Angiographic evaluation of hepatic arterial injury after cisplatin-based, transcatheater arterial chemoembolization for hepatocellular carcinoma in a 205-patient cohort

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Purpose

Transcatheter arterial chemoembolization (TACE) is an effective method for the palliative treatment of hepatocellular carcinoma (HCC) [1 on page 1]. HCC patients frequently require repeated TACE for the treatment of residual viable tumor or local recurrence. However, TACE for HCC may cause damage to the hepatic arteries, which leads to hepatic artery spasm and inflammatory constriction, and severe cases may lead to occlusion, dissection, intrahepatic and extrahepatic collateralization, and aneurysm formation in the hepatic artery [2-4 on page 1]. A direct result of irreversible occlusion is difficulty in selecting the artery for the next TACE procedure [5 on page 1].

Maeda et al. reported that the incidence of significant hepatic artery damage after TACE for HCC based on 33 patients and using epirubicin as a chemotherapeutic agent, was 16% per artery and 48% per patient [3 on page 1]. Geschwind et al. also reported that subsequent arterial patency seen on follow-up angiography after TACE performed for liver cancer and based on 160 patients, was 54.6 ~ 80.6% depending on the embolization protocol using oil, polyvinyl alcohol particles or gel-foam pledgets [6 on page 1]. However, both of these previous reports had limited numbers of study patients and short-term follow-up periods.

To our knowledge, published reports regarding the incidence or predictors of hepatic arterial injury (HAI) in a large series of cisplatin-based TACE treatments have been limited, although cisplatin is one of widely used chemotherapeutic regimens for HCC. Gaba reported the results of an online survey replied to by 268 Society of Interventional Radiology members, and regarding iodized oil chemoembolization for HCC, The preferred chemotherapeutic regimen consisted of 100 mg of cisplatin (44%), 50 mg of doxorubicin (58%), and 10 mg of mitomycin (59%) emulsified in 10 mL of iodized oil (71%) [7 on page 1]. Moreover, follow-up changes in the hepatic artery after HAI, have not yet been reported. Therefore, the purpose of this study is to evaluate the incidence, degree, interval change, and predictors of HAI after cisplatin-based TACE for HCC in a 205-patient cohort during the six-year follow-up.
Methods and Materials

Study subjects

Our institutional review board approved this study, and informed consent was waived due to the retrospective nature of the study. Between January 2006 and December 2006, we searched our institution's electronic database and identified 1302 consecutive patients who had undergone initial TACE for HCC. Among these patients, a total of 205 patients were included in this study according to the following criteria: (a) they were confirmed to have HCC by imaging and laboratory findings obtained before TACE; (b) they underwent three of more sessions of TACE; (c) they did not have any other subsequent treatment, such as surgery, radiofrequency ablation or percutaneous ethanol injection. There were 171 male and 34 female patients with an average age of 55.5 years (range 23~81 years). The presence of portal vein thrombosis seen on the initial CT scans, was detected in 78 (38%) patients. The Child-Pugh classification was class A in 154 (75.1%) patients, class B in 44 (21.5%) patients, and class C in 7 (3.4%) patients at the time of the initial TACE.

In all 205 patients, the diagnosis of HCC was based on a combination of the imaging findings and the increased serum level of a-fetoprotein and/or PIVKA II (protein-induced vitamin K antagonist-II). In all 205 study patients, contrast-medium-enhanced computed tomography (CT) was performed before TACE in order to evaluate the tumor characteristics and the possible presence of extrahepatic metastasis.

TACE

Arteriography of the superior mesenteric and common hepatic arteries was initially performed to assess the vascular anatomy, tumor location, and tumor vascularity and to confirm the portal vein patency. After selective catheterization of the feeding artery with the use of a microcatheter, cisplatin (Cisplan; Dong-A, Seosan, Korea) and an emulsion of iodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-sous-Bois, France) were infused into the feeding arteries.

The administered dose of cisplatin was 2 mg per kilogram of body weight, which was infused over 15 minutes without embolic particle administration. Embolization of the feeding arteries was then performed using 1-mm-diameter, absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA) until arterial flow stasis was achieved.

Hepatic arterial injury assessment

The angiographic findings were assessed by two interventional radiologists (J.H.S. and C.H.S, with 15 and three years of clinical experience, respectively), and a consensus interpretation was made. HAI was evaluated at each segmental hepatic artery using
a three-grade scale: 1, slight wall irregularity; 2, overt stenosis; and 3, occlusion (Fig. 1~4). Distal hepatic arteries directly supplying a tumor were not evaluated because the configuration of the arteries could be changed without HAI as a tumor shrinks or enlarges and could thus be confused with true HAI. The four, segmental, hepatic arteries were evaluated, i.e. the right anterior segmental hepatic artery, right posterior segmental hepatic artery, left lateral segmental artery, and the left medial segmental hepatic artery. When the first HAI occurs, the highest HAI grade among the segments of the hepatic arteries was defined as the HAI grade for that patient. The HAI interval change was categorized into three groups: progression; stable-state; and improvement. Progression was defined as aggravation of the HAI degree seen on the follow-up angiography compared with the previous angiography. Stable-state was defined as no definite interval change of the HAI degree, and improvement was defined as improvement of the HAI degree seen on the follow-up angiography compared with the previous angiography. To prevent misinterpreting arterial spasm as a genuine HAI, at least two angiography sessions before improvement was seen were required in order to claim consistent findings of HAI.
Fig. 1: Sequential change of the hepatic arterial injury (HAI), as seen in the common hepatic arteriograms of a 65-year-old male who underwent TACE. Normal hepatic arterial configuration and patency were seen at the initial session.

References: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR
Fig. 2: At the second session, slight wall irregularity (HAI grade 1) of both the right hepatic artery (arrow) and the middle hepatic artery (arrowhead) was observed.

References: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR
Fig. 3: At the fourth session, overt stenosis (grade 2) of the right hepatic artery (arrow) and the middle hepatic artery (arrowhead) was observed.

References: RADIOLIOGY, ASAN MEDICAL CENTER - Seoul/KR
Fig. 4: At the sixth session, occlusion (grade 3) of the middle hepatic artery (arrowhead) and more overt stenosis (grade 2) of the right HA were observed.

References: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR

Statistical analysis

The cumulative incidence of HAI was analyzed using the Kaplan-Meier method. Predictors or HAI, such as patient age, sex, portal vein thrombosis, and Child-Pugh classification, were analyzed using univariate logistic regression. Statistical analyses were performed using computer statistical software (SPSS, version 19.0; SPSS, Chicago, IL, USA), and p values less than .05 were considered to indicate a statistically significant difference.
Results

In the 205 study patients, a total of 1372 TACE sessions were evaluated (range 3 ~ 28 sessions per patient). There were no technical failures seen during hepatic angiography in TACE procedure. The follow-up period between the initial TACE and the last follow-up TACE ranged from 63 to 2420 days (median 492 days). The mean interval of the TACE procedures was 91 days.

HAI was observed in 50 of 205 patients (24.4%) during the follow-up period. The cumulative incidence of HAI during five sessions of TACE was 16.0% (95% CI, 10.21-21.77) and 52.1% (95% CI, 37.83-66.29) within 10 sessions of TACE and 68.0% (95% CI, 67.62-88.46) within 15 sessions of TACE (Table 1, Fig. 5). The initial HAI was interpreted as grades 1, 2, and 3 in 11 (22.0%), 17 (34.0%), and 22 (44.0%) patients, respectively. HAI occurred in the right anterior segmental hepatic artery in 24 of 50 patients (48%), in the right posterior segmental hepatic artery in 11 patients (22%), the right proximal hepatic artery in six patients (12%), the left medial segmental hepatic artery in five patients (10%), and in the left lateral segmental hepatic artery in four patients (8%). When the interval change was assessed assessed in 48 patients with available follow-up TACE, 40 patients (83.3%) showed progression of the HAI during the interval change, two patients (4.2%) showed stable-state, and six patients (12.5%) showed improvement (Fig. 6~8). In six patients with improvement of during the interval change, the grades before improvement were grades 2 and 3 in four and two patients, respectively. The univariate analysis for predictors of HAI revealed no significant predictors such as patient age, sex, portal vein thrombosis or Child-Pugh classification (Table 2).

Table 1. The incidence rate and cumulative incidence of hepatic arterial injury occurring after transcatheter arterial chemoembolization

<table>
<thead>
<tr>
<th>TACE sessions</th>
<th>Total number of patients</th>
<th>Number of injuries</th>
<th>Incidence rate</th>
<th>Cumulative number of injuries</th>
<th>Cumulative incidence</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>2</td>
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<td>3.90</td>
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<td>3.90</td>
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</tr>
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<td>3</td>
<td>197</td>
<td>9</td>
<td>4.57</td>
<td>17</td>
<td>8.29</td>
<td>4.52</td>
</tr>
<tr>
<td>4</td>
<td>136</td>
<td>6</td>
<td>4.41</td>
<td>23</td>
<td>12.34</td>
<td>7.54</td>
</tr>
<tr>
<td>5</td>
<td>96</td>
<td>4</td>
<td>4.17</td>
<td>27</td>
<td>15.99</td>
<td>10.21</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>5</td>
<td>7.69</td>
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<td>22.45</td>
<td>14.83</td>
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<td>7</td>
<td>47</td>
<td>3</td>
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<td>7.14</td>
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<td>52.06</td>
<td>37.83</td>
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<tr>
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<td>8</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>205</strong></td>
<td><strong>50</strong></td>
<td><strong>24.39</strong></td>
<td><strong>45</strong></td>
<td><strong>52.06</strong></td>
<td><strong>37.83</strong></td>
</tr>
</tbody>
</table>

†using the Kaplan-Meier method

**Fig. 5**: The cumulative incidence of HAI after TACE.

**References**: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR
Fig. 6: Improvement of HAI as seen in common hepatic arteriograms in a 76-year-old male who underwent TACE. Normal hepatic arterial configuration and patency were seen at the initial session.

References: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR
Fig. 7: At the second session, overt stenosis (HAI grade 2) of the right hepatic artery (arrow) was observed.

References: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR
Fig. 8: At the fifth session, overt stenosis (grade 2) of the right hepatic artery (arrow) and middle hepatic artery (arrowhead) was observed. After the fifth session, the HAI of the right hepatic artery showed gradual improvement. At the tenth session, normal configuration and patency of the right hepatic artery (arrow) were observed.

References: RADIOLOGY, ASAN MEDICAL CENTER - Seoul/KR

Table 2. Univariate logistic regression used to determine the risk factors for hepatic arterial injury.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.007</td>
<td>0.978</td>
<td>1.038</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1.583</td>
<td>0.656</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>PV thrombosis</td>
<td>present</td>
<td>0.794</td>
<td>0.400</td>
</tr>
<tr>
<td>Child Pugh score</td>
<td>A</td>
<td>2.158</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.333</td>
<td>0.188</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

It is suggested that hepatic artery interruption caused by repeated TACEs or arterial dissection, is the primary cause of extrahepatic collateral vessel development [8-10 on page 6]. Extrahepatic collateral vessel formation and irreversible occlusion of hepatic arteries cause difficulty when selecting the artery for the next TACE procedure [5 on page 6]. Since recanalization of the tumor vasculature is a prerequisite to a subsequent TACE procedure, it is of critical importance to be aware of the HAI following the TACE procedures. In our study, in patients who underwent three or more sessions of cisplatin-based TACE, the overall incidence of HAI was 24.4%, while the cumulative incidence of HAI was 16%, 52.1%, and 68.0% within five, 10, and 15 sessions of TACEs, respectively.

The cumulative HAI incidence of 16% during five sessions of TACE in our study is similar to the arterial patency rate of 80.6% following TACE of chemotherapy, oil and gelfoam pledgets in a study by Geschwind et al. [6 on page 6], although the follow-up period length and the session numbers analyzed were not specified in their study. In our study, when the follow-up period was extended to 10 or 15 sessions of TACE procedures, the HAI incidence increased to more than 50% (52.1% and 68.0%, respectively), and thus indicating that the more often patients undergo TACE, the more HAI occurs. This cumulative incidence of HAI seen after TACE is very important because it can predict the incidence of HAI based on the number of TACE sessions, and which may affect the type of patient care.

The overall HAI incidence of 24.4% in our study patients is much lower than that of 48% seen in the 33 patients in a study of Maeda et al. [3 on page 3]. In their study, they used epirubicin and as they assessed the HAI at the level of the subsegmental hepatic artery, the configuration change in the hepatic arteries, according to tumor shrinkage or enlargement, might have been included as part of the HAI. While, our study used cisplatin as a chemotherapeutic agent in a large number of study patients.

In our study, 22 patients (44.0%) presented with grade 3 (occlusion) HAI at their initial manifestation of HAI and which was relatively higher compared with incidence of 15% (5/33) seen in the study of Maeda et al. [3 on page 3]. One of the possible explanations is that we might have a shorter interval of TACE procedures, with the mean interval being 91 days and ranging between 29 days and 1087 days. If TACE procedures are done more frequently during a certain amount of time, they can result in cause continuous hepatic arterial damage caused by inflammation induced by the chemotherapeutic agent or hypoxia caused by the embolic effect [2 on page 11, 11 on page 11, 12 on page 12]. If the level of damage exceeds a certain point, morphologic change could happen suddenly and/or severely.

The gelfoam used in our study seems to be advantageous for keeping the hepatic artery patent. In another study, arterial patency was higher when gelfoam was used compared with PVA [6 on page 6]. Because gelfoam is an absorbable gelatin sponge particle, it
induces hypoxic damage to the tumor while minimizing the HAI due to its transient nature. However, the overall use of gelfoam as an embolic material is not very popular as only 17% of 268 the Society of Interventional Radiology members used gelfoam as a particle embolic agent, according to the TACE survey [7 on page ].

It is noteworthy that, when the interval change of HAI was assessed, six patients (12.5%) showed interval improvement during follow-up from grade 2 or 3 to grade 1 or 2-in our study. Hepatic artery spasm is usually reversible, although hepatic artery attenuation, stenosis, occlusion, and aneurysmal change have been seen to be irreversible [5 on page ]. To our knowledge, there has been no report showing interval change of the HAI following TACE or interval improvement of HAI following TACE. Although the possible causes of improvement of HAI after HAI are unclear, they may result from prolonged vasospasm or a reversible inflammatory component in the presumed HAI site. Although it would seem to be impossible to distinguish the superimposed reversible component from irreversible morphological change in injured arteries, we suggest that the subsequent TACE procedures should not be abandoned due to verified HAI as HAI may be reversible.

Maeda et al. reported that TACE is more likely to induce HAI in cirrhotic patients with impaired liver function [3 on page ]. They suggested that although the cause of HAI in cirrhotic liver was unclear, it might result from the biological factors responsible for impaired liver function or from a technical factor during careless catheterization beyond the tortuous arteries. However, in this study, univariate analysis for the predictors of HAI revealed no significant correlation between the HAI and the Child-Pugh classification. One possible explanation is that HAI might be influenced by chemotherapeutic agents or embolic materials rather than by a patient’s liver function. The other theory is that as patients with B or C Child-Pugh classification tend to have fewer numbers of TACE sessions, the incidence of HAI could be unclear.

Our study has several limitations, the first of which is its retrospective design. Due to the retrospective nature of this study, the follow-up interval between angiographic procedures was not uniform and was quite variable. Second, outcomes of the TACE procedures were not analyzed according to the HAI. Third, comparison-of various chemotherapeutic agents or embolic materials and protocols, was not made.

In conclusion, in our study the overall incidence of HAI was 24.4% in patients who underwent three of more sessions of cisplatin-based TACE, and the cumulative incidence of HAI increased as the number of TACE procedures increased. The initial presentation of HAI was most commonly grade 3 (arterial occlusion), and 12.5% of the patients with HAI showed improvement of their HAI grade during follow-up TACE procedures.
References


