Transcatheter arterial chemoembolization combined with percutaneous injection of ethanol-lipiodol mixture for treatment of hepatocellular carcinoma: a non-randomized controlled study of 122 cases

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Abstract: The aim is to evaluate effects and safety of the combination of transcatheter arterial chemoembolization (TACE) and percutaneous ethanol-lipiodol injection (PELI) for the treatment of unresectable hepatocellular carcinoma (HCC). A total of 122 patients (104 men and 18 women; mean age: 52 years old) with histopathologically proven HCC were consecutively enrolled for either the combination of TACE with PELI (the combo group) or TACE alone (the control group). Safety and toxicity of the combination therapy, and its effects on survival rates, progression-free survival (PFS), and local response were evaluated. Patients in the combo group had better local response than those in the control group had in stage II disease. Objective response rate in stage I, II and III disease was 84.6%, 78.6% and 59.3% in the combo group, and 66.7%, 45.8%, 31.0% in the control group, respectively. Both PFS and the cumulative survival curves showed that the combo group had better results than the control group had. In the combo group, PFS curve showed that both stage I and stage II disease had longer PFS than stage III had. Survival curve also showed that better survival rates were observed in stage I than that in stage III disease. The combination of TACE with PELI improved survival time of patients with unresectable HCC compared to TACE alone. Side effects were minor and delay in disease progression was obvious. A further study to better determine the efficacy of this combination therapy is warranted.

Keywords: Trans-catheter hepatic arterial chemoembolization, percutaneous ethanol-lipiodol injection, non-randomized control study, unresectable hepatocellular carcinoma

I. INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm in the world especially in Asia and sub-Saharan Africa (Llovet et al., 2008). Chronic type B hepatitis results in that 55% of the world’s primary hepatic carcinomas occur in China (Zhang et al., 2008). HCC has a poor prognosis due to its rapid infiltrating growth and complicating liver cirrhosis. Because of its insidious onset, many patients have their disease already in the advanced stage when it is finally diagnosed (Yuen et al., 2009). Approximately 20% of these patients have the opportunity of surgical resection. Unfortunately, 80% of them will suffer from recurrence during their temporal life span. HCCs are complicated with liver cirrhosis in 50%~90% of the cases, and because of the insensitivity to the orthodox treatments such as chemotherapy and radiotherapy, the management of unresectable HCC is still a formidable problem waiting to be overcome. Transcatheter hepatic arterial chemoembolization (TACE) is introduced as a palliative treatment and has gained fine clinical effectiveness (Bhattacharya et al., 1995). However, currently the long-term survival rate is still low. To raise therapeutic efficacy favorably, combining TACE with percutaneous ethanol injection (PEI) in the treatment of HCC was first suggested by Tanaka et al (1991). In our center, TACE combining with percutaneous ethanol-lipiodol injection (PELI) has been used in the treatment of unresectable HCC for years. In this study, we assessed whether the effectiveness of the combination of TACE with PELI is superior to that of TACE alone in the treatment of unresectable HCC. This trial was approved by the medical ethics committee of West China Hospital of Sichuan University.

II. MATERIALS AND METHODS

A. Patient characteristics
A total of 122 consecutive patients who had viable HCC histologically determined were included in this study from October 2007 to June 2008. Among them, there were 104 males and 18 females, with the age range from 23 to 76 years old (average 52 years old). All the patients undertook laboratory studies of tumor markers (alpha fetoprotein, ferroprotein) and imageology (enhancement CT, magnetic resonance imaging, color Doppler). Furthermore, CT-guided percutaneous core biopsy of the lesions was used to obtain pathological and immunohistochemical evidence.

B. Exclusive criteria

Patients enrolled in this study had histologically proven HCC and were ineligible for surgical resection. The exclusion criteria included: having received operation, chemotherapy, radiotherapy, radiofrequency ablation, microwave coagulation therapy, laser-induced thermotherapy or other anti-tumor therapies before; complete portal vein obstruction or tumor growth in the inferior caval vein; regional lymph node or distant metastasis or with a life expectancy shorter than 3 months; Child-Pugh C liver function. Also, patients with retraction of consent, pregnancy, uncontrolled serious infections, or hypersensitivity to iodine and alcohol were excluded for the enrollment.

C. Study design

Considering prognostic factors of HCC, we classified all enrolled patients using the 6th edition AJCC/UICC TNM staging system (Table 1) (Sobin et al., 2002). In each group, patients who were willing to accept the combination of TACE and PELI were assigned to the combo group, while those who were not willing to take PELI were assigned to the control group (TACE-only group). The clinical characteristics of enrolled patients were summarized in Table 2. Firstly, a diagnostic angiography was performed in all patients. For TACE, a 5F Rosch hepatic catheter (Terumo, Tokyo, Japan) was placed into the celiac trunk or the arteria hepatica communis routinely to identify number, location, contour, type, size, feeding arteries, and arteriovenous fistula (A-V fistula) of the tumor lesion. When A-V fistulas were found, embolization with pieces of gelatin sponge was performed. When it was needed, angiography of the superior mesenteric artery or the inferior phrenic arteries would be performed to look for other arterial branches supplying HCC. All patients in both groups received the same regimen of intra-arterial chemoperfusion (5-fluoro-2-deoxyuridine 800 mg/m², and vinorelbine 30 mg/m²). Then under fluoroscopic guidance, the catheter was placed into the feeding vessel, and iodized oil was injected very slowly. With reference to tumor size and deposition of iodized oil, the dosage of oil was estimated, and the volume was confined to 5 to 20 mL. The procedure was repeated with an interval and the period of time between the present and the next TACE was specified as at least 1 month. Patients in the control group received TACE with the same interval as those in the combo group. PELI was performed in patients of the combo group under CT guidance, by percutaneous injection of uniformly mixed absolute alcohol and iodized oil with the ratio of 1 to 10 (V/V). This procedure was scheduled on day 3 or 4 after TACE, and repeated with a 1-week interval. The injection volume of the mixture was confined to 2~10 mL each time, and determined for the next injection with regard to deposition of the mixture in the lesion.

D. Observation indexes

Before and after treatment, the patients’ clinical features were observed and documented in detail. Death of HCC was defined as the endpoint of observations. In different clinical stagings, adverse events, tumor response to treatment, progression-free survival (PFS), survival rate were major items to observe. All patients had a 12-month follow-up period which began from the first treatment day. Routine follow-up included laboratory study.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Table 1. Sixth Edition UICC TNM Classification of Hepatocellular Carcinoma (2002)
T1-Single tumor without vascular invasion; T2-Single tumor with vascular invasion, or multiple tumors, none >5 cm; T3-Multiple tumors, any >5 cm, or tumors involving major branch of portal or hepatic veins; T4-Tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum; N0- No metastasis in lymph node; N1- Regional lymph node metastasis; M1-Distant metastasis; M0- No metastasis at a distant place of AFP, ferroprotein, and abdominal enhancement CT or MRI result. These were performed every month in the primary quarter, and then once every 3 months if the tumor was stable. All adverse events must be reported, such as fever, abdominal pain, bile duct damage, liver rupture, infection, liver function impairment and so on. Meanwhile, toxic effects of the therapy were investigated according to the National Cancer Institute’s Common Toxicity Criteria (Ajani et al., 1990). Assessments of therapeutic effect were made for local response based on the response evaluation criteria in solid tumor (RECIST) (Therasse et al., 2000). A complete response was defined as disappearance of all HCC lesions documented by imaging analyses (ultrasound, CT, or MRI), and confirmed 4 or more weeks later. A partial response was defined as a greater than 50% reduction in tumor size based on the measurement of the two longest perpendicular diameters of the tumor. PFS was measured as the interval from the time of the first treatment to the date of new focus appearing by imageology. Survival duration was measured from the time of the final diagnosis to the date of the last follow-up or death.

**Table 2. Clinical Characteristics of Enrolled Patients**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Number of patients</th>
<th>Statistic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TACE+PELI (n=54)</td>
<td>TACE (n=68)</td>
</tr>
<tr>
<td><strong>Sex. M/F</strong></td>
<td>48/6</td>
<td>61/7</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td>26-72</td>
<td>23-76</td>
</tr>
<tr>
<td><strong>UICC TNM classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Stage II</td>
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<td>24</td>
</tr>
<tr>
<td>Stage III</td>
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<td>29</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type B/C/B+/C/NO</td>
<td>40/5/3/6</td>
<td>43/8/3/14</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child Pugh A/B/C</td>
<td>36/18/0</td>
<td>40/28/0</td>
</tr>
<tr>
<td>AFP(ng/ml)&lt;400&gt;400</td>
<td>20/34</td>
<td>26/42</td>
</tr>
</tbody>
</table>

**E. Statistical analysis**

SPSS 13.0 was applied as statistical software in this non-randomized control study. The statistics comparing the two groups at baseline was made using $\chi^2$ test. Differences in local response were estimated by Wilcoxon rank sum test, and that in PFS and survival rate were assessed by log-rank test. Results were considered statistically significant when the P value is less than 0.05.

**III. RESULTS**

In total, 122 patients were recruited into this trial. There was no statistical difference in baseline data of clinical features between the two groups (Table 2). Of the 122 patients, 54 (13, 14 and 27 patients in stage I, II and III, respectively) were enrolled into the combo group, while the remaining 68 (15, 24 and 29 patients in stage I, II and III, respectively) were enrolled into the control group of this nonrandomized clinical study. Patients in the control group received repeated TACE with a minimum time interval of 30 days for a total of 155 times (2.28 times/person), while those in the combo group totally received 134 times of TACE (2.48 times/person) and a total of 142 times of PELI (2.63 times/person).

**A. Adverse events**

No one in this study had treatment-related serious adverse events. All patients in the combo group experienced different degrees of fever, with body temperature fluctuations from 37.3 °C to 38.9 °C. A part of the patients (n=28) had slightly mild local pain within 2 to 3 days after PELI. One case in the combo group had localized hepatorrhaxis, which was relieved by antibiotics administration and symptomatic management through conventional supportive treatment. The most common side effects of TACE were fever, abdominal pain, and elevation of serum total bilirubin level. These side effects were transient and usually disappeared within a week.

**B. Local response**

Within the treatment course, enhancement CT scan or MRI was repeated with intervals of at least 1 month and the lesions were evaluated according to RECIST for local response to the treatment. When the follow-up ended June 30, 2009, 1 patient in the combo group and 4 in the control group were lost to follow-up. For each patient, the maximum efficacy was documented by CT or MRI follow-up and evaluated referring to data of the baseline
CT scan revealed rather good deposition of iodized oil and destruction of tumor tissue in the combo group. In stage I disease, the local response included 4 CRs, 7 PRs, 2 SDs, 0 PDs in the combo group, and 3 CRs, 7 PRs, 4 SDs, 2 PDs in the control group (P=0.272, Wilcoxon rank sum test). Local response in stages II disease included 2 CRs, 9 PRs, 2 SDs, 1 PDs, in the combo group and 0 CRs, 11 PRs, 7 SDs, 6 PDs in the control group (P=0.023, Wilcoxon test). The overall objective response rate in Stage I, II and III disease is 84.6%, 78.6% and 59.3% in the combo group, and 66.7%, 45.8%, 31.0% in the control group, respectively.

C. PFS and Survival

The overall median PFS in the combo and the control group was 7 months and 5 months, respectively. PFS curves showed that patients in the combo group had longer PFS than those in the control group (Log-rank test, chi-square=9.813, P=0.002). Moreover, subgroup analysis showed no statistically significant differences in PFS between stage I and stage III disease, but longer PFS was observed in patients of the combo group with stage II disease (chi-square =11.392, p=0.001). In the combo group, PFS curve showed that patients with either stage I or stage II disease had longer PFS than those with stage III disease had (chi-square=21.513, p=0.000; chi-square = 10.788, p=0.001), but the comparison of PFS had no statistical difference between patients with stage I and stage II disease (chi-square=3.216, p=0.073). The cumulative survival rates in the control group were 91.2% at 3 mo, 66.2% at 6 mo and 20.4% at 12 mo and the corresponding results in the combo group were 96.3%, 81.5%, and 33.3%, respectively. Comparison of overall survival in both groups resulted in statistically significant difference (Kaplan-Meier chi-square=4.875, P=0.027). Subgroup analysis of survival rates in different stages showed no statistical difference between the rates in the patients of the two groups with stage I (chi-square=2.166, p=0.141) and stage III (chi-square=1.128, p=0.288) disease. Patients with stage II disease in the combo group had a better survival rate than those in the control group had (chi-square =5.051, p=0.025). In the combo group, survival curve showed that patients with stage I disease had better survival rates than those with stage III disease had (chi-square=17.673, p=0.000), but the comparison of the rates between patients with stage I and stage II disease, or between patients with stage II and stage III disease had no statistical difference (chi-square=0.189, p=0.664; chi-square=2.863, p=0.091).

IV. DISCUSSION

Long-term results of HCC after resection are seldom curative, because of the high rate of tumor recurrence or the development of new tumors in the cirrhotic liver. Recently, many kinds of approaches including radiotherapy, radiofrequency ablation, microwave coagulation therapy, laser-induced thermo therapy are applied to treatment of HCC. However, these approaches have several common disadvantages. These include that therapeutic effects are observed as regional, and recurrence and metastasis of remnant tumor are fatal to the patients with infiltrative tumor growth.

As a palliative therapy, TACE is the most widely used treatment in patients with HCC who are considered unsuitable candidates for surgery and/or ablative therapies (Bismuth et al.,2000; Matsumata et al., 1989). TACE kills or damages cells through giving chemotherapeutics into tumor vessels. Iodized oil emulsion has a particular affinity to hypervascular hepatic tumors and is now commonly used in HCC chemoembolization. Owing to the creation of increase in permeability of cell membrane, functional disorder of tissue structure and process of lipid metabolism, iodized oil could be detained in tumor tissue
selectively. These effects will have an integrated impact to the tumor, in consequence, its blood supply is cut off and its tissue becomes necrotic, so that control of tumor growth will be achieved. However, for major tumors, it is difficult to make chemotherapeutics and iodized oil distribute everywhere in the tumor especially into the central areas. In addition, dual blood supply around the capsule, multiple collateral circulation, and recanalization of the embolized artery lead to the main limitations of TACE which result in incomplete necrosis of HCC (Camma et al., 2002).

To improve therapeutic efficacy, we combined TACE with PELI, the latter represents CT guided percutaneous injection of a mixture composed of ethanol and lipiodol. We observed the safety, availability, and efficacy of PELI. Considering TNM Staging was the major prognostic factor of HCC [14], we enrolled 122 HCC patients in different stages according to TNM classification of malignant tumors of UICC (Sobin et al., 2002).

The approach to using absolute alcohol to treat HCC was firstly reported in the 1990s (Gotohda et al., 2006). Absolute alcohol leads to solidification and dehydration of tumor cell, necrosis of vascular endothelial cell and thrombogenesis. Daniele B et al (2003) used absolute alcohol to treat small hepatoma, the 1- and 3-year survival rate being 91% and 65%, respectively. For large tumors, the sole use of absolute alcohol was difficult to obtain thorough deactivation of the tumor, and flushing dose would cause damage to the portal vein and the bile ducts. Thus we designated this mixture by which we intended to confer the dual benefits of better efficacy and less risk to the patients. The mixture consists of 10:1(V/V) of lipiodol and absolute alcohol. After sufficient mixing, the mixture looks yellowish white and seems less thick and less adhesive than the lipiodol in its original state by finger feeling. The mixture retains the nature of high affinity to tumor tissue, a feature of iodized oil treatment for HCC, at the same time it keeps the diffusion property of ethanol to some extent. When applied by multiple point injection, the mixture spread quickly in tumor tissue and stayed dispersed throughout tumor shadow which was revealed by CT, and deposited at site thereafter. Some cases demonstrated complete lipiodol deposition in entire tumor with a clear-cut demarcation line between normal tissue and the lesion.

TACE and PELI complement each other. TACE occludes tumor vessels by sinusoidal embolization with iodized oil which creates an impact on hepatic microcirculation, and thus destroys tumor cell and tissue by cutting off their blood supply. PELI destroys vestigial tumor cell and tissue, interrupts hepatic bypass circuit which receives blood from the inferior phrenic arteries and the portal vein, and reduces recurrence of tumor. Absolute alcohol and iodized oil deposited easily. Meanwhile, attention must be paid to several points in practice. Multiple points injection should be used when major tumor, and the procedure was usually repeated 1 week after. The injection must be controlled at low speed. If severe pain is complained or leakage of agent is suspected, the injection procedure must be terminated immediately. Low fever or dull pain can be removed by fluid replacement, and glucocorticoids can be used when necessary. In the present study, no obvious difference in adverse events was observed between the combo group and the control group, and no serious complications were shown in the combo group. In our study, patients in the combo group had local response better than those in the control group had for stage II (P=0.023, Wilcoxon rank test) and stage III (P=0.046, Wilcoxon rank test) disease. The objective response rate of patients with stage I, II and III disease were 84.6%, 78.6% and 59.3% in the combo group (TACE-PELI), and 66.7%, 45.8%, 31.0% in the control group (TACE), respectively. With both PFS and cumulative survival rate curves we showed better results in the combo group than that in the control group (Log-rank test, p<0.05), and this was true in subgroup analysis of stage II disease (Log-rank test, p<0.05).

However, of stage I and stage III disease, the results were not statistically significant. In the combo group, the Kaplan-Meier PFS curve showed that patients with both stage I and stage II HCC had longer PFS than those with stage III HCC had (Log-rank test, p<0.05), but the comparison of PFS between stage I and stage II HCC had no statistical difference (Log-rank test, p=0.073). Survival data using the Kaplan Meier survival curve showed that patients with stage II disease had better survival rates than those with stage III had (Log-rank test, p<0.05), but the comparison of cumulative survival between stage I and stage II HCC, or between stage I and stage III HCC had no statistical difference (Log-rank test, p=0.664; Log-rank test, p=0.091).

Nevertheless, our study has several limitations. We
didn’t use diameter and number of tumors as levels of stratification. Our single-center study enrolled modest number of cases, so multicentre and large-scale investigations to explore mechanism of unification were needed. The future task is to develop combination therapies of tumor for curative effects, apart from TACE and PELI, gene therapy, immuno therapy and targeted therapy would be used appropriately to treat HCC.

In conclusion, the combination of TACE and PELI compared with TACE alone prolongs both survival and PFS in patients with stage II HCC. This combination therapy is safe and well-tolerated, and side effects are mild and acceptable. In general, it confers dual benefits of better efficacy and less risk on HCC patients. A further study to better determine the efficacy of this combination therapy is warranted.

REFERENCES