Am J Transl Res 2021;13(12):13931-13940
www.ajtr.org /ISSN:1943-8141/AJTR0136825

Original Article

CalliSpheres® microspheres drug-eluting bead transhepatic artery chemoembolization with or without sorafenib for the treatment of large liver cancer: a multi-center retrospective study

Song Liu[1*], Guangji Yu[1], Qingdong Wang[1*], Long Li[1], Ying Liu[2], Ke Du[1], Fei Zhang[1], Bangli Zhao[1], Guangsheng Zhao[3]

[1]Department of Interventional Therapy, Linyi Cancer Hospital, Linyi, China; [2]Hepatobiliary and Pancreatic Center, Beijing Tsinghua Changgung Hospital, Beijing, China; [3]Department of Oncology, Affiliated Zhongshan Hospital of Dalian University, Dalian, China. [*]Equal contributors and co-first authors.

Received June 28, 2021; Accepted October 19, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Purpose: To explore the clinical efficacy and safety of CalliSpheres® microspheres drug-eluting bead transarterial chemoembolization (DEB-TACE) combined with sorafenib in the treatment of large liver cancer. Method: The study retrospectively analyzed 90 patients with large liver cancer. 42 patients who received DEB-TACE and sorafenib were included in the experimental group and 48 patients who received only DEB-TACE were included in the control group. The efficacy, TTP, OS and ARs were evaluated and further analysis was conducted on factors which might affect the prognosis. Results: As of June 2020. The median OS of the experimental group was significantly longer than that of the control group (18.6 months vs. 12.7 months), and the TTP was also longer in the experimental group (8.3 months vs. 6.9 months). Three months after the intervention, the ORR and DCR of the experimental group were significantly higher than those of the control group. The main ARs of the experimental group taking sorafenib included hand-foot syndrome, skin rash, diarrhea, fatigue, hypertension, and anorexia. And they could be alleviated through treatment of the symptoms. TACE-related ARs for both groups were fever, pain, nausea, and vomiting, and there was no significant difference. Logistic regression analysis showed that the combined sorafenib treatment was a protective factor improving the prognosis of patients with large liver cancer, and risk factors were the number of tumors and vascular invasion. Conclusion: DEB-TACE combined with sorafenib is safe and well tolerated in the treatment of large liver cancer. It can improve the tumor control rate and prolong the survival time.

Keywords: Transcatheter arterial chemoembolization, drug-eluting bead microspheres, hepatocellular carcinoma, sorafenib

Introduction

Transarterial chemoembolization (TACE) is an important treatment for unresectable liver cancer, and its combination with CalliSpheres drug-eluting bead microspheres (DEB-TACE) can achieve a high tumor response rate [1]. However, post-TACE ischemia and hypoxia can promote the increase of vascular endothelial growth factor receptor (VEGF) expression and tumor neovascularization, which can lead to tumor recurrence. This effect is particularly prominent in large liver cancers with abundant blood supply [2]. Sorafenib is a multi-kinase inhibitor that has the dual effects of anti-tumor angiogenesis and inhibiting tumor cell proliferation. It can inhibit the growth of residual tumors after TACE, thereby improving the middle and long-term efficacy of advanced liver cancer [3]. This study aims to explore the clinical efficacy and safety of DEB-TACE combined with sorafenib in the treatment of large liver cancer.

Materials and method

Participants

Patients with large liver cancer (>10 cm) who were admitted to the three centers of Linyi Tumor Hospital in Shandong Province, Zhong-

shan Hospital Affiliated to Dalian University, and Chang Gung Memorial Hospital Affiliated to Tsinghua University from January 2017 to June 2019 were selected. This study followed the relevant regulations in the Declaration of Helsinki and was approved by the Medical Ethics Committee of Linyi Tumor Hospital, Shandong Province [IRB Number: [2016] 078]. The enrolled patients all agreed to participate voluntarily and signed an informed consent form.

Inclusion criteria: (1) Diagnosed with primary liver cancer clinically or by liver biopsy; (2) Large liver cancer with single nodule diameter greater than 10 cm or the sum of multiple nodules greater than 10 cm; (3) BCLC stage B or C, Child classification Grade A or B, ECOG stamina score 0 to 2; (4) Age 18 to 80 years, with an estimated survival time of more than 3 months; (5) Patients who progressed after previous treatments such as c-TACE, ablation, radiotherapy and chemotherapy. Exclusion criteria: (1) Metastatic liver cancer; (2) Combined with severe dysfunction of other important organs separate from liver cancer; (3) Mental disorder, pregnancy, irregular follow-up or unable to follow-up; (4) BCLC stage A or D, Child classification Grade C, ECOG stamina score greater than 2.

Treatment

Preparation of CalliSpheres drug-eluting bead microspheres: Microspheres of 300 to 500 μm (1 g/bottle, Suzhou Hengrui Jialisheng Biomedical Technology Co., Ltd., National Instruments Note 20153771072) were used in this study. The microspheres and physiological saline were drawn out with a 20 ml syringe, and the syringe was placed vertically for 2 to 3 min. Until the microspheres were settled, the supernatant was pushed out as much as possible. In addition, 60 mg of epirubicin was dissolved with 5 ml of sterile water for injection. The syringe (20 ml) with microspheres and the syringe (5 ml) of epirubicin were connected through a three-way connection, and the epirubicin solution was slowly pushed into the syringe with the microspheres. The syringe containing the microspheres and chemotherapy drugs was then covered with a needle cap and shaken every 5 minutes for a total of 30 minutes for adsorption. Further, the microspheres carrying epirubicin and the non-ionic contrast agent iodixanol were mixed in a ratio of 1:1 and stood for 5 minutes.

Transarterial chemoembolization: Seldinger's method was used to puncture the right femoral artery, and a catheter was introduced into the right hepatic duct for routine celiac artery and common hepatic angiography. According to the tumor location, size, and whether the tumor staining was complete, auxiliary angiography of the ectopic blood supply arteries such as the diaphragmatic artery, superior mesenteric artery, left gastric artery, and right renal artery were performed to identify all the tumor's blood supply arteries. The microcatheter was inserted into the tumor supply artery, and 100 to 150 mg oxaliplatin was infused. Then the pre-configured drug-eluting bead microspheres were slowly injected (1 ml/min) in a pulse model, and the embolization was stopped when the flow rate of the contrast agent stopped. After pausing for 5 minutes, another angiography was performed, and the embolization was stopped when the tumor staining completely disappeared. If there was still tumor staining, additional embolization was performed, and an ordinary embolization microsphere was applied if necessary.

Oral medication: Sorafenib mesylate tablets (200 mg/tablet, Nexavar, Bayer Pharmaceuticals, Germany) were given for 3 to 5 days after the first TACE treatment. The starting dose was 400 mg twice a day. If there was an intolerable AR the dose was changed to 400 mg once a day, or stopped for about 1 week, with the full dose resumed after the symptoms were relieved. Our discontinuation criteria were disease progression or worsening, serious ARs, or decompensated liver function (Grade C).

Efficacy evaluation and adverse reaction observation: After the first TACE, a comprehensive assessment of the condition was performed every 4 to 6 weeks. The review included routine blood work, liver, and kidney function, AFp, chest CT scan and upper abdominal enhanced CT/MRI. From the imaging results, the tumor response was evaluated according to the mRECIST standard, as complete remission (CR), partial remission (PR), progressive disease, or stable disease (SD). While the tumor remained and progressed, additional interventional ther-

Table 1. General information of 90 patients with hepatocellular carcinoma

Clinical indicators	Experimental group (n=42)	Control group (n=48)	*P* value
Age (years)	60.3±14.0	59.7±13.2	0.417
Gender			0.709
Male	37	41	
Female	5	7	
History of liver disease			0.915
Hepatitis B	33	38	
Hepatitis C	4	5	
Alcoholic liver disease	3	3	
Others	2	2	
History of cirrhosis			0.977
Yes	20	23	
No	22	25	
Tumor diameter (cm)	11.5±3.7	11.0±3.0	0.241
Number of tumors			0.875
≤3	30	35	
>3	12	13	
Vascular invasion			0.975
Yes	13	15	
No	29	33	
Extrahepatic metastasis			0.756
Yes	6	8	
No	36	40	
ECOG score			0.996
0	14	16	
1	23	26	
2	5	6	
Child classification			0.924
A	31	35	
B	11	13	
BCLC stage			0.976
B	13	15	
C	29	33	
AFP level (ng/ml)			0.909
≤400	18	20	
>400	24	28	
Previous treatment			
Yes	7	8	1
No	35	40	

apy was considered. In addition, the objective response rate (CR + PR) and disease control rate (CR + PR + SD) of the two groups of patients were evaluated at 1 and 3 months after the first intervention. Safety was assessed by following the National Cancer Institute (National Cancer Institute, NCI) Common Terminology Criteria for Adverse Events (version 3.0).

Research endpoints: The primary endpoint of this study was OS, while the secondary endpoints included ORR, DCR, TTP, and safety. OS was defined as the time from the beginning of the first interventional treatment to the death of the patient or the last follow-up. TTP was defined as the time from the beginning of the first interventional treatment to the first objective progression of the tumor.

Statistical analysis: SPSS 20.0 software was used for statistical analysis of the data. The continuous data were represented as means ± standard deviations and tested using the independent sample t test. Categorical data (baseline data, ORR, DCR) were represented as percentages and analyzed with a chi-square test. TTP, OS, and corresponding curves between the two groups were analyzed by the Kaplan-Meier method. A log-rank test was used for comparison of survival rates between the two groups. Single-factor and multivariate Cox risk regression models were used to analyze related factors, and P<0.05 was considered statistically significant.

Results

From January 2017 to June 2019, a total of 90 patients with large liver cancer who met the inclusion criteria and received DEB-TACE treatment from Linyi Tumor Hospital, Dalian University Affiliated Zhongshan Hospital, and Tsinghua University Chang Gung Memorial Hospital were selected. Among them, 78 were males and 12 were females. Forty-two patients were in the experimental group (DEB-TACE combined with sorafenib treatment) and 48 patients in the control group (only DEB-TACE treatment). There were no significant differences between the two groups of patients in terms of age, gender, Child classification, ECOG score, etiology, or BCLC staging (*P*>0.05), as shown in **Table 1**.

Table 2. The short-term efficacy of the two groups of patients (cases, %)

1 month after the intervention	CR	PR	SD	PD	ORR	DCR
Experimental group (n=42)	7	25	10	0	76.19	100
Control group (n=48)	6	27	11	2	71.74	95.65
3 months after the intervention						
Experimental group (n=42)	10	22	7	1	80.00	97.50
Control group (n=48)	5	21	12	7	57.78	84.44

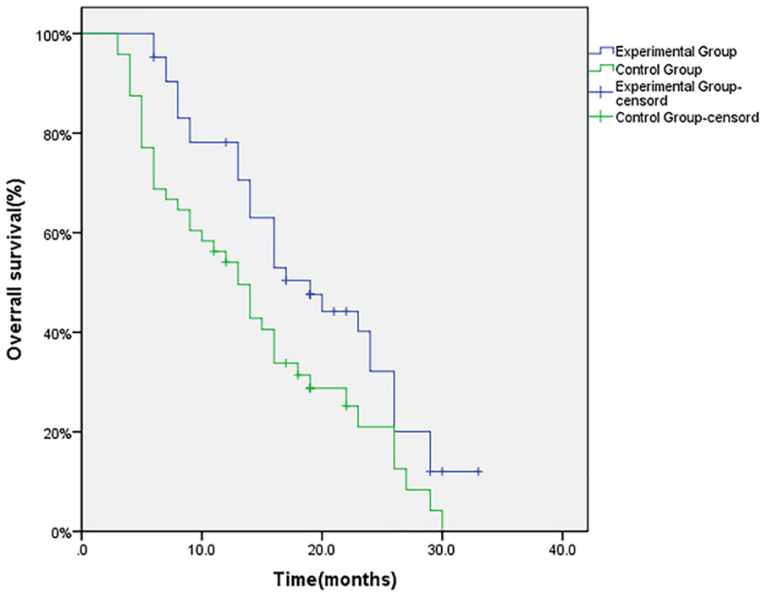

Figure 1. Comparison of overall survival curve between the two groups.

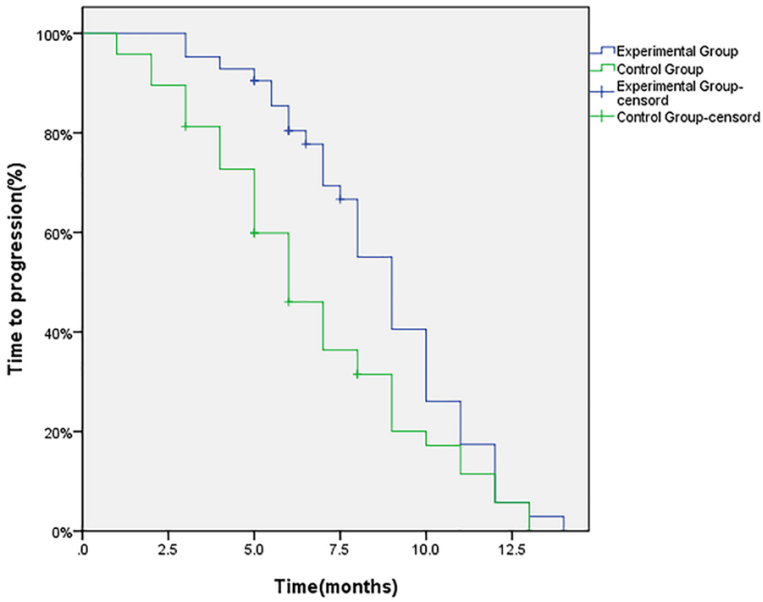

Figure 2. Comparison of time to progression curve between the two groups.

Short-term efficacy evaluation

One month after the first intervention, we obtained 88 of the 90 patients' imaging evaluations, including 42 in the experimental group and 46 in the control group. Three months after treatment, imaging evaluations were available for 85 patients, including 40 in the experimental group and 45 in the control group. According to the mRECIST1.1 evaluation standard, 1 month after the first intervention, the ORR (76.19% vs. 71.74%, χ^2=0.225, *P*=0.635) and DCR (100% vs. 95.65%, χ^2=1.868, *P*=0.176) of the experimental group were slightly higher than those of the control group. After three months, the ORR (80.00% vs. 57.78%, χ^2=4.825, *P*=0.028) and DCR (97.50% vs. 84.44%, χ^2=4.233, *P*=0.039) of experimental group were significantly higher than those of the control group, as shown in **Table 2**.

Survival period and survival rate

Until June 2020, the follow-up period was 8 to 36 months, with an average of 28.5 months. The median survival time of the experimental group was 18.6 months (95% CL 14.035 to 23.965), while for the control group it was 12.7 months (95% CL 9.815 to 16.185). The median survival time was significantly higher in the experimental group (χ^2=6.470, *P*=0.011). The median TTP of the experimental group was 8.3 months (95% CL 7.888 to 10.112), while it was 6.0 months in the control group (95% CL 4.768 to 7.232). There was also a significant difference between

Table 3. The occurrence of TACE-related adverse reactions after the first DEB-TACE in the two groups

Adverse reactions	Experimental group (n=42)	Control group (n=42)	*P* value
Fever	14	17	0.835
Pain	12	14	0.950
Nausea and vomiting	30	34	0.950
Liver abscess	0	0	1

Table 4. The occurrence of adverse reactions related to sorafenib in patients of the experimental group

Adverse reactions	Total numbers	Grade I	Grade II	Grade III	Grade IV
Hand-foot syndrome	24	17	4	3	0
Skin rash	9	7	2	0	0
Diarrhea	15	9	4	2	0
Fatigue	11	10	1	0	0
Hypertension	5	1	2	2	0
Anorexia	5	2	3	0	0

these two groups (χ^2=8.271, *P*=0.004) in this measure. As shown in **Figures 1** and **2**.

Adverse reaction

Patients in the experimental group had unique ARs after taking sorafenib, mainly presenting as hand-foot syndrome, skin rash, diarrhea, fatigue, hypertension, and anorexia. The severity of these ARs was less than the third grade and could be alleviated after treatment of the symptoms. There were no cases of withdrawal from the study. Two patients had grade 3 blood pressure increases; after a short period of suspension from treatment, they were given medical antihypertensive treatment and then restored to the original dose. Six patients were reduced to 400 mg/day due to intolerable hand-foot syndrome and diarrhea. The main ARs of patients receiving only DEB-TACE treatment included fever, pain, nausea, and vomiting. The duration was generally 5 to 7 days, and the ARs were all alleviated after symptomatic treatment with internal medicine. No serious complications such as liver abscess, gastrointestinal perforation, liver and kidney failure occurred, as shown in **Tables 3** and **4**.

Influencing factors analysis

Eleven items (age, gender, etiology, tumor number, vascular invasion, extrahepatic metastasis, ECOG score, Child classification, BCLC stage, AFP level, and treatment method) were separately analyzed with Cox single-factor analysis. The results showed that the number of tumors, vascular invasion, extrahepatic metastasis, and treatment methods were statistically significant factors (*P*<0.05). Multivariate Cox regression analysis showed that TACE combined with sorafenib treatment was a protective independent factor, and the number of tumors and vascular invasion were independent risk factors for the prognosis of patients (*P*<0.05), shown in **Table 5**.

Discussion

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world and the second leading cause of tumor death [4]. When the tumor diameter is more than 5 cm, it is clinically defined as large liver cancer. About 32% of patients are initially diagnosed as having large liver cancer, and another 10% to 20% of patients have tumors more than 10 cm in diameter [5]. Patients with large liver cancer are often in the middle and advanced stages of the tumor growth, and their prognosis is worse than that of patients with small liver cancer [6]. Because middle and late-stage liver cancer easily invades the blood vessels inside and outside the liver, and it is accompanied by varying degrees of liver cirrhosis, most patients cannot have radical surgery. The surgical resection rate for large liver cancer was less than 30%, and the 5-year survival rate after surgery was less than 40% [7, 8].

For unresectable large liver cancer, TACE is currently recognized as the preferred treatment method [9, 10]. Classical TACE (cTACE) is a mixture of iodized oil and chemotherapeutic drugs to selectively embolize tumor blood supply arteries, and cause tumor cell necrosis through cell ischemia and drug toxicity [11-13]. However, not all liver cancer tissues have a good lipiodol deposition effect, and the chemotherapeutic drugs will enter the systemic circulation due to the continuous erosion of blood flow, resulting in a decrease in the efficacy of local drugs and an increase in systemic adverse reactions (AR), which ultimately affects the degree of local

Table 5. Single-factor and multi-factor analysis of the prognosis of patients with large liver cancer

Item	Single-factor analysis		Multi-factor analysis		
	HR (95% CI)	*P* value	Regression coefficients	HR (95% CI)	*P* value
Age	0.976 (0.948-1.011)	0.703			
Gender	1.304 (0.450-3.782)	0.915			
Etiology	0.452 (0.045-3.237)	0.158			
ECOG score	1.58 (0.957-2.164)	0.094			
Child classification	1.601 (0.786-3.249)	0.054			
BCLC stage	1.792 (1.057-2.601)	0.107			
AFP level	1.206 (0.628-2.236)	0.219			
Extrahepatic metastasis	0.456 (0.248-1.339)	0.001	0.760	2.310 (1.673-3.554)	0.073
Tumor numbers	1.511 (0.809-2.751)	0.043	0.426	1.960 (1.017-3.758)	0.013
Vascular invasion	1.035 (0.573-1.676)	0.033	0.806	1.971 (1.193-3.255)	0.008
Treatment	0.193 (0.088-0.523)	0.002	-1.405	0.561 (0.327-0.965)	0.001

chemoembolization. With the development and application of novel embolic materials, DEBs have been continuously used in TACE therapy. DEBs are an ideal embolic material to carry chemotherapeutic drugs, permanently embolize tumor blood vessels and slowly release chemotherapeutic drugs in tumors. Compared with cTACE, DEB-TACE can achieve higher local tumor control rate and better safety [14, 15].

Most large liver cancers are rich in blood supply, and there are often multiple blood vessels involved in that blood supply, including the hepatic artery and portal vein. Kim et al. [16] reported the incidence of extrahepatic blood supply for tumors smaller than 4 cm to be less than 3%, and when the tumor diameter was larger than 6 cm, this incidence increased to 63%. Therefore, even with super-selective TACE it is difficult to achieve complete embolization of tumor arteries, and most of the lesions remain after surgery. Studies reported that the tumor necrosis rate for using TACE alone in the treatment of large liver cancer was only 2% [17]. Residual lesions after TACE also seriously affected the treatment effect and prognosis [18, 19]. In fact, as the diameter of liver cancer tumors increases, the incidence of subclinical lesions and the incidence of portal cancer thrombi also increase. The results of this study showed that 28 patients (31.11%) were diagnosed with large liver cancer accompanied by vascular invasion, 25 (27.78%) had multiple nodules, and both of these were independent factors affecting patients' prognoses. In addition, TACE could easily form a hypoxic microenvironment after tumor embolization, leading to changes in hypoxia-related factors and increasing the risk of tumor recurrence [20].

As a multi-kinase inhibitor, sorafenib can effectively inhibit tumor angiogenesis and tumor cell proliferation [21], and make up for the deficiency of TACE in the treatment of large liver cancer. Evidence-based medicine studies confirm that TACE combined with sorafenib can effectively control the growth of advanced HCC, improve prognosis, and prolong survival [22-24]. At present, a number of single-arm studies have confirmed that TACE combined with sorafenib was safe and effective in the treatment of patients with unresectable HCC. However, the results of randomized control trials have not yet reached a unified conclusion. In a double-blind, placebo-controlled, phase III clinical study of TACE combined with sorafenib in the treatment of unresectable HCC patients in Japan and South Korea, the results showed no difference in the primary endpoint TTP between the two groups (5.4 months vs. 3.7 months) [25]. This result was considered to be mainly related to the delay in the administration of sorafenib. Sorafenib was not used until 9 weeks after TACE, at which time new blood vessels and branches might have formed and tumor cells might have spread, resulting in no opportunity for a cumulative effect from sorafenib [26]. Another randomized, open-label, multi-center, phase II clinical study in Japan included a total of 156 patients with unresectable liver cancer. In that study, compared with TACE alone, TACE combined with sorafenib slowed the tumor invasion of blood vessels and extrahepatic metastasis and prolonged the progression-free

survival of patients up to 11.7 months. The study concluded that a longer period of taking sorafenib was a key factor in the success of the treatment [24].

CalliSpheres microspheres are DEBs independently researched and developed in China. They are colored microspheres with a smooth surface and a charge, with variable elasticity. These features give the microspheres compressibility in a space smaller than their own particle size and a degree of resilience, which can produce an accumulation of effects after embolization of the target vessel, and enhance the embolization effect [27]. The efficacy of TACE combined with Callispheres drug-eluting bead microspheres is currently widely recognized in clinical practice. Liu et al. [28] performed DEB-TACE treatment and cTACE treatment on 71 cases of massive liver cancer. Three months after the first treatment, the ORR and DCR of the DEB-TACE group were 60.00% and 86.66% respectively, and the median OS was 269 days (approximately 9 months). In this study, DEB-TACE also achieved the same tumor response. Massani et al. [29] retrospectively analyzed records of 28 liver cancer patients treated with DEB-TACE (3 patients in stage A, 4 in stage B, and 21 in stage C). The tumor diameter was 6.15 (±3.45) cm, and the median survival time was 22.7 months. In this study, the median survival time of the DEB-TACE treatment group was 12.7 months, which was shorter than that of the Massani study. It might be because many of the patients with large liver cancer enrolled in this study also had intrahepatic spread and portal vein invasion. The tumor burden was high, and the overall survival (OS) time was short. Compared with cTACE, although DEB-TACE could achieve a higher tumor response rate, it still could not achieve complete tumor embolization and necrosis, and it could not overcome the problem of tumor progression and recurrence caused by the increase of VEGF levels after surgery. Therefore, for patients with large liver cancer, DEB-TACE still needed to be combined with sorafenib, a targeted anti-angiogenesis drug.

DEB-TACE combined with sorafenib is rarely reported in the treatment of liver cancer. In a randomized, double-blind, phase II clinical study of sorafenib combined with DEB-TACE in the treatment of advanced liver cancer, it was found that the combined treatment did not improve the time of disease progression [30]. The study from Johns Hopkins University showed that for unresectable HCC, continuous application of sorafenib treatment, combined with DEB-TACE, could control local tumors well and bring survival benefits to patients [31]. In this study, the ORR and DCR of the experimental group were slightly higher than those of the control group 1 month after the first treatment, but there was no significant difference. The tumor response of the experimental group was significantly better than that of the control group 3 months after the treatment. In addition, compared with the control group, the experimental group's median OS (18.6 months vs. 12.7 months) and TTP (8.3 months vs. 6.0 months) were improved. This was consistent with the meta-analysis results of TACE combined with sorafenib in the treatment of advanced liver cancer [32]. Multivariate analysis found that using sorafenib was a protective factor for the prognosis of large liver cancer, which further suggested that the combination of sorafenib after DEB-TACE in large liver cancer patients was more meaningful for the prognosis of patients. The biggest advantage of DEB-TACE was the long-lasting chemoembolism effect, while sorafenib could reverse multidrug chemotherapy resistance and could further improve the effect of traditional chemotherapy drugs. This advantage might be better used in combination with DEB-TACE. In addition, significant necrosis and shrinkage of tumors could occur in the short-term after DEB-TACE. A combination with sorafenib could further effectively inhibit tumor angiogenesis and inhibit tumor growth in this early period. We found that in the experimental group of patients, DSA angiography showed that the tumor blood vessels were significantly reduced, slender, and even disappeared from the tumor angiography, indirectly confirming the ability of sorafenib to inhibit the expression of VEGF receptors. The normalization of blood vessels could recreate the tumor microenvironment, and it was also considered to be the basis of the microenvironment for the treatment of malignant tumors. DEB-TACE combined with molecular targeted therapy might also achieve this goal [33, 34].

Previous studies have shown that TACE combined with sorafenib might increase the possi-

bility of liver insufficiency [35]. In this study, the main ARs related to oral sorafenib were hand-foot syndrome, skin rash, diarrhea, fatigue, hypertension, and anorexia. All of them were at or lower than grade 3, which could be alleviated after treatment of the symptoms. Grade 4 ARs were not observed in our study, showing that DEB-TACE combined with sorafenib therapy has good safety in patients with large liver cancer, consistent with the findings of related studies [36]. Wang et al. [37] suggested that practitioners treating patients with sorafenib after TACE should pay attention to evaluation of the patient's basic condition. Good basic liver function was an important condition for improving the tolerance of sorafenib treatment and ensuring the continuity of treatment. The slow release of drugs after DEB-TACE could protect normal liver tissue to the greatest extent, especially for patients having large liver cancer with poor basic liver function.

The treatment of liver cancer has entered a new era of targeted therapy. The application of various multi-target drugs and immune checkpoint inhibitors has made liver cancer treatment more comprehensive and systematic. This study shows that CalliSpheres-TACE combined with sorafenib has a synergistic antitumor effect, which significantly prolongs the disease progression time and OS of patients with large liver cancer, with good safety, and tolerability. It can bring new hopes and choices to patients with large liver cancer. However, the incidence of liver cancer is greatly affected by region, with obvious differences in treatment response and prognosis. Due to economic conditions and national conditions, especially for patients with advanced liver cancer, a reasonable and economical treatment is still something front-line doctors need to consider when formulating a treatment plan. At the same time, global multi-center prospective studies are also necessary to further observe the effectiveness and safety of CalliSpheres-TACE combined with sorafenib.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Guangji Yu, Department of Interventional Therapy, Linyi Cancer Hospital, Intersction of Zhicheng Road and Zhongsheng Street, Linyi, China. Tel: +86-0539-8122978; E-mail: 531641406@qq.com; Dr. Guangsheng Zhao, Department of Oncology, Affiliated Zhongshan Hospital of Dalian University, No. 6 Jiefang Street, Dalian, China. E-mail: stiff66@126.com

References

[1] Wu B, Zhou J, Ling G, Zhu D and Long Q. CalliSpheres drug-eluting beads versus lipiodol transarterial chemoembolization in the treatment of hepatocellular carcinoma: a short-term efficacy and safety study. World J Surg Oncol 2018; 16: 69.

[2] Shim JH, Park JW, Kim JH, An M, Kong SY, Nam BH, Choi JI, Kim HB, Lee WJ and Kim CM. Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. Cancer Sci 2008; 99: 2037-2044.

[3] Aktas G, Kus T, Emin Kalender M, Kervancioglu S, Sevinc A, Kul S and Camci C. Sorafenib with TACE improves the survival of hepatocellular carcinoma patients with more than 10 cm tumor: a single-center retrospective study. J BUON 2017; 22: 150-156.

[4] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A and Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144: 1941-1953.

[5] Forner A, Reig M and Bruix J. Hepatocellular carcinoma. Lancet 2018; 391: 1301-1314.

[6] Jeong SO, Kim EB, Jeong SW, Jang JY, Lee SH, Kim SG, Cha SW, Kim YS, Cho YD, Kim HS, Kim BS, Kim YJ, Goo DE and Park SY. Predictive factors for complete response and recurrence after transarterial chemoembolization in hepatocellular carcinoma. Gut Liver 2017; 11: 409-416.

[7] Wakayama K, Kamiyama T, Yokoo H, Orimo T, Shimada S, Einama T, Kamachi H and Taketomi A. Huge hepatocellular carcinoma greater than 10 cm in diameter worsens prognosis by causing distant recurrence after curative resection. J Surg Oncol 2017; 115: 324-329.

[8] Ban D, Ogura T, Akahoshi K and Tanabe M. Current topics in the surgical treatments for hepatocellular carcinoma. Ann Gastroenterol Surg 2018; 2: 137-146.

[9] Kishore S, Friedman T and Madoff DC. Update on embolization therapies for hepatocellular carcinoma. Curr Oncol Rep 2017; 19: 40.

[10] Department of Medical Administration, National Health and Health Commission of the People's Republic of China. Guidelines for diagnosis and treatment of primary liver cancer in

China (2019 edition). Zhonghua Gan Zang Bing Za Zhi 2020; 28: 112-128.
[11] Stefanini GF, Amorati P, Biselli M, Mucci F, Celi A, Arienti V, Roversi R, Rossi C, Re G and Gasbarrini G. Efficacy of transarterial targeted treatments on survival of patients with hepatocellular carcinoma. An Italian experience. Cancer 1995; 75: 2427-2434.
[12] Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, Andreone P, Craxì A and Cottone M. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224: 47-54.
[13] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST and Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35: 1164-1171.
[14] Liang B, Xiang H, Ma C, Xiong B, Ma Y, Zhao C, Yao Y, Zhang Z, Chen C, Li H, Long Q, Zhou J, Luo C, Qiu H, Hu H, Zhao H, Zhou G and Zheng C. Comparison of chemoembolization with CalliSpheres(®) microspheres and conventional chemoembolization in the treatment of hepatocellular carcinoma: a multicenter retrospective study. Cancer Manag Res 2020; 12: 941-956.
[15] Xiang H, Long L, Yao Y, Fang Z, Zhang Z and Zhang Y. CalliSpheres drug-eluting bead transcatheter arterial chemoembolization presents with better efficacy and equal safety compared to conventional TACE in treating patients with hepatocellular carcinoma. Technol Cancer Res Treat 2019; 18: 1533033819830751.
[16] Kim HC, Chung JW, Lee W, Jae HJ and Park JH. Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. Radiographics 2005; 25 Suppl 1: S25-39.
[17] Lee YB, Lee DH, Cho Y, Yu SJ, Lee JH, Yoon JH, Lee HS, Kim HC, Yi NJ, Lee KW, Suh KS, Chung JW and Kim YJ. Comparison of transarterial chemoembolization and hepatic resection for large solitary hepatocellular carcinoma: a propensity score analysis. J Vasc Interv Radiol 2015; 26: 651-659.
[18] Sacco R, Mismas V, Marceglia S, Romano A, Giacomelli L, Bertini M, Federici G, Metrangolo S, Parisi G, Tumino E, Bresci G, Corti A, Tredici M, Piccinno M, Giorgi L, Bartolozzi C and Bargellini I. Transarterial radioembolization for hepatocellular carcinoma: an update and perspectives. World J Gastroenterol 2015; 21: 6518-6525.
[19] Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, Yamakado K, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T and Minami T; Liver Cancer Study Group of Japan. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. Oncology 2014; 87 Suppl 1: 22-31.
[20] Kajihara J, Tomimaru Y, Eguchi H, Yamada D, Wada H, Tomokuni A, Asaoka T, Kawamoto K, Marubashi S, Nagano H, Umeshita K, Doki Y and Mori M. The clinical impact of transcatheter arterial chemoembolization (TACE)-induced c-Met upregulation on TACE refractoriness in hepatocellular carcinoma. Dig Dis Sci 2016; 61: 1572-1581.
[21] Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R and Kelley S. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006; 5: 835-844.
[22] Zhu K, Huang J, Lai L, Huang W, Cai M, Zhou J, Guo Y and Chen J. Medium or large hepatocellular carcinoma: sorafenib combined with transarterial chemoembolization and radiofrequency ablation. Radiology 2018; 288: 300-307.
[23] Huang Y, Chen B, Liu N, Li N, Dao H, Chen W and Yang J. Overall survival in response to sorafenib with transarterial chemoembolization for BCLC stage B hepatocellular carcinoma: propensity score analysis. Int J Clin Pharmacol Ther 2017; 55: 498-508.
[24] Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, Izumi N, Yamasaki T, Nojiri S, Hino K, Tsumura H, Kuzuya T, Isoda N, Yasui K, Aino H, Ido A, Kawabe N, Nakao K, Wada Y, Yokosuka O, Yoshimura K, Okusaka T, Furuse J, Kokudo N, Okita K, Johnson PJ and Arai Y; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 2020; 69: 1492-1501.
[25] Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G and Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011; 47: 2117-2127.
[26] Kudo M and Arizumi T. Transarterial chemoembolization in combination with a molecular targeted agent: lessons learned from negative trials (post-TACE, BRISK-TA, SPACE, ORIENTAL, and TACE-2). Oncology 2017; 93 Suppl 1: 127-134.
[27] Guan YS, He Q, Jin Y and Yao F. Development of CalliSpheres® embolic microspheres. Zhonghua Gan Zang Bing Za Zhi 2016; 24: 549-551.

[28] Liu JF, Duan XH, Ren JZ, Jiao DC and Han XW. Comparative effect of CalliSpheres drug loading microspheres and lipiodol transarterial chemoembolization in the treatment of huge primary liver cancer. Zhonghua Gan Zang Bing Za Zhi 2019; 27: 460-462.

[29] Massani M, Stecca T, Ruffolo C and Bassi N. Should we routinely use DEBTACE for unresectable HCC? cTACE versus DEBTACE: a single-center survival analysis. Updates Surg 2017; 69: 67-73.

[30] Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, Paik SW, Reig M, Kim DY, Chau GY, Luca A, Del Arbol LR, Leberre MA, Niu W, Nicholson K, Meinhardt G and Bruix J. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol 2016; 64: 1090-1098.

[31] Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N and Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011; 29: 3960-3967.

[32] Li L, Zhao W, Wang M, Hu J, Wang E, Zhao Y and Liu L. Transarterial chemoembolization plus sorafenib for the management of unresectable hepatocellular carcinoma: a systematic review and meta-analysis. BMC Gastroenterol 2018; 18: 138.

[33] Fukumura D, Kloepper J, Amoozgar Z, Duda DG and Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol 2018; 15: 325-340.

[34] Huang Y, Kim BYS, Chan CK, Hahn SM, Weissman IL and Jiang W. Improving immune-vascular crosstalk for cancer immunotherapy. Nat Rev Immunol 2018; 18: 195-203.

[35] Zhang Y, Fan W, Wang Y, Lu L, Fu S, Yang J, Huang Y, Yao W and Li J. Sorafenib with and without transarterial chemoembolization for advanced hepatocellular carcinoma with main portal vein tumor thrombosis: a retrospective analysis. Oncologist 2015; 20: 1417-1424.

[36] Chien SC, Chen CY, Cheng PN, Liu YS, Cheng HC, Chuang CH, Chang TT, Chiu HC, Lin YJ and Chiu YC. Combined transarterial embolization/chemoembolization-based locoregional treatment with sorafenib prolongs the survival in patients with advanced hepatocellular carcinoma and preserved liver function: a propensity score matching study. Liver Cancer 2019; 8: 186-202.

[37] Wang WD, Hou SN, Chen D, Jiang XY, Ni JY, Chen YT, Sun HL, Luo JH and Xu LF. Analysis of curative and prognostic effects of combined therapy of transarterial chemoembolization and sorafenib in hepatocellular carcinoma. Zhonghua Gan Zang Bing Za Zhi 2018; 26: 690-693.