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ORIGINAL ARTICLE

Efficacy of licartin combined with transcatheter hepatic arterial chemoembolization in the treatment of middle-advanced primary liver cancer

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Summary

Purpose: *To explore the clinical efficacy and safety of Licartin combined with transcatheter hepatic arterial chemoembolization (TACE) in the treatment of middle-advanced primary liver cancer.*

Methods: *The clinical data of 112 patients with middle-advanced primary liver cancer treated in our hospital from March 2015 to March 2017 were collected. Fifty-six patients underwent TACE combined with Licartin (Licartin+TACE group), while the remaining 56 patients were treated with TACE alone (TACE group). The short-term efficacy, peripheral hemogram, liver function, alpha fetoprotein (AFP) level, count of circulating tumor cells (CTCs) and cluster of differentiation (CD)147 phenotype before and after treatment were assessed in both groups, the incidence of adverse reactions was compared, and the postoperative survival and disease development were recorded during follow-up.*

Results: *At 2 weeks after treatment, the levels of ALT and AST were significantly higher in Licartin + TACE group than those in TACE group ($p<0.05$). After treatment, the white blood cell count (WBC) and platelet count (PLT) obviously declined in both groups, and they were obviously lower in Licartin + TACE group than those in TACE group ($p<0.05$). After treatment, the count of CTCs evidently declined in both groups compared with that before treatment ($p<0.05$), and it was evidently lower in Licartin + TACE group than in TACE group ($p<0.001$). All patients were followed up for 3-36 months. In Licartin + TACE group and TACE group, the mean overall survival (OS) was 13.1±3.6 months and 11.3±2.8 months, respectively, and the mean progression-free survival (PFS) was 7.9±1.4 months and 6.1±1.2 months, respectively. At the end of follow-up, the Kaplan-Meier survival curves were plotted and log-rank test found that the OS rate was remarkably superior in Licartin + TACE group to that in TACE group ($p=0.047$), but the PFS rate had no statistically significant difference between the two groups ($p=0.372$).*

Conclusions: *Licartin combined with TACE has better efficacy than TACE alone in the treatment of middle-advanced primary liver cancer, with tolerable adverse reactions, which prolongs patients' survival time.*

Key words: *licartin, transcatheter hepatic arterial chemoembolization, primary liver cancer, middle-advanced stage*

Introduction

Liver cancer is one of the most common malignant tumors with the highest mortality rate and a high postoperative recurrence rate. Most patients with liver cancer have lost the opportunity of radical treatment based on surgical resection when diagnosed [1]. Currently, transcatheter hepatic ar-

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terial chemoembolization (TACE) is the main treatment method for patients with middle-advanced liver cancer. However, the disease is prone to local recurrence and metastasis after operation, and the long-term efficacy needs urgently to be improved [2,3].

Radioimmunotherapy is a new treatment method for advanced liver cancer in recent years, which kills tumor cells with radionuclides based on specific targeting monoclonal antibody [4]. Licartin (iodine [^{131}I] metuximab) is a new radionuclide-labeled antibody targeted drug for hepatocellular carcinoma. It binds to the HAb18G/cluster of differentiation (CD)147 antigen specifically expressed on the surface of liver cancer cells to block the signal transduction pathway mediated by HAb18G/CD147 antigen, and inhibits the invasion and metastasis of liver cancer cells. At the same time, ^{131}I radionuclides are concentrated at the tumor site due to antigen-antibody binding, damaging the DNA of liver cancer cells and ultimately causing cell death [5,6]. According to clinical trials, ^{131}I metuximab can significantly improve the quality of life and prolong the overall survival time of patients with primary hepatocellular carcinoma [7,8]. In this study, the clinical data of patients with middle-advanced primary liver cancer undergoing Licartin combined with TACE were retrospectively analyzed, and its clinical efficacy and safety were explored.

Methods

General data

The clinical data of 112 patients clinically or pathologically diagnosed with inoperable middle-advanced primary liver cancer in our hospital from March 2015 to March 2017 were collected. Inclusion criteria: 1) patients aged 18-78 years old; 2) those in Barcelona Clinic Liver Cancer (BCLC) stage B-C; 3) those with Child-Pugh class A-B liver function; 4) those without receiving chemotherapy within 4 weeks; 5) those with the physical condition Eastern Cooperative Oncology Group (ECOG) score of 0-2 points; 6) those without complete occlusion of main portal vein; 7) those with a tumor-occupying rate <70%; and 8) those with an estimated survival time ≥3 months. Exclusion criteria: 1) patients with severe liver dysfunction (Child-Pugh class C); 2) those with complete occlusion of main portal vein; 3) those with a tumor-occupying rate ≥70%; 4) those with extensive metastatic tumors; 5) those allergic to Licartin; 6) those with severe impairment of thyroid function; 7) those with severe

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Licartin +TACE group (n=56)* *n (%)*	*TACE group (n=56)* *n (%)*	*p value*
Gender (Male/Female)	44/12	38/18	0.286
Age (years)	56.74±9.81	58.18±10.22	0.449
Cell morphological classification			0.688
Massive type	36 (64.3)	39 (69.6)	
Multiple nodules type	20 (35.7)	17 (30.4)	
Number of tumor lesions			0.292
1	6 (10.7)	11 (19.6)	
≥2	50 (89.3)	45 (80.4)	
BCLC staging			0.221
B	18 (32.1)	13 (23.2)	
C	38 (67.9)	43 (76.8)	
Child-Pugh class			0.333
A	31 (55.4)	37 (66.1)	
B	25 (44.6)	19 (33.9)	
AFP (ng/ml)			0.285
≥20	30 (53.6)	36 (64.3)	
<20	26 (46.4)	20 (35.7)	
Portal vein tumor thrombus	27 (48.2)	22 (39.3)	0.446
ECOG score			0.803
0	14 (25.0)	12 (21.4)	
1	25 (44.6)	29 (51.8)	
2	17 (30.4)	15 (26.8)	

TACE: Transcatheter arterial chemoembolization; AFP: Alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group

disease in the heart, lung, kidney or blood system; or 8) those with a history of malignant tumors. According to different therapeutic regimens, 56 patients underwent TACE combined with Licartin (Licartin + TACE group), while the remaining 56 patients were treated with TACE alone (TACE group). There were 82 males and 30 females aged 18-78 years with an average of 57.4 years. The baseline data such as gender, age, tumor morphology, number of tumors, BCLC stage and Child-Pugh class of liver function had no statistically significant differences between the two groups (p>0.05), and they were comparable (Table 1). All patients enrolled abided by the *Declaration of Helsinki*, and signed the informed consent. This study was approved by the Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine.

Treatment methods

Licartin + TACE: Metuximab skin test and iodine allergy test were performed before treatment. Compound iodine solution was orally taken from 3 days before operation for 10 days (0.5 mL/time, 3 times/d). The dosage of ^{131}I was determined based on the patient's body weight [27.75 MBq/kg (0.75 mCi/kg)]. The femoral artery was intubated using the Seldinger's technique for arteriography of celiac trunk and superior mesenteric artery, and the supplying vessel of tumor was determined. Then a 5F-RH catheter was inserted into the supplying vessel for embolization (10-30 mL of lipiodol + 30 mg of pirarubicin) and perfusion (40-60 mg of cisplatin + 1 g of fluorouracil), after which Licartin was injected within 5-10 min. The catheter was washed with normal saline and withdrawn, followed by compression hemostasis for 15 min. After operation, the patients routinely underwent liver-protecting, stomach-protecting and anti-tumor therapies, as well as antiemetic, analgesic, antipyretic and anti-infective treatments according to the postoperative reactions of patients. The patients were transferred from the anti-radiation ward to the general ward after 2 days.

TACE: The femoral artery was intubated using the Seldinger's technique for arteriography of celiac trunk and superior mesenteric artery, and the supplying vessel of tumor was determined. Then, a 5F-RH catheter was inserted into the supplying vessel for embolization (10-30 mL of lipiodol + 30 mg of pirarubicin) and perfusion (40-60 mg of cisplatin + 1 g of fluorouracil). The catheter was washed with normal saline and withdrawn, followed by compression hemostasis for 15 min. After operation, the patients routinely underwent liver-protecting therapy such as glycyrrhizin tablets and glutathione.

Observation indexes

Four weeks after interventional therapy, CT or MRI were performed to evaluate the efficacy based on the modified Response Evaluation Criteria In Solid Tumors. Complete response (CR): All target lesions (enhancement image in the arterial phase) disappear; partial response (PR): The total diameter of target lesions (enhancement image in the arterial phase) declines by ≥30%; stable disease (SD): The total diameter of target lesions (enhancement image in the arterial phase) declines less than PR or increases less than progressive disease (PD); PD: The total diameter of target lesions (enhancement image in the arterial phase) increases by ≥20% or there are new lesions [9]. The overall response rate (CR + PR) and disease control rate (CR + PR + SD) were calculated.

At 1 week before treatment and 2 weeks after treatment, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL) and albumin (ALB) and blood routine counts were recorded, and the incidence of postoperative adverse reactions (fever, nausea, vomiting, abdominal pain and diarrhea) was observed. One week before treatment and 1 month after treatment, 5 mL of peripheral blood were collected, in which the CD147 phenotype was identified and circulating tumor cells (CTCs) were counted via immunohistochemical staining. In 5 randomly-selected fields under a high-power microscope (×400), 100 cells were counted. CTCs had characteristics of malignant tumor such as intact nucleus, large volume, a high nucleus/cytoplasm ratio, and oval or circular shape, with corresponding cell size, morphology, brightness and color. Then, the score was given to the staining degree: 0 point (no color), 1 point (light yellow), 2 points (brown yellow) and 3 points (dark brown). The percentage of positive cells was also scored: 0 point (<5%), 1 point (5-25%), 2 points (26-50%), 3 points (51-75%), and 4 points (>75%). The above two scores were added: 0 point was recorded as "-", 1-2 points as "+", 3-4 points as "++", and 5-7 points as "+++". Finally, 0-1 point indicated $CD147^-$, while 2-7 points indicated $CD147^+$.

The clinical data of patients were collected every month through outpatient or telephone follow-up till December 31, 2019. The endpoint event was tumor recurrence, metastasis or death of patients. The overall survival (OS) and progression-free survival (PFS) were calculated from the date of enrollment. In survival analysis, the data of those lost to follow-up were processed as censored data in the last effective follow-up.

Statistics

SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Measurement data were expressed as mean±standard deviation. Differences between groups were analyzed by Student's t-test. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test assessed differences between the two groups. P<0.05 suggested statistically significant difference.

Results

Comparison of short-term efficacy between the two groups

All 112 patients successfully underwent the interventional operation. The efficacy was evaluated 1 month after operation. It was found that there was 0 case of CR, 19 cases of PR, 33 cases of SD and

4 cases of PD in Licartin+TACE group, and 0 case of CR, 16 cases of PR, 31 cases of SD and 9 cases of PD in TACE group. In Licartin+TACE group and TACE group, the overall response rate was 33.9% (19/56) and 28.6% (16/56), and the disease control rate (CR+PR+SD) was 92.9% (52/56) and 83.9% (47/56), respectively, showing no statistically significant differences (p=0.541, p=0.140) (Table 2).

Table 2. Clinical effective rates of the two studied groups

	Licartin +TACE group (n=56) n (%)	*TACE group (n=56) n (%)*	*p value*
CR	0 (0)	0 (0)	
PR	19 (33.9)	16 (28.6)	
SD	33 (58.9)	31 (55.4)	
PD	4 (7.1)	9 (16.1)	
ORR	19 (33.9)	16 (28.6)	0.541
CBR	52 (92.9)	47 (83.9)	0.140

TACE: Transcatheter arterial chemoembolization; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Overall response rate; CBR: Clinical benefit rate

Comparison of adverse reactions between the two groups

There were no statistically significant differences in liver function indexes ALT, AST, TBIL, ALB and AFP, peripheral blood white blood cell count (WBC) and platelet count (PLT) between the two groups before treatment (p>0.05). After treatment, the levels of ALT, AST and TBIL rose in both groups compared with those before treatment. At 2 weeks after treatment, the levels of ALT and AST were significantly higher in Licartin+TACE group than those in TACE group [(58.61±10.48) U/L *vs.* 53.29±9.89) U/L, (56.38±12.32) U/L *vs.* (52.65±13.09) U/L] (p=0.039, p=0.048). In Licartin+TACE group, the level of TBIL also rose after treatment, but it had no statistically significant difference compared with that in TACE group (p=0.268). After treatment, the levels of ALB and AFP declined in both groups compared with those before treatment, but they had no statistically significant differences between the two groups (p=0.085, p=0.434). Grade I-II liver damage occurred in patients, and it gradually recovered within 1-2 months after operation.

Table 3. Comparison of liver function indexes and peripheral blood cell count of patients in the two studied groups

Parameters	*Licartin +TACE group (n=56)*	*TACE group (n=56)*	*p value*
ALT (U/L)			
Pretreatment	46.69±23.42	48.15±24.94	0.488
Posttreatment	58.61±10.48	53.29±9.89	0.039
AST (U/L)			
Pretreatment	48.15±24.77	50.21±24.63	0.383
Posttreatment	56.38±12.32	52.65±13.09	0.048
TBIL (μmol/L)			
Pretreatment	15.62±6.08	14.43±5.56	0.282
Posttreatment	17.57±8.13	15.96±7.14	0.268
ALB (g/L)			
Pretreatment	37.12±5.13	36.29±4.79	0.378
Posttreatment	36.60±5.27	35.11±5.03	0.085
AFP (ng/ml)			
Pretreatment	1041.20±613.14	978.41±517.33	0.559
Posttreatment	714.66±492.70	788.49±501.24	0.434
RBC (10^{12}/L)			
Pretreatment	3.93±0.76	3.87±0.81	0.687
Posttreatment	3.80±0.69	3.72±0.73	0.552
WBC (10^9/L)			
Pretreatment	5.31±2.97	5.05±2.54	0.520
Posttreatment	3.76±2.44	4.71±2.86	0.031
PLT (10^9/L)			
Pretreatment	127.07±42.59	132.56±44.46	0.406
Posttreatment	103.61±40.07	118.38±43.49	0.029

TACE: Transcatheter arterial chemoembolization; ALT: Alanine transaminase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; ALB: Albumin; AFP: Alpha fetoprotein; RBC: Red blood cell; WBC: White blood cell; PLT: Platelet

In terms of bone marrow suppression, the WBC and PLT declined in both groups after treatment. At 2 weeks after treatment, the WBC and PLT were obviously lower in Licartin+TACE group than those in TACE group [(3.76±2.44)×10^9/L *vs.* (4.71±2.86)×10^9/L, (103.61±40.07)×10^9/L *vs.* (118.38±43.49)×10^9/L] (p=0.031, p=0.029). The patients in both groups had mainly grade I-II transient bone marrow suppression that was improved after symptomatic treatment (Table 3).

Post-embolization syndrome is the most common symptom after interventional operation, including hepatalgia, nausea, vomiting and fever. In this study, the above symptoms occurred in varying degrees in Licartin+TACE group within 1 week after operation, but the incidence rate had no significant difference compared with that in TACE group (p>0.05) (Table 4).

Comparison of count of CTCs and CD147 expression between the two groups

In Licartin+TACE group, CTCs were detected in 51 cases, and the positive detection rate was 91.1%, including 34 cases (66.7%) of $CD147^+$. In TACE group, CTCs were detected in 52 cases, and the positive detection rate was 92.9%, including 33 cases (63.5%) of $CD147^+$. No statistically significant difference was found between the two groups (p>0.05).

Table 4. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*Licartin +TACE group (n=56) n (%)*	*TACE group (n=56) n (%)*	*p value*
Hepatalgia	8 (14.3)	5 (8.9)	0.376
Fever	40 (71.4)	36 (64.3)	0.418
Nausea and vomiting	33 (58.9)	27 (48.2)	0.256
Fatigue and poor appetite	39 (69.6)	34 (60.7)	0.321
Diarrhea	11 (19.6)	16 (28.6)	0.269

TACE: Transcatheter arterial chemoembolization

Table 5. Comparison of CTCs number and CD147 expression of patients in the two studied groups

	Licartin +TACE group (n=56)	*TACE group (n=56)*	*p value*
CTCs + cases (%)	51 (91.1)	52 (92.9)	0.728
CD147 + cases (%)	34 (66.7)	33 (63.5)	0.552
CTCs count			
Pretreatment	37.67±8.01	36.03±9.19	0.316
Posttreatment	24.54±7.17	31.36±8.15	0.001

TACE: Transcatheter arterial chemoembolization; CTCs: Circulating tumor cells

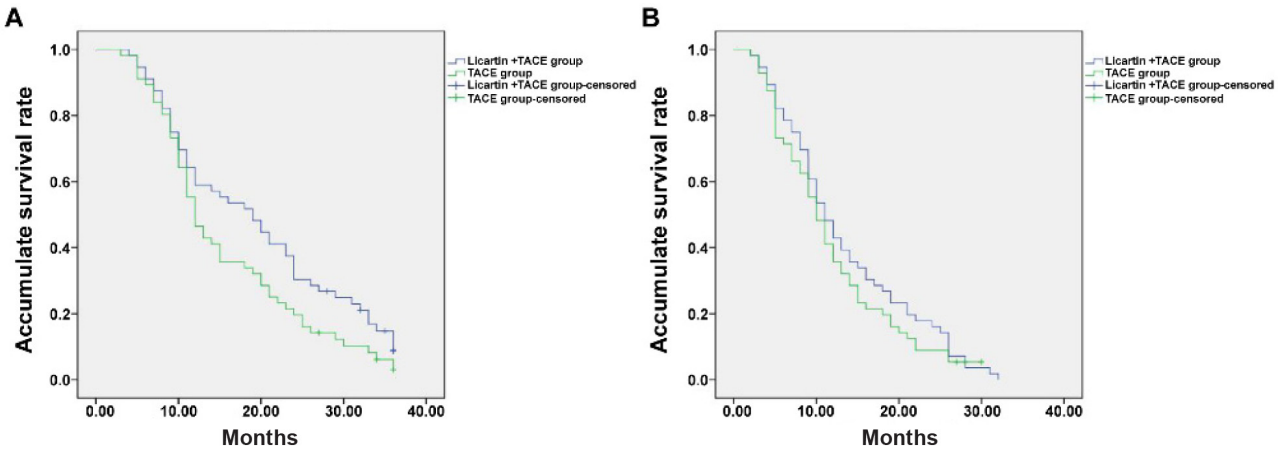

Figure 1. Kaplan-Meier survival curves of middle-advanced hepatocellular carcinoma patients. **A:** The overall survival rate of patients in Licartin+TACE group was significantly higher than that of TACE group (p=0.047). **B:** The difference between progression-free survival rate of patients in Licartin+TACE group and TACE group had no statistical significance (p=0.372).

Besides, there was no statistically significant difference in the count of CTCs detected before treatment between the two groups (p=0.316). After treatment, the count of CTCs declined evidently in both groups compared with that before treatment (p<0.05), and it was evidently lower in Licartin+TACE group than that in TACE group (p<0.001) (Table 5).

Follow-up results of patients' survival status

All patients were followed up for 3-36 months. In Licartin+TACE group and TACE group, the mean OS was 13.1±3.6 months and 11.3±2.8 months, respectively, and the mean PFS was 7.9±1.4 months and 6.1±1.2 months, respectively. In the two groups, the 1-, 2- and 3-year OS rates were 58.9% (33/56) *vs.* 46.4% (26/56), 30.4% (17/56) *vs.* 19.6% (11/56), and 12.5% (7/56) *vs.* 5.4% (3/56), respectively. The 1-, 2- and 3-year PFS rates were 42.9% (24/56) *vs.* 33.9% (19/56), 16.1% (9/56) *vs.* 7.1% (4/56), and 0% *vs.* 0%, respectively. At the end of follow-up, the Kaplan-Meier survival and log-rank test showed that the OS rate was remarkably superior in Licartin+TACE group to that in TACE group (p=0.047), but the PFS rate had no statistically significant difference between the two groups (p=0.372) (Figure 1).

Discussion

Licartin is a novel ^{131}I-labeled monoclonal antibody used for targeted radiotherapy of liver cancer, which is also a first-class national new drug for targeted therapy of hepatocellular carcinoma with monoclonal antibody HAb18F(ab')^2. The drugs are injected directly into the proper hepatic artery via interventional perfusion, and high-concentration metuximab-HAb18F(ab')^2 can bind to the HAb18G antigen in the membrane proteins of liver cancer cells, so that radioactive ^{131}I is delivered to the tumor site. Then β-rays emitted by ^{131}I decay cause ionizing radiation, thereby exerting a therapeutic effect [10,11]. The drug can be obviously taken up by liver cancer tissues, but its content is very low in other tissues. Tumor tissues are continuously radiated with time, thereby realizing high-dose radiation of local lesions. Moreover, β-rays can only penetrate through 2.0 mm-thick tissues, so its damage to surrounding normal tissues is small [12].

In recent years, there have been a few reports about Licartin combined with various intervention means and different modes of administration. For example, Bian et al [13] compared the efficacy of radiofrequency ablation with or without monoclonal antibody in the treatment of 127 patients with primary liver cancer. The results showed that the 1- and 2-year recurrence rates were 31.8% and 58.5%, respectively, in combination group, significantly lower than those in radiofrequency ablation group (56.3% and 70.9%). It was found in a similar study of West China Hospital that the 1-month tumor control rate and 1-year survival rate were 71.23% and 60.49%, respectively, in monoclonal antibody+TACE group, obviously higher than those in TACE group [14]. In terms of the route of administration, a study has shown that monoclonal antibodies can be administered safely via not only arteries but also veins [15]. Xu et al [16] used Licartin via intravenous injection to prevent liver cancer recurrence after liver transplantation, and they found that the 1-year recurrence rate declined obviously in monoclonal antibody group compared with that in placebo group (27% *vs.* 57%, p=0.017), and the 1-year survival rate was higher in monoclonal antibody group (83% *vs.* 62%). In addition, Zhang et al [5] found that besides the antitumor effect, monoclonal antibodies can also promote the proliferation of oncolytic viruses in tumors. Therefore, researchers put forward the application of Licartin combined with oncolytic virus in the treatment of liver cancer.

In this study, the results showed that the clinical response rate and disease control rate had no statistically significant differences in the treatment of middle-advanced liver cancer between Licartin+TACE group and TACE group (p>0.05). The liver damage and blood toxicity of the drug were mainly manifested as increased levels of TBIL and transaminases, and decreased WBC and PLT. After treatment, both WBC and PLT were markedly lower in Licartin+TACE group than those in TACE group, while ALT and AST were markedly higher in Licartin+TACE group than those in TACE group. The possible reason is that as a targeted drug, Licartin mainly accumulates in liver cancer tissues, so ^{131}I will cause certain damage to liver function, without obvious damage to normal tissues. The adverse reactions were mostly temporary or mild-moderate, which were improved after symptomatic treatment.

CTCs are tumor cells released by primary tumor lesions and metastatic lesions into the blood, which can serve as a golden index for the early monitoring of tumor recurrence, guidance of chemotherapy regimen and evaluation of efficacy. CTCs can not only reflect the characteristics of primary tumor lesions, but also effectively exhibit the characteristics of metastatic lesions [17,18]. Therefore, it is of great significance to isolate, enrich and count peripheral blood CTCs, and identify their molecular phenotype for the development of clinical individualized therapeutic regimen for patients with liver cancer [19]. It has been proved that the expression of CD147 is higher in liver cancer tissues, up to 57.00-73.53% [20]. In this study, the detection rates

of CTCs and CD147 were higher, consistent with previous reports. It was found that the number of CTCs could be greatly reduced in Licartin+TACE group, and the efficacy was better than that in TACE group. According to the follow-up results, the OS rate was remarkably superior in Licartin+TACE group to that in TACE group (p=0.047).

As a retrospective study, this study has certain limitations. For example, the sample size was limited, the follow-up time was not long enough, and the follow-up content was not comprehensive enough. Besides, the effects of different therapeutic regimens on the quality of life and other subjective feelings of patients were not further analyzed, and the possible influencing factors for the efficacy of Licartin were not further analyzed either. In the future, the conclusion made in this study needs to be confirmed by more rigorous large-sample prospective multicenter randomized studies.

Conclusions

Licartin combined with TACE has better efficacy than TACE alone in the treatment of middle-advanced primary liver cancer, with tolerable adverse reactions, which prolongs patient survival time.

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Conflict of interests

The authors declare no conflict of interests.

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