Antibiotic Prophylaxis in Transcatheter Treatment of Hepatocellular Carcinoma: an Open Randomized Prospective Study of Oral Versus Intravenous Administration

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Abstract

Background  Transcatheter arterial chemoembolization (TACE) and transcatheter arterial infusion chemotherapy (TAI) are increasingly used to treat inoperable liver malignancies. It has not been determined whether standard oral and intravenous administration of antibiotics have different prophylactic effects against post-TACE/TAI infection. We compared the efficacy of oral levofloxacin (LVFX) and intravenous cephazolin (CEZ) in patients receiving TACE/TAI for hepatocellular carcinoma (HCC) using a prospective design.

Patients and Methods  One hundred twenty-nine eligible subjects with HCC treated by TACE/TAI were analyzed in this study. Patients were randomly assigned by the envelope method to groups who received either intravenous infusion of CEZ at 2 g/day or oral administration of LVFX at 300 mg/day for 5 days. Laboratory data, changes in antibiotic administration from the standard ones, duration of hospital stay, side effects of antibiotics, and infectious complications were assessed.

Results  There were no significant differences in the WBC counts and serum CRP levels between the groups; there were also no significant inter-group differences in the numbers of infectious and other adverse events.

Conclusion  Our study findings suggest that the results of peroral administration of LVFX for the prevention of post-procedure infectious complications in patients receiving TACE/TAI for HCC are not inferior to those of intravenous administration of CEZ.

Key words: transcatheter arterial chemoembolization, hepatocellular carcinoma, prophylaxis; levofloxacin, cephazolin, randomized prospective study

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Introduction  Transcatheter arterial chemoembolization (TACE) is increasingly being used to treat inoperable primary and secondary liver malignancies. The procedure is generally well tolerated, with major complications in only 4-7% of procedures and a 30-day mortality of approximately 1% (4, 5). However, the procedure has been associated with several complications such as acute hepatic failure (2.6% of cases), liver infarction (0.3%), hepatic biloma formation (0.8%), liver abscess (0-1.4%), or septicemia (2.6-11%) (5-8). A standard antibiotic regimen with intravenous cephalosporin has been used for prophylaxis against such post-procedural infectious complications (9). However, intravenous administration of antibiotics increases the medical work load and creates pain and inconvenience for patients. Peroral administration of antibiotics may have a limited effect because the plasma drug concentration achieved may not be sufficient, even though the associated work load is...
lighter and less of a burden is imposed on patients. However, it has not been determined whether intravenous or oral administration provides better prophylaxis against infectious complications after TACE. Prophylactic administration of cephazolin (CEZ) and levofloxacin (LVFX) is commonly used for patients undergoing invasive procedures for liver and biliary diseases (9-12).

Therefore, we compared the efficacy of oral LVFX and intravenous CEZ for prophylaxis against infectious complications in patients undergoing transcatheter therapy for hepatocellular carcinoma using a prospective study design.

**Patients and Methods**

**Patients**

Patients were eligible for enrollment if they had hepatocellular carcinoma (HCC) and were scheduled to undergo TACE or transcatheter arterial infusion chemotherapy (TAI). In all the patients, HCC was clinically diagnosed on the basis of elevated serum levels of tumor markers (alpha fetoprotein and/or des-gamma-carboxyl prothrombin) and early enhancement of hepatic nodules by dynamic CT. One hundred eighty-three subjects with HCC were scheduled to undergo transcatheter arterial therapy at Hyogo Prefectural Awaji Hospital between October 2007 and March 2009 (Fig. 1). The exclusion criteria were: 1) under 19 or over 85 years of age 2) with severe cardiovascular, hematologic, or renal disease, 3) pregnant or lactating mothers, 4) known hypersensitivity to either of the antibiotics, 5) receiving drugs that might affect CEZ or LVFX, and 6) concomitant treatment with other antibiotics. We did not perform transcatheter treatment for any patients with a history of biliary reconstructive surgery, since it has been reported that such patients tend to develop liver abscess and sepsis (13). Six subjects were excluded from the protocol because of the presence of some of these exclusion criteria (three were over 85 years old, and the others had drug allergy). Thirty-three patients did not agree to participate. Therefore, 144 subjects were enrolled in this prospective study and randomly assigned to two groups after providing written informed consent, in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Hyogo Prefectural Awaji Hospital.

**Study design**

Patients were randomly assigned by the envelope method to two groups. In the CEZ group, CEZ was administered intravenously at 2 g/day twice a day, from the morning of the therapy day for 5 days. In the LVFX group, LVFX was administered orally at 300 mg/day three times a day, from the morning of the therapy day for 5 days. All patients received prophylactic antibiotics more than two hours before transcatheter treatment. The antibiotic administration period could be prolonged, or its dose altered, if the physician judged that the effect of the antibiotic was insufficient, on the basis of persistent fever and an increase in the serum level of C-reactive protein (CRP).

Patients were assessed before treatment, and at the 4th and 6th days after the start of treatment. After three months of the treatment, a final assessment was also done. Laboratory tests including CRP and blood leukocyte count, period of antibiotic administration, alteration of the dose of antibiotics, length of hospital stay, side effects of the antibiotics, and infectious complications within 3 months after the treatment were evaluated to compare the effectiveness of the two
kinds of antibiotic prophylaxis. Pyrexia was not evaluated because post-embolization syndrome, characterized by nausea, vomiting, abdominal pain, and fever, occurs in up to 90% of patients (4, 5, 14). We defined post-procedure infection based on the basis of the criteria for defining “deep incisional surgical site infection” (SSI) as detailed in the Centers for Disease Control and Prevention (CDC) guidelines (15). In all patients who underwent transcatheter treatment, dynamic computed tomography (CT) was performed at approximately 10 days and 1-3 months after treatment in order to assess the effectiveness of treatment and the possible presence of liver abscess, cholangitis, or remote infection.

Using a questionnaire, we asked each enrolled patient whether they preferred oral or intravenous administration of antibiotics, and if they had previously received transcatheter therapy and/or had been given either of the antibiotics used in this study.

Transcatheter arterial treatment

After access to the common femoral artery had been obtained, diagnostic celiac and selective hepatic arteriography (CAS-110A; Toshiba, Japan) was performed to delineate the feeding arteries of the tumors and to confirm the patency of the portal vein. CT was also performed during arterial portography to further confirm the patency of the portal vein. After hypervascular hepatocellular carcinoma had been identified, the tumor feeding arteries were selectively catheterized with a transfemorally inserted 4.2-Fr catheter or by a coaxially placed 2.2 or 2.7-Fr catheter (Progreat; Terumo, Japan). In all patients who underwent transcatheter treatment, dynamic computed tomography (CT) was performed to further confirm the patency of the portal vein. Dynamic computed tomography (CT) was also performed during arterial portography to further confirm the patency of the portal vein. CT was also performed during arterial portography to further confirm the patency of the portal vein. After hypervascular hepatocellular carcinoma had been identified, the tumor feeding arteries were selectively catheterized with a transfemorally inserted 4.2-Fr catheter or by a coaxially placed 2.2 or 2.7-Fr catheter (Progreat; Terumo, Japan). In the majority of 2.2 or 2.7-Fr catheter (Progreat; Terumo, Japan), the feeding arteries represented at least a second-order branch of the right or left hepatic artery. The chemotherapeutic agents consisted of epirubicin hydrochloride 40 mg (Farmorubicin; Pfizer, Japan) and mitomycin C 10 mg (Kyowa Hakko-Kirin, Japan) dissolved in 2.5 mL of contrast material. Iopamidol (Iopamiron 300; Bracco, Italy) was emulsified with 5 mL iodized oil (Lipiodol; Guerbet, France) and injected into the feeding arteries. The volume administered depended on the size and vascularity of the tumor, with approximately 10 mg of epirubicin hydrochloride and 2.5 mg of mitomycin C administered per 1 cm of tumor diameter. If arterial inflow reduction of the lesion was not achieved and the patient had class A liver function according to the Child-Pugh criteria, arterial embolization was performed with 1.6-8.0 mg of 0.9-1.5-mm absorbable gelatin particles (Gelpart; Nihon Kayaku, Japan).

If the patient who had portal thrombus or an inappropriate arterial anatomy for embolization, 100 mg cisplatinum (IActall; Nihon Kayaku, Japan) was infused via the hepatic artery. Patients were sedated during the procedure with an intramuscular injection of 25 mg hydroxyzine pamoate. Pain control was achieved with pentazocine. Metoclopramide hydrochloride was administered for antiemesis.

Statistical analysis

Post-transcatheter treatment infections are reported to occur in 3.7%, 4-8%, 3.3%, and 11% of patients (5, 8, 16, 17). Therefore we assumed that infectious events were likely to occur in 6% of patients. On this basis, one infectious event is likely to occur in one of every 50 patients at the 95% confidence level in accordance with the Rule of Three. The sample size of 108 (54 in each group) patients was chosen to provide at least 80% power to detect a common odds ratio of 1.2. The result was tested with Lehr’s formula. An odds ratio of 1.2 would indicate a clinically significant difference between the two treatments. In the present study, 144 patients underwent randomization, with 138 treated by TACE/TAI, of whom 129 were included in the analysis. Mann-Whitney U test was used to test the significance of differences among the groups. Chi-squared test was used for categorical data analysis. Repeated measures ANOVA was used for the corresponding laboratory tests. Independent factors were expressed as relative risk with 95% confidence intervals. Differences at $p<0.05$ were considered significant.

Results

Baseline characteristics of the patients

One hundred forty-four patients were enrolled and assigned to two groups. Seventy-two patients were assigned to the CEZ group and the other 72 were assigned to the LVFX group. Eight patients in the CEZ group were excluded from analysis because of incorrect administration of antibiotics in one patient, simple diagnostic angiography without TACE/TAI in one patient, and inappropriate blood sample collection in six patients. Seven patients in the LVFX group were also excluded from analysis because of inappropriate blood sample collection in two patients, and simple diagnostic angiography without TACE/TAI in five patients (Fig. 1). There were no significant differences between the two groups in terms of baseline characteristics before and after exclusion of these 15 cases (Table 1-a, b).

Adverse and infectious events

The numbers of adverse and infectious events are described in Table 2. The adverse events included transient elevation of serum transaminase and creatinine, and diarrhea, nausea, and peripheral venous thrombosis. All adverse events were within grade III (Common Terminology Criteria for Adverse Events; CTCAE v3.0).

The infectious events included pneumonia and biloma. One case of pneumonia was diagnosed on the second post-therapy day after catheter treatment in the CEZ group. In addition, 1 patient in the LVFX group who had liver infarction immediately after TACE also developed a biloma as a complication.

There were no significant differences between the CEZ and LVFX groups with regard to the number of infectious events ($p=0.483$) and adverse events ($p=0.983$) (Table 2). If the physician judged the effect of antibiotic administration...
Table 1-a. Baseline Characteristics of All Analyzed Patients

<table>
<thead>
<tr>
<th></th>
<th>CEZ</th>
<th>LVFX</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>72</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)*</td>
<td>72.2±8.6</td>
<td>71.3±8.5</td>
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<td>Male/ Female</td>
<td>51/21</td>
<td>52/20</td>
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<td>JIS score (0/1/2/3/4/5)</td>
<td>8/28/23/7/6/0</td>
<td>9/24/30/5/4/0</td>
<td>0.904</td>
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<tr>
<td>Child-Pugh grade (A/B/C)</td>
<td>51/20/1</td>
<td>50/20/2</td>
<td>0.988</td>
</tr>
<tr>
<td>TMN stage (I/II/III/IV)</td>
<td>11/33/22/6</td>
<td>12/31/27/2</td>
<td>0.690</td>
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<td>Pathogenesis of cirrhosis (HCV/HBV/alcohol/others)</td>
<td>49/9/2/12</td>
<td>51/3/6/12</td>
<td>0.353</td>
</tr>
<tr>
<td>WBC (µL)*</td>
<td>4674±1988</td>
<td>4455±1571</td>
<td>0.373</td>
</tr>
<tr>
<td>CRP (mg/dL)*</td>
<td>0.30±0.57</td>
<td>0.22±0.29</td>
<td>0.469</td>
</tr>
<tr>
<td>AST (IU/L)*</td>
<td>66±48</td>
<td>61±49</td>
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<tr>
<td>ALT (IU/L)*</td>
<td>50±35</td>
<td>45±28</td>
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</table>

*Mean ± SE

Table 1-b. Baseline Characteristics of Analyzed Patients

<table>
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<tr>
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<th>CEZ</th>
<th>LVFX</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Number of subjects</td>
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<td>65</td>
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<tr>
<td>Mean age (yr)*</td>
<td>72.7±8.5</td>
<td>72.0±8.2</td>
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<tr>
<td>Male/ Female</td>
<td>46/18</td>
<td>45/20</td>
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<td>JIS score (0/1/2/3/4/5)</td>
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<td>7/22/27/5/4/0</td>
<td>0.912</td>
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<tr>
<td>Child-Pugh grade (A/B/C)</td>
<td>43/20/1</td>
<td>46/17/2</td>
<td>0.923</td>
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<td>TMN stage (I/II/III/IV)</td>
<td>9/30/19/6</td>
<td>9/28/26/2</td>
<td>0.581</td>
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<tr>
<td>Pathogenesis of cirrhosis (HCV/HBV/alcohol/others)</td>
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<td>48/3/5/9</td>
<td>0.420</td>
</tr>
<tr>
<td>WBC (µL)*</td>
<td>4742±2004</td>
<td>4512±1557</td>
<td>0.371</td>
</tr>
<tr>
<td>CRP (mg/dL)*</td>
<td>0.32±0.58</td>
<td>0.22±0.30</td>
<td>0.420</td>
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<td>AST (IU/L)*</td>
<td>68±50</td>
<td>61±51</td>
<td>0.171</td>
</tr>
<tr>
<td>ALT (IU/L)*</td>
<td>51±36</td>
<td>44±29</td>
<td>0.228</td>
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</table>

*Mean ± SE

Changes in inflammatory markers

Peripheral leukocyte counts and serum CRP levels peaked on the 4th day after transcatheter treatment. There was no significant inter-group difference in these parameters at any of the assessed time points (Figs. 2, and 3). We also classified the enrolled patients into TACE-treated (n=121) and TAI-treated (n=8) subgroups, and assessed their differences in regard to inflammatory markers based on CEZ or LVFX.
Figure 2. Changes in peripheral leukocyte number. There was no significant difference in the leukocyte counts between the CEZ (n=64) and LVFX (n=65) groups. Statistical analysis was done by repeated measures ANOVA.

Figure 3. Changes in serum CRP levels. There was no significant difference in serum CRP level between the CEZ (n=64) and LVFX (n=65) groups. Statistical analysis was done by repeated measures ANOVA.

administration. However, there were no differences for CRP or peripheral leukocyte counts between the 2 antibiotics in this subgroup analysis.

Patient preference

We investigated whether the patients preferred oral or intravenous administration of antibiotics. The patients who had previously received transcatheter therapy, and had already been exposed to these two antibiotics were investigated. We were able to obtain 48 replies from the 56 applicable patients, among whom 36 (75%) stated that they preferred oral administration of prophylactic antibiotics (Table 3).
For the treatment of diseases, invasive procedures carrying a risk of infection are sometimes necessary. Among invasive procedures for the non-surgical treatment of HCC, transcatheter arterial embolization, chemoembolization, and chemotherapy are those most widely used. These procedures carry risks for several types of infection. First, a percutaneous arterial approach carries a risk of infection caused by bacteria on the skin via the skin puncture route. Secondly, necrotic tumor tissue in the liver can become a source of infection, especially through bacterial reflux via the biliary system from the intestine (13). In fact, transcatheter treatment of HCC is reportedly accompanied by post-procedure infectious complications in 3-11% of cases (5, 8, 16, 17).

Since bacterial infection can be introduced not only via the percutaneous route but also via the trans-biliary route, various kinds of gram-positive and -negative bacteria including *Streptococcus* species, *Klebsiella* species, and *Escherichia coli* have been reported to be pathogenic organisms (5, 8, 9, 16). Patients with HCC often have hepatic functional damage and decreased resistance to bacterial infection. Once post-procedure infectious complications have occurred, the condition of some patients will deteriorate, with a subsequently undesirable outcome. Therefore, administration of prophylactic antibiotics is widely performed in patients being treated for HCC.

Post-procedure infectious complications of HCC are caused by gram-positive and gram-negative bacteria. Therefore, antibiotics with a wide bacterial spectrum, such as penicillin, cephalosporin, and quinolones, are usually selected for prophylaxis against infectious complications. In Japan, intravenous drip-infusion of cephalosporin is the most widely used prophylactic treatment for patients with HCC, although evidence of its effectiveness is still lacking (18, 19). Drip infusion of drugs may confine patients to bed, and thus increase the workload of medical staff on hospital wards. Peroral administration of antibiotics is easier prophylaxis, peroral administration of antibiotics is preferable, as might be expected.

Although we did not measure the health-related quality of life (HRQOL) of the enrolled patients, it is important to note that the majority of patients preferred peroral LVFX over intravenous CEZ. It is probably not surprising that the HRQOL of the patients receiving twice-daily drip-infusion antibiotics for 5 days was reduced, because of the need to remain in bed, and the pain caused by venopuncture.

This study had some limitations in terms of design. First, for ethical reasons, we were unable to set up a control group without antibiotic administration. Prophylactic administration of antibiotics after non-surgical invasive treatment of HCC is already a standard treatment in Japan, and setting up a group without antibiotic administration would therefore not be approved. Accordingly, the value of antibiotic administration cannot be established from this study, although it was possible to conclude that LVFX administered perorally and by intravenous drip infusion had similar effects (12, 20). Second, we failed to measure the HRQOL of the enrolled patients using a standard measure of QOL such as SF-36. Therefore, investigation of HRQOL may be an important extension of this study in the future. Third, tumor necrosis induced by transcatheter treatment elevates the number of peripheral leukocytes and the level of CRP. However, the exclusive effects of an infectious complication cannot be detected by those parameters. Therefore, we examined the enrolled patients 3 months after treatment, which revealed 2 with infectious complications even with antibiotics administrations. Fourth, bacteremia after hepatic angiography was not routinely tested in this study. Chen et al (21) reported the possibility of bacteremia following hepatic angiography and transcatheter arterial embolization (TAE). They studied bacterial infections in 231 HCC patients who underwent 287
angiographic procedures without antibiotic prophylaxis. Of those, 111 were simple hepatic angiographies, which found 4 patients complicated by transient asymptomatic bacteremia. In addition, 9 of the 176 TAE procedures were associated with bacteremia or symptomatic bacterial infection. It may be worthwhile to test for bacteremia after angiographic procedures in patients with and without antibiotic prophylaxis in a future study.

In the present patients, WBC and CRP were elevated in spite of administration of antibiotics in both groups, which may not indicate the necessity of prophylactic antibiotics in such cases. Geschwind et al (9) performed a prospective randomized controlled study of the effects of two kinds of prophylactic antibiotics to prevent liver abscesses after TACE in patients with HCC and a history of biliary reconstructive surgery. None of 4 patients administered intravenous tazobactam/piperacillin for prophylaxis developed a hepatic abscess after TACE. On the other hand, all 4 patients administered cephalexin developed hepatic abscesses. None of our patients had a history of biliary reconstructive surgery, however, they were in a compromised state due to liver cirrhosis. Therefore, prophylactic administration of antibiotics is necessary at the point of transcatheter treatment in patients with liver cirrhosis and HCC.

In conclusion, the present study has clarified that treatment with peroral LVFX for prophylaxis against postprocedural infectious complications in patients with HCC treated by TACE/TAI has similar effectiveness to treatment with intravenous CEZ.

References