Predictors of short-term local recurrence after balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma

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Aims and objectives

Transcatheter arterial chemoembolization (TACE) is a widely accepted and effective therapy for unresectable hepatocellular carcinoma (HCC) (1). Various anticancer drugs can be used for TACE, including doxorubicin, epirubicin, cisplatin and mitomycin, but the superiority of any particular drug in terms of effectiveness has not been established (2). Miriplatin hydrate (Miripla®; Dainippon Sumitomo Pharma Co., Osaka, Japan), a novel lipophilic cisplatin derivative that can be suspended in lipiodol (3), became commercially available in 2010. Theoretically, miriplatin is a good agent in terms of its higher solubility, stability in lipiodol, and gradual release within the tumor. However, a 2012 study revealed that the rate of local recurrence in patients treated with miriplatin was significantly higher than that in patients treated with epirubicin with mitomycin (4). This is due to the high viscosity of miriplatin-lipiodol suspension (5). Some researchers have tested creative TACE methods to overcome the high viscosity problem and improve the therapeutic effect (TE); these methods including warming miriplatin (5) and balloon-occluded TACE (B-TACE) (2).

B-TACE was first introduced by Irie et al. (6). They reported that selective B-TACE with doxorubicin and mitomycin induced dense lipiodol accumulation in HCC nodules. Ishikawa et al. revealed that B-TACE with miriplatin achieved relatively good local control of HCC (11.1 % at 6 mos and 26.2% at 12 mos (2). The mechanism of this improved local control effect might be explained by the presence of anastomotic vessels, the viscosity of lipiodol emulsion, and the difference in size between the peripheral vessels in normal parenchyma and the vessels feeding into the HCC (6). Ishikawa mentioned that altering hemodynamics might be a main factor under balloon occlusion (2).

Computed tomography during hepatic arteriography (CTHA) is a sophisticated method for estimating the hepatic arterial flow. We speculated that CTHA under balloon occlusion can provide useful information for the analysis of hemodynamic changes. The aim of the present study was to reveal the relationship between changes of arterial flow in HCC nodules under balloon occlusion and local TE by means of CTHA. We also addressed other predictive factors of local recurrence after B-TACE using miriplatin.
Methods and materials

Patients

From May 2014 to August 2014, 50 consecutive patients with hypervascular HCC who were scheduled to receive B-TACE using miriplatin were enrolled. The exclusion criteria were: [1] death after B-TACE (pneumonia, one case; rupture of duodenal varices, one case); [2] HCCs with a total sum of tumor diam. > 6 cm according to a previous report (5) (seven cases), additional treatment such as surgical resection, radiofrequency ablation or percutaneous ethanol injection therapy within the follow up period (seven cases), or chemotherapy without embolization (five cases).

Finally, a total of 29 patients with 35 HCC nodules were enrolled in this study. The clinical characteristics of the study population are summarized in Table 1. All patients underwent pretreatment physical and laboratory examinations, ultrasound, and three-phase dynamic CT or gadoxetic-enhanced MRI. Hypervascular HCC was diagnosed by means of the imaging findings in addition to high serum levels of tumor markers (alpha-fetoprotein [AFP] and des-gamma-carboxyprothrombin [DCP]).

TACE

For each patient, the TACE procedure was as follows. The femoral artery was catheterized under local anesthesia, and a 4-Fr catheter was inserted into the celiac or common hepatic artery. Then a 3-Fr coaxial micro-balloon catheter (Logos, Piolax, Yokohama, Japan) was advanced into the hepatic artery that supplied the target tumor. CT hepatic arteriography was performed before and after inflation of the balloon. Subsequently, miriplatin-lipiodol suspension was injected followed by gelatin sponge particle (Gelpart; Nippon Kayaku, Tokyo). Miriplatin was prepared by mixing 30 or 60 mg (1 or 2 vials) of miriplatin hydrate in 3 mL or 6 mL of lipiodol. The maximum dose of miriplatin was limited to 120 mg.

CTHA

CTHA was performed with an interventional radiology computed tomography (IVR-CT) system (Infinix Celeve/Active, Toshiba Medical Systems, Tokyo). This system is
equipped with 16 detector-row CT. The catheter tip was advanced as close to the
tumor as possible. Standard CTHA and CTHA with balloon occlusion (BO-CTHA) were
performed for the area(s) containing at least one HCC nodule. When there were more
than two HCCs, CTHA was performed for the largest lesion.

The parameters for the scanning were as follows: collimation, 1 mm; reconstruction, 3
mm; pitch, 15: amperage, 300 mAs; kilovoltage, 120 kVp. The CTHA data acquisition
began 7-10 sec (first phase) and 30 sec (second phase) after the initiation of a
transcatheter hepatic arterial injection of 10-50 mL of nonionic contrast material
(iopamidol, Iopamiron® 150 iodine, 150 mg I/mL; Bayer HealthCare, Osaka, Japan)
at a speed of 0.5-2.5 mL/sec using the automated power injector. The appropriate
injection rate for CTHA was determined to be the maximum injection rate (which basically
depended on the vessel caliber) that would not cause a backward flow of contrast material
on the hepatic arteriography. The injection rate was the same before and after the inflation
of the balloon. The contrast medium was injected until the completion of the scanning of
the first phase. Plain CT was performed immediately after the B-TACE.

Assessment of the CT findings

Two experienced abdominal and interventional radiologists (AN, YU) blinded to the
patients’ information reviewed the findings obtained by the standard
CTHA and BO-CTHA and the post-treatment plain CT. The tumor locations were
classified into two groups: the central portion of the liver (segments 1 and 4) and others
(segments 2, 3 and 5-8). All lesions were classified into one of the following groups on
the basis of the enhancement pattern observed on CTHA: Group A, nodules that showed
high enhancement accompanied by corona enhancement (7) on the BO-CTHA (Fig.
1a-e); Group B, nodules that showed high enhancement without corona enhancement
on the BO-CTHA (Fig. 2a-d); Group C, nodules that showed decreased enhancement
or perfusion defect on BO-CTHA compared to standard CTHA, regardless of corona
enhancement (Fig. 3a-d). The CT value of lipiodol in the HCC nodule was measured by
using a region of interest (ROI) in the tumor. The lesion density is presented in Hounsfield
units (HUs) on CT.

Assessment of the therapeutic effect (TE)

The assessment of chemotherapy was evaluated by dynamic CT at 1 to 4 months after
B-TACE. The degree of lipiodol accumulation was classified into four grades according
to the Response Evaluation Criteria in Cancer of the Liver (8). The four TE grades were
defined as follows: TE4, 100% necrosis/size of tumor; TE3, 50%-99%; TE2, up to 50%
or tumor enlargement < 25%; and TE1, tumor enlargement of 25% or more, regardless
of the extent of necrosis (8). TE is classified into two groups: good, TE1 and TE2; poor,
TE3 and TE4.

Statistical analysis

We examined the categorical variables by Fisher exact test. These variables included sex
(male, female), Child-Pugh class (A, B, C), AFP (< 20, ≥ 20), DCP (< 40, ≥ 40), previous
TACE (yes, no), location of tumor (segment 1/4, others), and level of balloon occlusion
(peripheral to the subsegmental branch, segmental to lobar branch). We used the Kruskal
Wallis test to analyze the correlation between the CTHA findings (Group A, B, C) and
the TE; first, we compared the TE among three groups. If a significant difference was
obtained, we compared it between each pair of groups. Continuous variables such as age
and CT value were examined by Student t-test. All statistical analyses were performed
with JMP software (version 11, SAS Institute) for Microsoft Windows.
Table 1. Demographic characteristics and pretreatment assessment of 29 patients who underwent B-TACE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nodules, 1/2/3</td>
<td>24/4/1</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>72 (39–83)</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>21/8</td>
</tr>
<tr>
<td>Etiology, HBV/HCV/AL/others</td>
<td>5/17/3/4</td>
</tr>
<tr>
<td>Child-Pugh class, A/B/C</td>
<td>25/4/0</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.6 (2.2–4.2)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1.0 (0.5–3.29)</td>
</tr>
<tr>
<td>Prothrombin activity, %</td>
<td>78 (51–111)</td>
</tr>
<tr>
<td>Platelets, ×10^3/μL</td>
<td>112 (31–219)</td>
</tr>
<tr>
<td>AFP, ng/mL</td>
<td>13.7 (2–3791)</td>
</tr>
<tr>
<td>DCP, AU/L</td>
<td>39 (9–2043)</td>
</tr>
</tbody>
</table>

Data are median and range in age, albumin, total bilirubin, prothrombin activity, platelet, AFP and DCP. HBV, hepatitis B virus; HCV, hepatitis C virus; AL, alcohol; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin.
Fig. 1: A 73-year-old male with two HCCs (thick arrow, arrowhead) in segment 4. (a) Digital subtraction angiography (DSA) showed two hypervascular masses (cranial: thick arrow, caudal; arrowhead). Note the deflated balloon at the tip of catheter (thin arrow). (b) First phase of standard CTHA in segment 4 showed a hyperintense mass (cranial tumor, thick arrow). (c) Second phase of standard CTHA in segment 4 showed corona enhancement around the tumor. (d) First phase BO-CTHA in segment 4 showed a hyperattenuated mass. (e) Second phase BO-CTHA in segment 4 also showed corona enhancement around the tumor. This tumor was classified as Group A. (f) Plain CT obtained immediately after B-TACE showed good accumulation in the tumor, but a CT value measured relatively low at 788 HU, and contrast-enhanced CT at 2 mos after B-TACE (g) showed the washout of lipiodol and early enhancement in the tumor (thin arrow), indicating poor TE.
Fig. 3: An 80-year-old female with HCC in segment 1 (thick white arrow). The patient has a history of partial hepatectomy. (a) Arterial phase of dynamic MRI showed a hyperintense mass (thick white arrow). (b) DSA of right hepatic artery (RHA) showed a tumor stain in segment 1 (thick white arrow). Communicating arcade was noted (thin black arrow). (c) First-phase standard CTHA of the RHA showed a hyperattenuated mass in segment 1. The mass was not observed in the DSA of the RHA with a balloon (thin arrow) occlusion of RHA (d). A communicating arcade was not also seen. (e) The mass (arrow) was not enhanced in BO-CTHA. The mass was probably fed by the communicating arcade via the left hepatic artery (LHA) in the condition of RHA occlusion. (f) During the drug infusion, the lipiodol suspension flow soon ceased in the RHA and started to inflow into the tumor in segment 1 (white arrow). Lipiodol droplets were running in the communicating arcade (thin black arrow) from the right to left side. (g) Plain CT obtained immediately after B-TACE showed good accumulation in the tumor with a CT value of 953 HU. Lipiodol suspension distributed not only in the right lobe but also in the left lobe. Plain (h) and arterial phases (i) of dynamic CT at 1 month after B-TACE showed lipiodol washout and early enhancement, indicating a poor TE. Despite the relatively high CT value immediately after B-TACE, most of the lipiodol was washed out. This is presumably because the inflow from the communicating arcade via the LHA would wash away the lipiodol suspension.
Fig. 2: A 73-year-old male with two HCCs (thick arrow, arrowhead) in segment 4. (a) First-phase standard CTHA in segment 4 showed a hyperattenuated mass (caudal tumor, arrowhead). (b) Second-phase standard CTHA in segment 4 showed corona enhancement around the tumor. (c) First-phase BO-CTHA in segment 4 showed a hyperattenuated mass. (d) Second-phase BO-CTHA in segment 4 did not show corona enhancement around the tumor. This tumor was classified as Group B. (e) Plain CT obtained immediately after B-TACE showed good accumulation in the tumor with a high CT value at 1408 HU. In addition, a lipiodol-accumulated HCC is seen in segment 5 (thin arrow), which was treated using miriplatin without gelatin sponge particles. (f) Contrast-enhanced CT at 2 mos after B-TACE showed dense lipiodol accumulation in the tumor. The tumor decreased in size without early enhancement. In addition, the tumor in segment 5 showed the washout of lipiodol and faint early enhancement (thin arrow), indicating a viable lesion.
Results

The results are shown in Table 2. Good TE was observed in 15 of the 35 lesions (42.9%) at 1-4 months after B-TACE. There was no significant difference between the poor (TE1/2) and good (TE3/4) groups in age, sex, Child-Pugh class, AFP level, DCP level, history of previous TACE or tumor location. Thirteen of the 23 patients who were injected with miriplatin-lipiodol suspension from a peripheral to subsegmental branch showed a good response (TE3/4), whereas 2 of the 12 patients who were injected with miriplatin-lipiodol suspension from a segmental branch to lobar branch showed a poor response (TE1/2), a significant difference (p=0.034). The CTHA findings and TE were significantly correlated (p=0.003). The Group C tumors (Fig. 3a-i) showed significantly poor TE compared to the Group B tumor (Fig. 2a-f) (p=0.002). Groups A and C differed but not significantly (p=0.075, Fig. 1a-g). There was no significant difference between Group A and Group B (p=0.350). The CT values obtained immediately after B-TACE were correlated with the TE (p=0.037).
### Table 2. Therapeutic effect after balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic effect</th>
<th></th>
<th></th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>Poor (TE1/2)</td>
<td>Good (TE3/4)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean ± SD</td>
<td>73.1± 2.1</td>
<td>70.1±2.5</td>
<td>0.366</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>16</td>
<td>11</td>
<td>0.700</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh class</td>
<td>A</td>
<td>17</td>
<td>11</td>
<td>0.430</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>&lt;20</td>
<td>12</td>
<td>10</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>≥20</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>DCP (mAU/mL)</td>
<td>&lt;40</td>
<td>8</td>
<td>9</td>
<td>0.315</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>History of previous TACE</td>
<td>Yes</td>
<td>13</td>
<td>11</td>
<td>0.721</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td>S1 or S4</td>
<td>6</td>
<td>2</td>
<td>0.419</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Level of balloon occlusion:</td>
<td>Peripheral/subsegmental</td>
<td>10</td>
<td>13</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Segmental 1obar</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CTHA finding:</td>
<td>Group A</td>
<td>5</td>
<td>5</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>13</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CT value after B-TACE (HU)</td>
<td>711.8±74.2</td>
<td>958.5±65.7</td>
<td>0.037</td>
<td></td>
</tr>
</tbody>
</table>

AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin.

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Conclusion

Three types of hepatic artery play an important role in the hemodynamic change under balloon occlusion (6): peribiliary plexus (9), interlobar communicating arcade (10), and isolated artery (11) (Fig. 3). In Group A, the corona phenomenon (7) was observed in the second phase of BO-CTHA. We think that in this group, the arterial blood pressure did not decrease due to prominent collateral arterial flow such as that in the peribiliary plexus and interlobar communicating arcade beyond the occluded portion or due to inadequate balloon inflation. Thus, the intratumoral arterial blood pressure overcomes the portal venous pressure surrounding the tumor, resulting in the corona phenomenon.

The corona phenomenon was not observed in Group B, in which the intratumoral arterial pressure probably decreased and might be nearly equal to the portal venous pressure in the surrounding tumor. In such a condition, the corona phenomenon cannot be seen. In the present study, even though no significant difference was observed in local control between Groups A and B, there was a tendency for Group B to show better local control than Group A.

Dense lipiodol accumulation was obtained when the balloon-occluded arterial stump pressure decreased to 64 mmHg or less in a previous study (6), which is in agreement with our present findings. Lipiodol suspension could be pushed into the tumor more easily in Group B. In Group C, we suspect that collateral tumor vessels such as the isolated artery feed directly the tumor instead of the original feeding artery under the condition of balloon occlusion. In the beginning of the infusion, most of the lipiodol suspension runs through the artery in the noncancerous liver parenchyma but instantly ceases to flow, and then it flows into the original feeding artery, leading to a good accumulation of lipiodol suspension in the tumor immediately after treatment. However, because collateral tumor vessels may develop well in such tumors, the lipiodol would wash out rapidly.

In the present study, the TE was worse than that in a previous evaluation (2) showing an only 11% overall local recurrence rate at 6 months. This might be due to a problem specific to miriplatin or to the radiologist's technical skill at microcatheter advancement to the more distal part of the hepatic artery. There were no significant differences between the good TE group and the poor TE group in age, sex, Child-Pugh class, previous TACE, or tumor location. As for tumor location, even though no significant difference was observed, 6 of 8 cases (75%) in the central portion (segments 4 and 1) showed a poor therapeutic effect. This is probably because the catheter access for the feeding artery is difficult in segments 4 and 1 in general, and migration or spillover of the drug into the communicating arcade is frequent (Fig. 2f).
With regard to the occlusion level of balloon, our proximal occlusion cases (segmental or lobar artery) showed poor TE. This may be because the amount of drug would be smaller compared to the cases treated with the infusion of drug from a peripheral to subsegmental artery and because the intratumoral arterial pressure would not decrease enough due to collateral flow. Finally, the plain CT value immediately after treatment was a predictive factor of TE in our study, which is in concordance with the previous report (2).

In conclusion, the intratumoral arterial flow can change, presumably due to a collateral pathway under balloon occlusion. B-TACE for HCC lesions showing decreased perfusion or perfusion defect on BO-CTHA compared to standard CTHA can be expected to achieve only a poor short-term therapeutic effect as well as a proximal level of balloon occlusion and lower CT value immediately after treatment.
Fig. 4: Changes in the intrahepatic arterial flow with and without balloon occlusion. Without balloon occlusion, the feeding artery flows into the tumor and drains out to the hepatic parenchyma, forming corona enhancement. In Group A, the feeding artery is reconstructed by the peribiliary plexus and communicating arcade distal to the balloon occlusion. The arterial inflow was kept in the tumor, and the intra-arterial pressure around the tumor was preserved. Corona enhancement was thus observed. In Group B, the collateral arteries such as the peribiliary plexus and communication arcade do not develop enough to maintain the intratumoral arterial pressure. Corona enhancement is not present in this group. In Group C, collateral arteries including the isolated artery, peribiliary artery and communicating arcade feed the tumor entirely or partially. These flows do not contain contrast material, and thus CTHA shows decreased perfusion or perfusion defect. CA, catheter; FA, feeding artery; N, the area of contrast distribution in noncancerous liver parenchyma; T, tumor; C, coronal enhancement; BA, balloon (inflated); PP, peribiliary plexus; CoA, communicating arcade; IA, isolated artery.

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