Int J Clin Exp Med 2018;11(2):1192-1199
www.ijcem.com /ISSN:1940-5901/IJCEM0055798

Original Article

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

Zhong-Liang Li[1*], Bao-Shan Hu[2*], Yong-Kang Liu[2*], You-Bing Zheng[2], Xu He[1], Yong Li[1], Li-Gong Lu[1]

[1]Department of Interventional Radiology, Zhuhai People's Hospital, Guangdong Cardiovascular Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China; [2]Department of Interventional Radiology, Cancer Center, Guangdong Cardiovascular Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou 510515, Guangdong, China. [*]Equal contributors.

Received January 20, 2017; Accepted November 26, 2017; Epub February 15, 2018; Published February 28, 2018

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 owning 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

Table 1. The criteria of inclusion and exclusion for HCC patients

The inclusion criteria were as follows:	The exclusion criteria were as follows:
BCLC stage B or C for HCC	Extrahepatic metastasis
The Child-Pugh liver function class score ≤ 7; and the Eastern Cooperative Oncology Group(ECOG) performance status score ≤ 1	Invasion in the main portal vein, vena cava, or other major vascular components
A life expectancy of 12 weeks or more	Previous shunt surgery
Main tumor size > 5 cm and the target lesion has at least one diameter line available for measurement	Oover 80 years old
Has never received systemic treatment, such as oral molecularly targeted drugs or systemic chemotherapy	Advanced liver disease (Child-Pugh score > 7)
Has adequate hematologic function (defined as platelet count > 6×10^9 platelets/L; hemoglobin > 90 g/L; and prothrombin time < 3 s above control); and adequate renal function (defined as serum creatinine ≤ 1.5 × the upper limit of normal)	Cardiac ejection fraction < 35%

Study of the Liver, EASL) guidelines for HCC management, transcatheter 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 achieves 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 toload 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

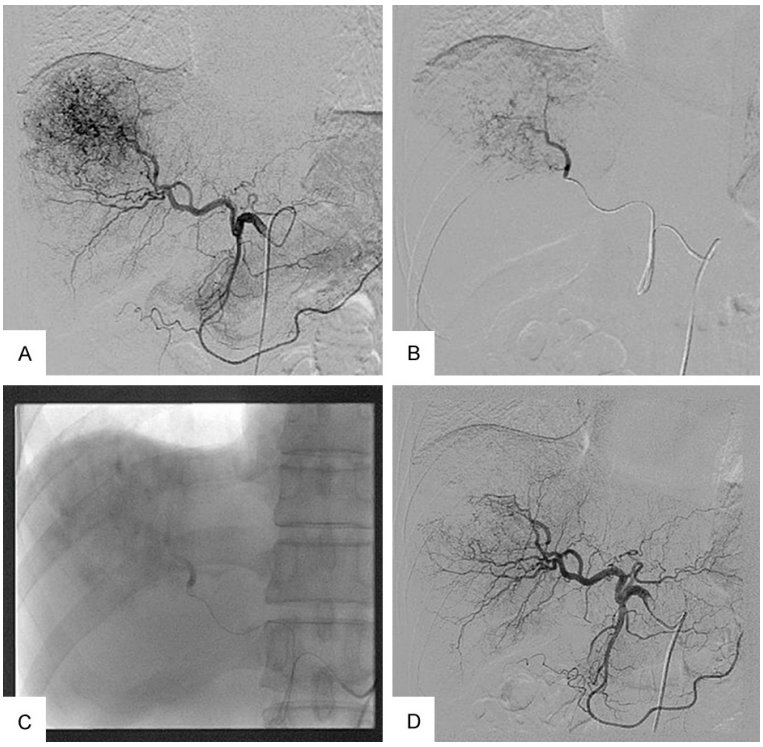

Figure 1. A. Before embolization, angiogram showed highly vascularized lesion of tumor in the right hepatic lobe. B. Confirmation of the main tumor artery. C. Injection of drug-eluting beads. D. After embolization, the tumor stain was completely disappeared.

(lobaplatin-eluting microspheres): TACEs in this group were performed with a 50 mg vial of HepaSphere (HepaSphere™: Biosphere Medical; Roissy CDG Cedex, France), which had a diameter ranging from 50 μm to 100 μm and was preloaded with 50 mg lobaplatin.

Preparation of lobaplatin-eluting microspheres: (1) To get HepaSphere swollen at least 10 minutes by mixing with 10 ml normalsaline, then remove the clear supernatant extract and remain the swollen particles, while the swollen particles were elastic and compressible but still held their spherical shape. (2) To dissolve 50 mg lobaplatin in 5 ml non-ionic contrast medium. (3) 30 minutes were allowed for the swollen particles to expand and absorb the lobaplatin sufficiently after got the former mixed with the solution of lobaplatin.

Operation of TACE: All the TACE operations were performed by experienced interventional radiologists at our hospital according to a standard operation as previously described [9]. 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 intratumoral 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-

Table 2. Clinical and pathological characteristics of patients

Characteristic	Group-LEM (n = 35)	Group-LLM (n = 35)	P
Sex			0.734
Men	29 (82.86%)	31 (88.57%)	
Women	6 (17.14%)	4 (11.43%)	
Age, years			0.632
< 55	18 (51.43%)	16 (45.17%)	
≥ 55	17 (48.57%)	19 (54.83%)	
Liver cirrhosis			0.461
+	23 (65.71%)	20 (57.14%)	
-	12 (34.29%)	15 (42.86%)	
Child-Pugh stage			0.808
A	21 (60.00%)	20 (57.14%)	
B	14 (40.00%)	15 (42.86%)	
ECOG score			0.434
0	26 (74.29%)	23 (65.71%)	
1	9 (25.71%)	12 (34.29%)	
Hepatitis B surface antigen			0.743
+	30 (85.71%)	29 (82.86%)	
-	5 (14.29%)	6 (17.14%)	
Alpha-fetoprotein (ng/mL)			0.743
≥ 200 P	29 (82.86%)	30 (85.71%)	
< 200 P	6 (17.14%)	5 (14.29%)	
Main tumor size (cm)			0.382
≥ 5, ≤ 10	26 (74.29%)	29 (82.86%)	
> 10	9 (25.71%)	6 (17.14%)	

se or as progressive disease; IV. progressive disease (PD), indicating an increase of more than 20% in the sum of the greatest dimension of viable (ie, enhancing) target lesions. To assess the effects of treatment, we also evaluated the DCR (disease control rate), which was calculated as (CR + PR + SD)/n, and the ORR (objective response rate), which was calculated as (CR + PR)/n.

Safety evaluation

Safety was assessed through the analysis of vital signs, physical examinations, clinical and laboratory tests, and adverse events (AEs). The complications related to TACE were summarized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The AEs occurring within 6 weeks after TACE were considered as treatment relevant; whenever they occurred after 6 weeks, they were reported only if a causal correlation was suspected.

Statistical analysis

X^2 and Fisher's exact tests for categorical variables were used for group comparisons. A P value < 0.05 was considered statistically significant. All the statistical analyses were performed by using IBM SPSS20 (SPSS Statistics V20; IBM Corporation; Somers, N.Y., USA).

Results

Patient characteristics

A database of 70 patients, 35 in Group-LLM and 35 in Group-LEM respectively, with advanced HCC admitted to Guangdong General Hospital from January 2016 to October 2016 was evaluated retrospectively.

There were no statistically significant differences in the baseline characteristics of age, gender, Child-Pugh class, main tumor size, hepatitis B surface antigen and α-fetoprotein between the two groups (**Table 2**).

The overall median follow-up period after TACE procedure was 8 weeks. No patient was lost to follow-up. During the follow-up period, each patient just received palliative care and symptomatictreatment, without another TACE or other locoregionaltreatment such as localablation.

The end point of embolization of all liver lesions was achieved after every TACE procedure and the technical success rate was 100%.

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 difference sinDCR 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-

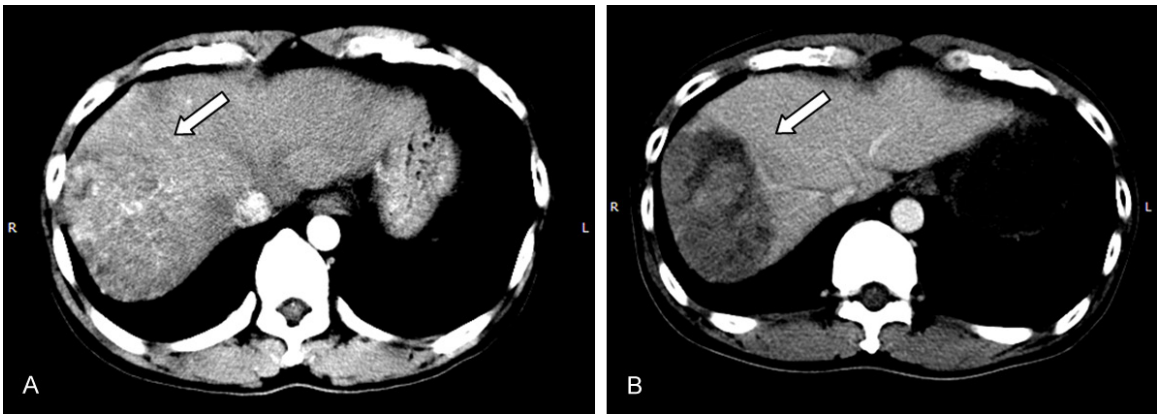

Figure 2. A. CT before TACE: highly intratumoral enhancement lesion in the right hepatic lobe. B. CT after TACE: disappearance of any intratumoral enhancement in target lesion.

Table 3. DCR and ORR of groups

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

*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.

Table 4. Complications and AEs related to TACE procedure

Complications	Group-LEM (n = 35)			Group-LLM (n = 35)			*p* value
	Grade 1-2	Grade 3-4	N1*	Grade 1-2	Grade 3-4	N2**	N1 vs N2
Abdominal pain	15	1	16 (45.71%)	23	5	28 (80.00%)	0.039
Vomit	6	0	6 (17.14%)	9	0	9 (25.71%)	0.382
Nausea	11	0	11 (31.43%)	13	0	13 (37.14%)	0.615
Fever	16	1	17 (48.57%)	19	0	19 (54.29%)	0.632
Liver dysfunction	7	1	8 (22.86%)	13	3	16 (45.71%)	0.044
Renal failure	1	0	1 (2.86%)	3	0	3 (8.57%)	0.614
Thrombocytopenia	1	0	1 (2.86%)	8	0	8 (22.86%)	0.028
Anemia	1	0	1 (2.86%)	0	0	0 (0.00%)	1
Leukopenia	1	0	1 (2.86%)	1	0	1 (2.86%)	1

*N1 means the summation of AEs (Grade 1-4) in Group-LEM. **N2 means the summation of AEs (Grade 1-4) in Group-LLM.

rding 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 immerged 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-methylcyclobutaneplatium (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 embolization and type of embolic material used [21]. Similarly, the commonest adverse event was PES featuring fever, nausea, vomit 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 survivalanalysis to getthe factors which couldaffectprognosis. (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.

Acknowledgements

This project is supported by National Natural Science Foundation of China (Grant No. 81571785), Science and Technology Foundation of Guangdong Province, China (Grant No. 2011A030400009) and Natural Science Foundation of Guangdong Province, China (Grant No. 508289803067).

Disclosure of conflict of interest

None.

Address correspondence to: Li-Gong Lu, Department of Interventional Radiology, Zhuhai People's Hospital, Guangdong Cardiovascular Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China. E-mail: luligong123@163.com

References

[1] El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.

[2] Gomes MA, Priolli DG, Tralhão JG and Botelho MF. Hepatocellular carcinoma: epidemiology, biology, diagnosis, and therapies. Rev Assoc Med Bras 2013; 59: 514-24.

[3] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, Forman D and Bray F. Reprint of: cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European Journal of Cancer 2015; 51: 1201-1202.

[4] Forner A, Reig ME, de Lope CR and Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010; 30: 61-74.

[5] Benson AB 3rd; National Comprehensive Cancer Network. Hepatobiliary cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2003; 1: 94-108.

[6] Llovet JM, Burroughs A and Bruix J. Hepatocellular carcinoma. Wiener Medizinische Wochenschrift 2014; 3: 55.

[7] Llovet JM and Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37: 429-42.

[8] Bruix J and Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.

[9] Brown DB, Cardella JF, Sacks D, Goldberg SN, Gervais DA, Rajan DK, Vedantham S, Miller DL, Brountzos EN and Grassi CJ. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 2006; 17: 225-32.

[10] Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS and Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res 2006; 12: 2563-7.

[11] Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46: 474-81.

[12] Jordan O, Denys A, De Baere T, Boulens N, Doelker E. Comparative study of chemoembolization loadable beads: in vitro drug release and physical properties of DC bead and hepasphere loaded with doxorubicin and irinotecan. J Vasc Interv Radiol 2010; 21: 1084-90.

[13] Maeda N, Osuga K, Higashihara H, Mikami K, Tomoda K, Hori S, Nakazawa T and Nakamura

H. In vitro characterization of cisplatin-loaded superabsorbent polymer microspheres designed for chemoembolization. J Vasc Interv Radiol 2010; 21: 877-881.

[14] Poggi G, Quaretti P, Minoia C, Bernardo G, Bonora MR, Gaggeri R, Ronchi A, Saluzzo CM, Azzaretti A, Rodolico G, Montagna M, Amatu A, Teragni C, Palumbo I, Traverso E, Tonini S, Villani L, Scelsi M, Baiardi P, Felisi MG, Sottotetti F, Tagliaferri B, Riccardi A. Transhepatic arterial chemoembolization with oxaliplatin-eluting microspheres (OEM-TACE) for unresectable hepatic tumors. Anticancer Res 2008; 28: 3835-42.

[15] Zhou B, Shan H, Zhu KS, Jiang ZB, Guan SH, Meng XC and Zeng XC. Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. J Vasc Interv Radiol 2010; 21: 333-338.

[16] Aliberti C, Benea G, Tilli M and Fiorentini G. Chemoembolization (TACE) of unresectable intrahepatic cholangiocarcinoma with slow-release doxorubicin-eluting beads: preliminary results. Cardiovasc Intervent Radiol 2008; 31: 883-8.

[17] Nicolini A, Martinetti L, Crespi S, Maggioni M and Sangiovanni A. Transarterial chemoembolization with epirubicin-eluting beads versus transarterial embolization before liver transplantation for hepatocellular carcinoma. J Vasc Interv Radiol 2010; 21: 327-32.

[18] Seki A and Hori S. Switching the loaded agent from epirubicin to cisplatin: salvage transcatheter arterial chemoembolization with drug-eluting microspheres for unresectable hepatocellular carcinoma. Cardiovasc Intervent Radiol 2012; 35: 555-62.

[19] Lencioni R and Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60.

[20] Osuga K, Hori S, Hiraishi K, Sugiura T, Hata Y, Higashihara H, Maeda N, Tomoda K and Nakamura H. Bland embolization of hepatocellular carcinoma using superabsorbent polymer microspheres. Cardiovasc Intervent Radiol 2008; 31: 1108-1116.

[21] Malagari K, Pomoni M, Moschouris H, Kelekis A, Charokopakis A, Bouma E, Spyridopoulos T, Chatziioannou A, Sotirchos V, Karampelas T, Tamvakopoulos C, Filippiadis D, Karagiannis E, Marinis A, Koskinas J, Kelekis DA. Chemoembolization of hepatocellular carcinoma with hepasphere 30-60 μm. Safety and efficacy study. Cardiovasc Intervent Radiol 2014; 37: 165-75.

[22] Giunchedi P, Maestri M, Gavini E, Dionigi P and Rassu G. Transarterial chemoembolization of hepatocellular carcinoma. Agents and drugs: an overview. Part 1. Expert Opin Drug Deliv 2013; 10: 679-690.

[23] Mckeage MJ. Lobaplatin: a new antitumour platinum drug. Expert Opin Investig Drugs 2001; 10: 119-28.

[24] Wu Q, Qin SK, Teng FM, Chen CJ and Wang R. Lobaplatin arrests cell cycle progression in human hepatocellular carcinoma cells. J Hematol Oncol 2010; 3: 43.

[25] Perabo FG and Müller SC. New agents for treatment of advanced transitional cell carcinoma. Ann Oncol 2007; 18: 835-843.

[26] Ali I, Wani WA, Saleem K and Haque A. Platinum compounds: a hope for future cancer chemotherapy. Anticancer Agents Med Chem 2013; 13: 296.

[27] Song MJ, Chun HJ, Song DS, Kim HY, Yoo SH, Park CH, Bae SH, Choi JY, Chang UI, Yang JM, Lee HG, Yoon SK. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012; 57: 1244-1250.

[28] Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R; PRECISION V Investigators. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010; 33: 41-52.