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Original Article
Transhepatic arterial chemoembolizations with lobaplatin-eluting microspheres for the treatment of unresectable hepatocellular carcinoma

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Abstract: Objective: To assess the clinical safety and efficacy of Transhepatic Arterial Chemoembolizations (TACE) with lobaplatin-eluting microspheres in treating unresectable hepatocellular carcinoma (HCC). Materials and Methods: A total of 70 patients with unresectable hepatocellular carcinoma and preserved liver function, who were treated with TACE using lobaplatin-eluting microspheres (Group-LEM, as experimental group) or using lobaplatin-lipiodol mixtures (Group-LLM, as control group), were evaluated retrospectively. Tumor response was determined with follow-up computed tomography after each chemoembolized procedure according to modified Response Evaluation Criteria in Solid Tumors (mRECIST). The side effects and complications were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Results: A database of 70 patients with advanced HCC admitted to Guangdong General Hospital between January 2016 and October 2016 was evaluated retrospectively. Four weeks after TACE procedure, radiological evaluation of tumour response was available in all patients, According to mRECIST, disease control rate (DCR) and objective response rate (ORR) differed significantly between Group-LEM and Group-LLM (60.00% vs 31.43%, and 22.86% vs 2.86%). The most common adverse event was postembolization syndrome (PES), with 18 in Group-LEM and 24 in Group-LLM respectively. Liver dysfunction and thrombocytopenia also had significant difference through comparative analysis between Group-LEM and Group-LLM (8 vs 16, and 1 vs 8). There were neither periprocedural deaths nor adverse events (AEs) of grade 5 documented in all patients. Conclusion: TACE with lobaplatin-eluting microspheres is a safe and feasible treatment without major adverse events in treating unresectable hepatocellular carcinoma. However, the long-term effects of this treatment need further observation.

Keywords: TACE, lobaplatin, drug-eluting microsphere, HCC

Introduction
As the fifth prevalent cancer, hepatocellular carcinoma (HCC) has the third highest mortality rate worldwide [1, 2]. In 2012, it was estimated that there was a total of 782,000 new liver cancer cases, and approximately half of them were in China [3].

Because it takes time for HCC to show obvious symptoms, over 80% of patients lose the chance of curative hepatectomy owing to lagging diagnosis and poor prognosis [4]. Still, for patients who are diagnosed early enough, there is a chance that they are eventually deemed as not eligible for curative hepatectomy because of elements like the progression of HCC, vascular invasion, liver dysfunction. And even for patients who have successfully finished their hepatectomy, many of them would suffer from a wide variety of relapses of HCC [5, 6].

However, according to Barcelona Clinic Liver Cancer (BCLC) staging and management, endorsed by the American (American Association for the Study of Liver Diseases, AASLD) and European (European Association for the
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Study of the Liver, EASL) guidelines for HCC management, transscatheter arterial chemoembolisation (TACE) is recommended as a first-line therapy for unresectable intermediate-stage HCC (stage B), and evidence obtained from randomized controlled trials has confirmed its favorable effect on improving median survival [7, 8].

The conventional TACE technique uses emulsions, which are mixtures of lipiodols and chemotherapy drugs, as arterial embolisations [9]. Unfortunately, the process of emulsification is unstable and the components begin to separate as soon as they are injected into the hepatic arterial circulation so these embolisations fail to obtain the highest sustained concentration of drugs within the tumor [10].

Nowadays, the drug-eluting beads, which are loaded with chemotherapeutic agents, can deliver directly into the tumor. Thus, it can achieve high intratumoral concentration and low plasma concentration, and becomes prevalent in clinical practice [11]. Among different kinds of microspheres, the superabsorbent polymer microspheres (HepaSphere™: Biosphere Medical; Roissy CDG Cedex, France) have the ability to load with several types of chemotherapeutic agents, such as doxorubicin [12], cisplatin [13], oxaliplatin [14].

Similar with other antineoplastic drugs, lobaplatin, the third generation of platinum anti-tumor drug, also has a proven survival benefit in TACE [15]. But it is still uncertain about the clinical efficacy when loading lobaplatin into drug-eluting microspheres in proceeding TACE, while several clinical trials demonstrated that drug-eluting beads, loading with cisplatin, oxaliplatin or doxorubicin [16], were feasible and effective embolic materials for unresectable advanced HCC [17, 18].

Therefore, we expect to investigate the clinical safety and efficacy of TACE with lobaplatin-loaded microspheres in patients with unresectable HCC in this retrospective study.

Materials and methods

Study population

All patients met the diagnostic criteria for HCC based on radiologic or histologic grounds according to the American Association for the Study of the Liver guidelines and were not suitable candidates for resection [8].

Patients with unresectable biopsy-proved HCC without extrahepatic metastases and vascular contraindications to chemoembolization (portal vein thrombosis or arteriovenous shunting) were evaluated for eligibility. The Barcelona Clinic Liver Cancer (BCLC) system was utilized for staging (Table 1).

TACE protocol

Grouping: (1) Group-LLM (lobaplatin-lipiodol mixtures): patients received TACE using a mixture of 50 mg dry lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd.; Hainan, China), iodised oil (Lipiodol: Laboratoire Guerbet; Aulnay-Sous-Bois, France) and appropriate non-ionic contrast medium (Iodixanol Injection: GE Healthcare Ireland; Ireland). (2) Group-LEM

<table>
<thead>
<tr>
<th>Table 1. The criteria of inclusion and exclusion for HCC patients</th>
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<tbody>
<tr>
<td><strong>The inclusion criteria were as follows:</strong></td>
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<tr>
<td>BCLC stage B or C for HCC</td>
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<tr>
<td>The Child-Pugh liver function class score ≤ 7; and the Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 1</td>
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<tr>
<td>A life expectancy of 12 weeks or more</td>
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<tr>
<td>Main tumor size &gt; 5 cm and the target lesion has at least one diameter line available for measurement</td>
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<td>Has never received systemic treatment, such as oral molecularly targeted drugs or systemic chemotherapy</td>
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<tr>
<td>Has adequate hematologic function (defined as platelet count &gt; 6 × 10⁹ platelets/L; hemoglobin &gt; 90 g/L; and prothrombin time &lt; 3 s above control); and adequate renal function (defined as serum creatinine ≤ 1.5 × the upper limit of normal)</td>
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</table>
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After hepatic and superior mesenteric artery angiography to map liver vascular anatomy, check for arteriovenous shunts, and identification of arterial tumor supply, feeding arteries were superselectively catheterized with the use of a 2.7-Fr microcatheter (Progreat; TERUMO Corporation; Japan). Slow injection of the embolic materials followed until intra-tumoral vascularity was obliterated and slow flow was observed. Lesions supplied from extrahepatic arteries, including the right and left inferior phrenic artery, intercostal artery, internal thoracic artery or renal capsular artery, were allowed to be treated. The end point of the embolization was complete disappearance or a remarkable decrease of the tumor staining on a hepatic arteriogram (Figure 1).

**Follow-up**

After TACE procedure, patients were required to be followed up according to our institutional protocol every 4 weeks. Each follow-up session included a detailed history and physical examination, Eastern Cooperative Oncology Group’s performance status classification (ECOG PS classification), Child-Pugh score evaluation, serum alpha fetoprotein (AFP), and an abdominal enhanced computed tomography (CT), or magnetic resonance imaging (MRI).

**Efficacy evaluation**

Four weeks after TACE, radiologic tumor response was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [19]. However, the evaluation was classified into four grades: I. complete response (CR), indicating disappearance of any intratumoral enhancement in all target lesions; II. partial response (PR), indicating decrease of less than 30% in the sum of the greatest dimension of viable (ie, enhancing) target lesions; III. stable disease (SD), indicating not enough shrinkage or increase to qualify as a partial respon-

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Figure 1. A. Before embolization, angiogram showed highly vascularized lesion of tumor in the right hepatic lobe. B. Confirmation of the main tumor artery. C. Injection of drug-eluting beads. D. After embolization, the tumor stain was completely disappeared.
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Tumor response

Four weeks after TACE procedure, radiological evaluation of the tumor response was available in all patients. (Figure 2) DCR and ORR are shown in Table 3. In Group-LEM, the DCR is 60.00% and the ORR is 22.86%, while in Group-LLM, the DCR is 31.43% and the ORR is 2.86%. There are significant differences in DCR and ORR between the two groups (P1 = 0.016 and P2 = 0.028 respectively) (Table 3).

Safety

The complications and AEs related to TACE procedure were summarized in Table 4 acco-
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Table 3. DCR and ORR of groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>DCR (%)</th>
<th>P1*</th>
<th>ORR (%)</th>
<th>P2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-LEM (n = 35)</td>
<td>1 (2.86%)</td>
<td>7 (20.00%)</td>
<td>13 (37.14%)</td>
<td>14 (40.00%)</td>
<td>60.00</td>
<td>0.016</td>
<td>22.86</td>
<td>0.028</td>
</tr>
<tr>
<td>Group-LLM (n = 35)</td>
<td>0 (0.00%)</td>
<td>1 (2.86%)</td>
<td>10 (28.57%)</td>
<td>24 (68.57%)</td>
<td>31.43</td>
<td>2.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P1 means the P value from comparison of Group-LEM and Group-LLM in DCR. **P2 means the P value from comparison of Group-LEM and Group-LLM in ORR.

According to the CTCAE version 4.0 criteria. There were no AEs of grade 5 in all patients.

But approximately 64.29% of patients, 18 in Group-LEM and 24 in Group-LLM developed postembolization syndrome (PES) featuring fever, nausea, vomit and abdominal pain, which was recorded as the most common adverse event in this study. And it required the administration of codeine and acetaminophen for control of pain and fever. There was significant difference in the occurrence of abdominal pain after TACE between groups (P = 0.039). The liver dysfunction and thrombocytopenia also had significant difference through comparative analysis between Group-LEM and Group-LLM (Table 4).

There were no periprocedural death, hepatic abscess, biliary or vascular damage, alopecia or peripheral neurological symptoms occurred during the follow-up period.

Discussion

As the standard treatment for patients with HCC in the BCLC intermediate stage, transcatheter arterial chemoembolisation (TACE) is also used in early-stage HCC patients, who are...
excluded from potentially curative treatment [7, 8]. However, owing to the lack of standardisation of the procedure and escape of the chemotherapeutic agent from the treated portion of liver, the conventional TACE, which uses emulsions mixing with lipiodols and chemotherapy drugs as arterial embolisations, fails to obtain the optimal sustained concentration of drugs within the tumor.

So, based on this condition, the drug-eluting beads, which can deliver directly into the tumor with its loaded chemotherapeutic agents, are getting more and more clinical significance. One option among these drug-eluting beads is HepaSphere, which is a nonbiodegradable, spherical, dry particle made of a sodium acrylate and vinyl alcohol copolymer with a particle size that can be calibrated in increments of approximately 50 µm between 50 µm and 200 µm. HepaSphere swells within several minutes after being immersed into fluid, and the swollen particles are elastic and compressible but maintain their spherical shape [13, 20]. We could summary form a series of studies that it is a feasible and effective treatment for unresectable HCC when using HepaSphere, loading with epirubicin hydrochloride, oxaliplatin or other antineoplastic drugs, as embolisations in TACE [14, 21].

It should also be noted that there is no standardized usage of chemotherapy drugs in TACE, so there are a good list of alternatives, including epirubicin hydrochloride, mitomycin, hydroxycamptothecine, 5-fluorouracil, platinum chemotherapy drugs [22]. One of these drugs is lobaplatin (D-19466; 1,2-diammino-methyl-cyclobutaneplatium (II)-lactate), which is the third generation of platinum anti-tumor drug [23]. It can obstruct the process of DNA replication and transcription by affecting the formation of DNA-drug adducts, mainly as GG and AG intra-strand cross-links [24]. Moreover, lobaplatin shows its antitumour activity by arresting cell cycle progression in G1 and G2/M phases time-dependently which might be associated with the down-regulation of cyclin B, CDK1, CDC25C, phosphorylated CDK1 (pCDK1), pCDK4, Rb, E2F, and pRb, and the up-regulation of p53, p21, and p27 [25, 26].

When lobaplatin is applied in TACE for hepatic carcinoma, it shows higher efficiency, longer survival, better water-solubility and lower toxicity compared with other chemotherapy drugs [15]. The adverse reactions of lobaplatin were mostly reported in the intravenous clinical application, and the commonest adverse reaction was the dose-limiting toxicity of thrombocytopenia. Meanwhile, reactions of digestive system (including nausea, vomiting and bloating), renal toxicity and neurotoxicity had also been reported [24, 26].

In this study, 70 patients with advanced HCC were evaluated retrospectively after performing TACE with lobaplatin-loaded microspheres, while lobaplatin was loaded into drug-eluting beads for clinical use for the first time. According to the results, there were neither AEs of grade 5 in all patients nor cases of hepatic abscess, biliary or vascular damage, alopecia or peripheral neurological symptoms, indicating that it was a feasible treatment when lobaplatin was applied in TACE.

Moreover, as shown in Table 3, DCR and ORR differed significantly between the two groups, suggesting that using lobaplatin-loaded microspheres in TACE can get better clinical efficacy. This phenomenon is in line with what was reported by Song using drug-eluting beads. These authors also reported a better response using drug-eluting beads in intermediate-stage HCC, suggesting that this technique could facilitate treatment of larger lesions [27]. One of the reasons for this may be that drug-eluting beads in TACE increases the concentration of anticancer drugs and prolongs the dwelling time of the drugs in tumor cells, thereby enhancing the effects of cytotoxic anticancer drugs [11]. Another factor contributing to the good local response may be the higher flexibility of HepaSphere compared with other embolic agents, which allows deeper penetration into the tumor microvasculature and achieves more tumor necrosis.

In literature, postembolization syndrome (PES) was reported to occur in 60-80% of patients undergoing TACE in general, regardless of the diversity in the range and degree of embolisation and type of embolic material used [21]. Similarly, the commonest adverse event was PES featuring fever, nausea, vomiting and abdominal pain, occurring in approximately 64.29% of study subjects in our research. And we can conclude from Table 4 that lobaplatin-loaded microspheres cause less periprocedural pain after TACE and a lower rate of liver function impairment or thrombocytopenia as compar-
ed with control group. Therefore the liver function and general condition of patients can be maintained. And similar results can be found in previous studies [28].

Another advantage of HepaSphere lies in that it can release the chemotherapeutic agents slowly into neoplastic tissue so that it can get longer retention of the drugs within the tumor and lower systemic concentration of the drugs [11].

There are several limitations in this study: (1) Because of the strict eligibility criteria, the sample size was not very large. The findings might be more definitive if a larger number of cases were included. (2) As a single-center analysis. The results may not be generalizable to patients with HCC in other countries. (3) Longer follow-up time should have been given to perform survival analysis to get the factors which could affect prognosis. (4) Interrelated statistics about lobaplatin pharmacokinetics after TACE, such as concentration versus time curves, the peak drug concentrations should be further clarified.

In conclusion, TACE with lobaplatin-eluting microspheres is a safe and feasible treatment without major adverse events in treating unresectable hepatocellular carcinoma. However, long-term effects of this treatment need further observation, so a randomized, controlled and prospective multi-center study with a larger sample size is necessary.

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Disclosure of conflict of interest

None.

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