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

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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).¹³ 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...
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.\textsuperscript{4–8} MPT also has the
advantage of causing few adverse effects such as vascular
damage or renal disturbance.\textsuperscript{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.\textsuperscript{11,12}
The inferior local control associated with MPT can be attrib-
uted to its reduced ability to induce vascular damage, higher
viscosity, and slower release from the tumor.\textsuperscript{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 intrapro-
cedural angiography and cone-beam CT imaging findings,
according to the American Association for Study of Liver
Disease guidelines.\textsuperscript{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.\textsuperscript{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 classifica-
tion refers to single tumors, \( \leq 2 \) 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, treat-
ment 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
microwire 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 ($P = 0.038$).

Univariate analysis revealed that hepatitis B surface antigen positivity ($P = 0.024$), hepatitis C virus antibody negativity ($P < 0.001$), a serum $\alpha$-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 ($P = 0.063$).

<table>
<thead>
<tr>
<th>Table 1 Patient, tumor, and treatment profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Age (years)$^a$</td>
</tr>
<tr>
<td>HBS antigen (positive/negative)</td>
</tr>
<tr>
<td>HCV antibody (positive/negative)</td>
</tr>
<tr>
<td>Child-Pugh class (A/B/C)</td>
</tr>
<tr>
<td>TNM stage (I/II/III)$^b$</td>
</tr>
</tbody>
</table>

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.$^{16}$

Abbreviations: MPT, miriplatin; EPI, epirubicin; HBS, hepatitis B surface; HCV, hepatitis C virus; aFP, $\alpha$-fetoprotein.

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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. 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 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 and Seko et al 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. 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 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

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

Note: 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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Multivariate Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody (positive)</td>
<td>4.0 (1.5–10.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum AFP level (≥20 ng/mL)</td>
<td>2.2 (0.9–5.1)</td>
<td>0.052</td>
</tr>
<tr>
<td>EPI use (positive)</td>
<td>0.2 (0.1–0.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: Data in parenthesis denote 95% confidence intervals.

Abbreviations: HCV, hepatitis C virus; AFP, α-fetoprotein; EPI, epirubicin.

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).
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 arterioporal shunting, intra- and extra-hepatic collaterals, and aneurysm formation. 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.21 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

| 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            | (26/4/3/0) | 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           |
| Hypalbuminemia | 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.
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.

References