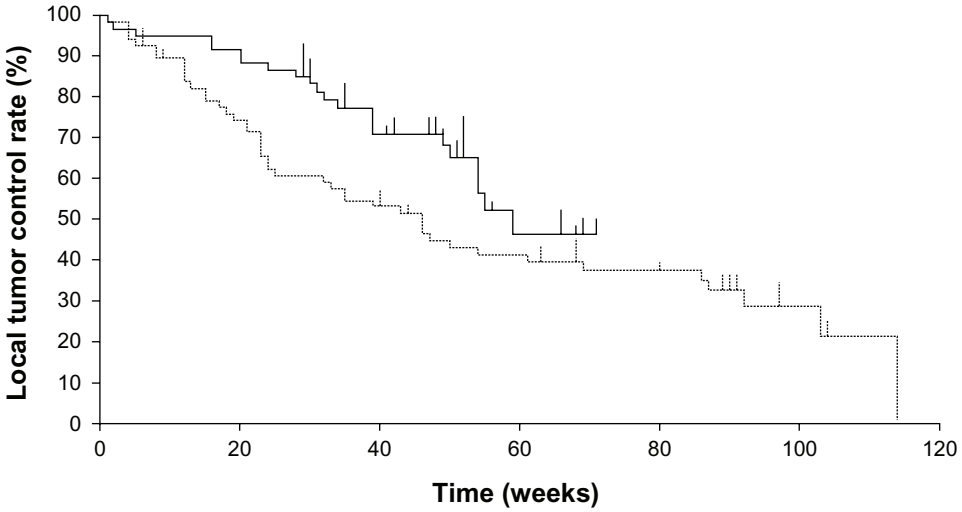

Figure 1 Comparison of local control rates between the miriplatin plus low-dose epirubicin (solid line) and miriplatin (dotted line) groups in chemoembolization of hepatocellular carcinoma. The miriplatin plus low-dose epirubicin group showed significantly better local tumor control than the miriplatin group ($P = 0.038$).

Discussion

Unlike other hydrophilic anticancer drugs, MPT can be easily dissolved in the carrier agent Lipiodol since it possesses lipophilic side chains. When the MPT-Lipiodol suspension accumulates at the tumor, gradual release of active platinum is expected over a prolonged period. However, the amount of active platinum released from an MPT suspension over a 28-day period is only 5.9% of the initial dose.[16] This observation suggests that MPT must be retained at the tumor site for a prolonged period of time in order to exert an adequate antitumor effect. Yanaihara et al[17] reported that initial CT accumulation rates are significantly lower after TACE using MPT than after TACE using EPI, whereas there was no significant difference in local control rates between both groups over a 1-year period when favorable Lipiodol accumulation had been observed on initial CT. This study indicates that favorable local tumor control could be achieved if MPT accumulates sufficiently within the tumor at initial TACE.

Methods for enhancing the accumulation of MPT have been addressed in several studies. Kora et al[18] and Seko et al[19] independently demonstrated that warming the MPT-Lipiodol suspension up to 40°C increased the therapeutic efficacy of TACE by reducing the viscosity of this chemotherapeutic agent. Indeed, experimental studies confirmed that the viscosity of the MPT suspension decreased as the temperature was elevated, thereby reducing injection pressure through a microcatheter.[20,21] According to these studies, a lower viscosity of the MPT-Lipiodol suspension can enhance its distal delivery, thereby achieving sufficient initial accumulation of the agent in the target tumor.

Recently, Iwazawa et al[9] reported that more severe arterial damage was observed by using EPI than by using MPT in TACE for HCC. They concluded that therapeutic occlusion of tumor feeder vessels was associated with lower local recurrence. According to their observations, the use of

Table 2 Univariate analysis of factors affecting local tumor recurrence after chemoembolization

Factor	Univariate	
	Hazard ratio[a]	*P*-value
Sex (male)	0.5 (0.2–1.2)	0.162
Age (≥70 years)	1.8 (0.8–3.6)	0.102
HBS antigen (positive)	0.3 (0.1–0.8)	0.024
HCV antibody (positive)	4.7 (1.9–11.5)	<0.001
Child-Pugh class (B or C)	1.5 (0.7–3.3)	0.244
TNM stage (III)	1.2 (0.5–2.6)	0.547
Previous treatment (recurrence)	1.3 (0.6–2.9)	0.450
Serum AFP level (≥20 ng/mL)	2.8 (1.3–5.8)	0.004
Tumor size (≥20 mm)	1.8 (0.8–4.0)	0.115
Treatment area (segment/lobe)	1.2 (0.5–2.8)	0.576
Lipiodol dose (≥3 mL)	1.6 (0.8–3.3)	0.144
MPT dose (≥70 mg)	1.4 (0.6–2.9)	0.346
EPI use (positive)	0.3 (0.1–0.6)	0.001

Note: [a]Data in parenthesis denote 95% confidence intervals.
Abbreviations: HBS, hepatitis B surface; HCV, hepatitis C virus; AFP, α-fetoprotein; MPT, miriplatin; EPI, epirubicin.

Table 3 Multivariate analysis of factors affecting local tumor recurrence after chemoembolization

Factor	Multivariate	
	Hazard ratio[a]	*P*-value
HCV antibody (positive)	4.0 (1.5–10.7)	0.005
Serum AFP level (≥20 ng/mL)	2.2 (0.9–5.1)	0.052
EPI use (positive)	0.2 (0.1–0.5)	0.001

Note: [a]Data in parenthesis denote 95% confidence intervals.
Abbreviations: HCV, hepatitis C virus; AFP, α-fetoprotein; EPI, epirubicin.

Table 4 Adverse events observed after chemoembolization

Adverse event	MPT group (n = 36)			MPT + EPI group (n = 30)			*P*-value
	Overall	Gr 3/4	Gr (1/2/3/4)	Overall	Gr 3/4	Gr (1/2/3/4)	Overall
Fever	44	0	(13/3/0/0)	60	0	(17/1/0/0)	0.252
Nausea	50	0	(16/2/0/0)	40	0	(12/0/0/0)	0.260
Vomiting	28	0	(10/0/0/0)	20	0	(6/0/0/0)	–
Pain	42	0	(10/5/0/0)	43	0	(11/2/0/0)	0.296
Fatigue	53	0	(17/2/0/0)	37	0	(11/0/0/0)	0.295
AST increase	97	14	(26/4/5/0)	97	7	(22/5/2/0)	0.775
ALT increase	92	8	(27/3/3/0)	97	3	(23/5/1/0)	0.910
Amylase increase	50	6	(14/2/2/0)	37	10	(6/2/3/0)	0.195
Hypoalbuminemia	69	3	(16/8/1/0)	87	0	(19/7/0/0)	0.448
Bilirubin increase	97	11	(14/17/4/0)	83	7	(13/10/2/0)	0.361
Creatinine increase	61	0	(18/4/0/0)	60	0	(16/2/0/0)	0.553
Leukopenia	39	3	(9/4/1/0)	30	0	(6/3/0/0)	0.850
Neutropenia	42	11	(5/6/3/1)	30	10	(5/1/1/2)	0.753
Lymphopenia	92	42	(5/13/12/3)	100	47	(9/7/7/7)	0.965
Eosinophilia	6	0	(2/0/0/0)	10	0	(3/0/0/0)	–
Anemia	72	3	(20/5/1/0)	80	3	(19/4/1/0)	0.871
Thrombocytopenia	81	17	(15/8/6/0)	80	3	(14/9/1/0)	0.363

Notes: Data are represented as percentages; numbers in parenthesis denote the number of cases categorized as each grade according to the National Cancer Institute Common Terminology Criteria (version 4.0).
Abbreviations: MPT, miriplatin; EPI, epirubicin; Gr, grade; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

vascular-toxic agents such as EPI can induce greater vascular occlusion of tumor feeder vessels. This leads to better local tumor control due to prolonged tumor ischemia. However, use of high-dose EPI can cause severe vascular alterations such as arterioportal shunting, intra- and extra-hepatic collateralizations, and aneurysm formation.[22] Such vascular complications may interfere with subsequent catheterization, thus compromising treatment success and clinical outcome.

Combination therapy of MPT with low-dose EPI in the treatment of HCC was first described by Iwazawa et al.[23] In short-term observation periods, they showed that TACE using MPT with low-dose EPI was associated with an increased objective response and comparable adverse effects compared with TACE using MPT alone. However, whether combination therapy with MPT and low-dose EPI actually improves long-term therapeutic efficacy compared with TACE using MPT alone has not yet been investigated. To our knowledge, the current study is the first to demonstrate that TACE using MPT plus low-dose EPI resulted in better local tumor control after 1 year than TACE using MPT alone.

There are several advantages to using low-dose EPI in combination with MPT during TACE. The addition of low-dose EPI may induce certain vascular injuries, thereby preventing early recanalization of the tumor feeder vessels. Long-term retention of the chemotherapeutic agents, initially accumulated at the tumor, can be anticipated by reducing arterial blood flow into the tumor. Furthermore, long-standing ischemia can also enhance the antitumor effect. Generally, oil suspensions have higher viscosity than water-in-oil emulsions. The viscosity of the MPT suspension may be higher than that of the MPT-EPI emulsion. In addition, we found that the oil droplets of the MPT-EPI emulsion delivered to the tumor were generally much smaller than those of the MPT suspension. The low viscosity and small chemotherapeutic droplets of the MPT-EPI emulsion may prevent the unintentional early occlusion of narrow tumor feeder vessels before the anticancer agents have completely filled in the entire tumor. EPI is a hydrophilic anticancer agent; therefore, a prompt antitumor effect just after therapy can be expected. Conversely, MPT retained at the target tumor site may exert prolonged antitumor activity by the gradual release of active platinum. Consequently, combined use of MPT and EPI is expected to result in complementary and long-lasting antitumor effects. Furthermore, compared with high-dose EPI, low-dose EPI used in a combination therapy can reduce vascular toxicity and preserve liver function, thereby providing patients with potential opportunities for future treatments.

There are limitations to this present study. First, the study was retrospective; thus, there may have been selection and information biases. Second, HCC was not histologically confirmed. All study lesions were diagnosed on the basis of imaging findings and elevated serum levels of tumor markers. Third, the sample size was fairly small. Study of a larger number of subjects may be necessary to confirm the current results. Fourth, chemoembolization was performed more

distally on the MPT + EPI group than on the MPT group. This difference might have affected the local tumor control rate. Fifth, the observation period for the MPT + EPI group was relatively short. Longer-term observation might have produced a different outcome. Finally, the concomitant use of MPT and EPI in TACE may limit second-line drug options, when tumors become unresponsive.

Conclusion

Combination therapy using MPT plus low-dose EPI for TACE improved local tumor control in HCC patients with adverse effects comparable to those encountered on using TACE with MPT alone. Additional usage of EPI for TACE using MPT was an independent factor associated with better local tumor control in TACE for HCC.

Disclosure

The authors report no conflicts of interest in this work.

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