RESEARCH ARTICLE

Lobaplatin-TACE Combined with Radioactive [125]I Seed Implantation for Treatment of Primary Hepatocellular Carcinoma

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Abstract

Aim: To investigate the efficacy and safety of lobaplatin-transcatheter arterial chemoembolization (TACE) combined with radioactive ^{125}I seed implantation in treatment of primary hepatocellular carcinoma (HCC). **Methods:** 75 patients with primary HCC were enrolled in the study, among them 43 receiving lobaplatin-TACE (TACE group) and 32 lobaplatin-TACE combined with ^{125}I seed implantation (TACE+[125]I group). After treatment, the local remission rates and postoperative complications of two groups were compared using the Pearson Chi-square test. Overall survival in the two groups was calculated using Kaplan-Meier survival curves and the differences were tested using Log-rank test. **Results:** There were 7 cases of complete response (CR), 13 of partial response (PR), 6 of stable disease (SD) and 17 of progressive disease (PD) in the TACE group, with 13 cases of CR, 9 of PR, 5 of SD and 5 of PD in the TACE+[125]I group. The disease control rates of TACE and TACE+[125]I group were 60.5% (26/43) and 84.4% (27/32), respectively, with a significant difference between them ($P < 0.05$). The survival rates at 6, 12 and 18 months in the TACE group were 100.0%, 81.8% and 50.0%, respectively, and those in TACE+[125]I group were 100.0%, 93.8% and 65.6%. The mean survival times in the TACE and TACE+[125]I groups were 19.5 and 22.9 months, respectively. There was a significant difference in the overall survival rate between two groups ($P < 0.05$). No serious complications were encountered in either group. **Conclusion:** Lobaplatin-TACE combined with ^{125}I seed implantation is favorable and safe for treatment of primary HCC.

Keywords: Primary hepatocellular carcinoma - [125]I seed - transcatheter arterial chemoembolization - lobaplatin

Introduction

Primary hepatocellular carcinoma (HCC), with a climbing incidence year by year, is one of the most common malignant tumors and presents a spreading trend worldwide (Sherman, 2010). Current principal means for the treatment of HCC include surgical treatment (liver resection and liver transplantation), regional treatment (transcatheter arterial chemoembolization (TACE)) and topical therapy (ablation therapy, etc.) (Bruix and Sherman, 2011; Forner et al., 2012; Shi et al., 2013). However, when the patients refer to the hospital, most of them have been at the latest stage and consequently few of them can undergo surgical treatment. Moreover, the recurrence rate of HCC is high. Its 5-year recurrence rate can be up to 80%, while less than 20% of the recurrent HCC can get a re-resection (Bruix and Sherman, 2011). Liver transplantation can be a favorable approach for the treatment of liver cancer in the final stage, but the donors are very scarce and the cost is huge. Ultimately, most of the patients have to receive regional or topical treatment.

In this regard, finding out new technologies and new methods for treating liver cancer has been an important frontier issue for long time. TACE can effectively control the development of tumor and alleviate the suffering of patients and thereby can prolong the survival time of patients (Llovet and Bruix, 2003; Cha et al., 2010). However, due to it is not a radical approach, TACE has to be carried out repeatedly on patients and cause liver injury repeatedly that most patients can not bear. Lobaplatin is the third generation of platinum with low liver toxicity. Thus, it can also be used for the treatment of liver cancer (Gietema et al., 1993; McKeage, 2001). As a means of brachytherapy, ^{125}I radioactive seed implantation can get high local control rate and low complication rate in the treatment of malignant tumors. Moreover, it can improve the patient's quality of life and prolong their survival time (Dawson and Lawrence, 2004). In the United States and other countries, it has been used as a standard treatment for early prostate cancer. In China, it has even been widened to treat the systemic solid tumors, such as pancreatic cancer, head and neck tumors. It has also achieved significant

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Table 1. General Data of Subjects

Clinical parameters	TACE group (n = 43)	TACE+[125]I group (n = 32)	P
Age			0.713
≥ 50	21	17	
< 50	22	15	
Gender			0.386
Male	39	31	
Female	4	1	
AFP (ng/ml)			0.552
≤ 1000	12	7	
> 1000	31	25	
No. of tumors			0.242
1~3	26	15	
>3	17	17	
TNM stage (UICC)			0.897
II	2	1	
IIIA	15	12	
IIIB	15	10	
IVA	9	7	
IVB	2	2	
Hepatitis			0.805
HBV	31	23	
HCV	1	0	
Negative	11	9	
Child-Pugh grade			0.615
A	38	27	
B	5	5	
PVTT	3	6	0.159
Extrahepatic metastases	2	3	0.645

efficacy in treating liver cancer (Li et al., 2010; Zhang et al., 2010; Meng et al., 2012; Wang et al., 2012). This study was designed to combine lobaplatin-TACE with radioactive ^{125}I seed implantation for the treatment of advanced primary liver cancer, so as to provide a new model for the treatment of liver cancer.

Materials and Methods

General data

From January 2010 to February 2012, a total of 138 patients with advanced primary HCC were referred for lobaplatin-TACE and/or ^{125}I seed implantation therapy. All the procedures in this study were permitted by the ethics committee of Cancer Center of Zhongshan University.

Inclusion criteria: (1) Male or female, age ≤ 75 years. (2) Primary HCC was diagnosed based on imaging examination (CT, MRI and B-mode ultrasound), tumor markers and/or histological examination. (3) The patients can not tolerate surgery due to their physical condition or because the operation is too hard to be carried out (including more than 3 tumor foci or the remaining liver may not maintain its normal function after the operation). (4) Imaging manifestation: tumor diameter ≤ 5 cm, single or multiple; complicated with portal vein thrombosis; complicated with liver metastasis but evaluated to be controllable. (5) Child-Pugh classification of liver function was in class A/class B. (6) Normal bone marrow function. (7) Expected survival time was more than 3 months. (8) Informed consent was obtained from each patient. (9) Medical history data are intact.

Exclusion criteria: (1) Patients were also treated with
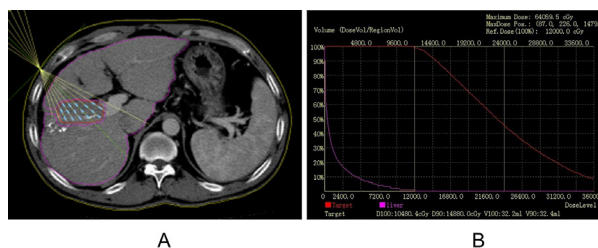
Figure 1. Treatment Planning Before Operation. (A) Simulative diagrams of needle insertions and seeds implantation before verifying the relationships between each CT layer D90 and tumor by simulating picking up the seeds according to real-time intraoperative distribution. (B) Dose-volume Histogram (DVH) before operation

other interventional therapies, such as radio frequency current ablation, microwave ablation, chemical ablation and others. (2) Patients could not receive the treatment program due to the complications, such as severe hypertension, diabetes and so on.

79 patients met the above criteria, but only 75 of them finished the follow-up finally. According to their wills, 45 of them volunteered to receive lobaplatin-TACE treatment alone (TACE group) and the other 34 patients volunteered to undergo TACE combined with radioactive ^{125}I seed implantation therapy (TACE+[125]I group). However, 2 patients in TACE group dropped out during the TACE treatment. In the TACE+[125]I group, there was also 1 case dropping out during the treatment and 1 case loss of follow-up. Finally, there were 43 patients in TACE group and 32 patients in TACE+[125]I group. The general data of the enrolled patients were listed in Table 1.

Surgical procedures

TACE TACE was performed using Seldinger technique. Briefly, catheter was catheterized through the femoral artery to proper hepatic artery or superior mesenteric artery. Arterial angiography was used to determine the blood supply of the lesion. Then the catheter was selectively or super-selectively catheterized into the tumor feeding artery. After that, iodized oil emulsifier containing lobaplatin (50 mg per tube, Chang'an International Pharmaceutical Co., Ltd., Hainan, China) was injected into the tumor feeding artery through the catheter at a dosage of 10 mg to 50 mg each time with an average of 33.3 mg, so as to block the tumor blood flow and fill the tumor with iodine oil emulsifier. The operation should be carried out for the patients in every 4-8 weeks. Radioactive ^{125}I seed implantation therapy ^{125}I seeds (Model 6711, Atomic Hi-Tech Co., Ltd., Beijing, China) were implanted into patients generally at 2 to 4 weeks after TACE. The activity of ^{125}I seeds was 0.6 to 0.8mCi with a half-life of 59.4 days. Its mean energy was 27 to 32KeV and the matched peripheral dose was set to 120 Gy. The conventional CT scanning was conducted to determine the lesion location for ^{125}I seed implantation. The implantation procedures were as follows: Firstly, treatment planning was made before the operation (Figure 1A and 1B): the appropriate puncture point and inserting line were determined according to the tumor size, shape and location, and then the number, radiation dose and distribution of ^{125}I seeds were calculated. Secondly, after

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Table 2. Local Remission Rates in Two Groups (%/n)

Groups	CR	PR	SD	PD	DCR
TACE (n = 43)	16.28%/7	30.23%/13	13.95%/6	39.53%/17	60.47%/26
TACE+^{125}I (n = 32)	40.63%/13	28.13%/9	15.63%/5	15.63%/5	84.37%*/27

*$P < 0.05$ compare with TACE group

Table 3. Survival Time and Survival Rate in Two Groups

Group	Survival rate (%)			Mean
	6 months	12 months	18 months	(months)
TACE (n = 43)	100	81.81	50	19.5
TACE+^{125}I (n = 32)	100	93.75	65.63	22.9*

*$P < 0.05$ compare with TACE group

the patient was locally anesthetized with 1% lidocaine, 18G seeds implanting needle was punctured into the tumor tissue with the guide of CT. As its tip reached the predetermined target area and was about 0.5cm far away from the distal end, the seeds were implanted retrusively with intervals of about 0.5-1.0 cm. The spaces between rows of seeds were about 1.0-1.5cm. After the operation, CT scan was performed to check whether the seeds were ectopic or shedding. Once the case happened, the seeds should be replanted promptly. Last, quality verification at 3-7 days after the operation (Figure 2A and 2B): if D90 does not cover all of the levels of the tumor, a second seeds implantation should be carried out for supplement therapy in half a month (Figure 3).

Follow-up

Survival time was determined from the TACE and ^{125}I seed implantation time. At 3-7 days after treatment and prior to discharge, the biochemical indicators of liver function and clinical manifestations (ascites, jaundice, etc.) were observed, respectively. After discharge, blood tests were carried out every two weeks, and CT, MR or PET-CT was also performed every treatment period (1-3 months, mean 2 months) to check the tumor.

Evaluation criteria

The evaluation criteria referred to the revised RECIST. (1) Complete response (CR): Disappearance of all target lesions or their functional activities (PET-CT examination shows negative and serological detection of AFP shows normal). (2) Partial response (PR): At least a 30% decrease in the sum of the long diameters of target lesions, taking as reference the baseline sum diameters; CT scan shows the formation of coagulation necrosis or cavity in the center of the tumor as well as PET-CT displays a decline of SUV. (3) Stable disease (SD): No sufficient shrinkage of the sum of the long diameters of baseline lesions to qualify for PR and no central necrosis. (4) Progressive disease (PD): At least a 20% increase in the sum of long diameters of new intrahepatic lesions or new lesions in situ and their absolute values greater than 5mm, or appearance of new extrahepatic lesions; PET-CT examination shows increased SUV. (5) Disease control rate (DCR): (CR+PR+SD)/n.

All measurements on the lesions were performed on the PACS workstation (Centricity® Radiology RA1000, GE Healthcare, WI, USA). Both measurements and
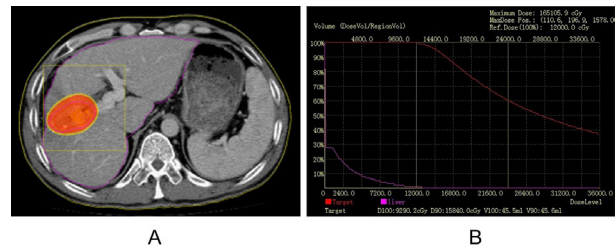
Figure 2. Quality Verification after Operation. (A) Dose verification after ^{125}I seeds implantation. The portal vein developed well and the original low-density areas were replaced by ^{125}I seeds and lipiodol. (B) Dose-volume Histogram (DVH) after operation
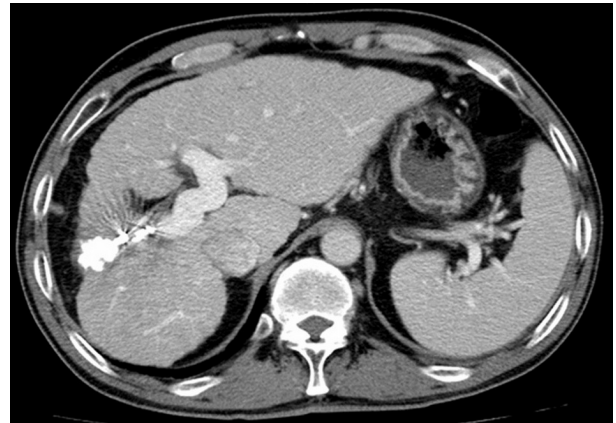
Figure 3. A Representative of CT Images at 23.5 Months after TACE Combined with ^{125}I Seeds Implantation (Right Branch of ^{125}I Implantation)

efficacy evaluations of the lesions were performed by two professional radiologists independently (working for 21 years and 3 years, respectively). If the follow-up result was CR or PR, the imaging follow-up intervals could be extended to two months. If no sign of recurrence was observed one year later, the imaging follow-up intervals could be correspondingly extended to three months. Two years later, patients were reviewed every six months. Any time PD was found, treatment should be added.

Statistical analysis

All data were analyzed using SPSS16.0 statistics software (Chicago, IL, USA). The general data and the postoperative complications were compared using Pearson Chi-square test. The overall survivals of the two groups were calculated using Kaplan-Meier survival curves and their differences were tested using Log-rank test. $P < 0.05$ was considered statistically significant.

Results

Therapeutic efficacy

32 patients in TACE group underwent a total of 50 times of TACE (1-2 times per patient) with an average of 1.56 times. 43 patients in TACE+^{125}I group underwent 96 times of TACE (1-7 times per patient) with an average of 2.23 times. ^{125}I seeds implantations were performed for 54 times (1-3 times per patient) with an average of 1.69 times. The evaluations of target lesions were listed in Table 2. There were 7 cases of CR, 13 cases of PR, 6 cases of SD
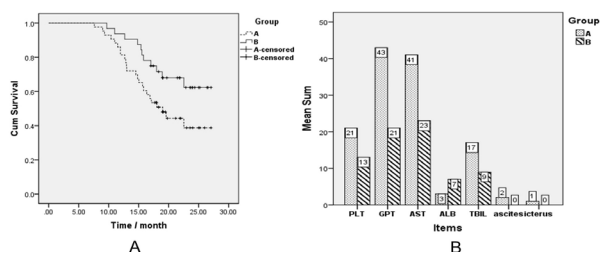
Figure 4. Overall Survival Rates and Complications in Two Groups. (A) Overall survival rate curves in two groups (Kaplan-Meier). A, TACE; B, TACE+^{125}I group; $P = 0.043$. (B) Complications in two groups. A, TACE; B, TACE+^{125}I group

and 17 cases of PD in TACE group, with 13 cases of CR, 9 cases of PR, 5 cases of SD and 5 cases of PD in TACE+^{125}I group. The DCRs of TACE and TACE+^{125}I group were 60.47% (26/43) and 84.37% (27/32), respectively, with significant difference between them ($P < 0.05$).

Survival time and survival rate

The follow-up was ended at April 2013. As shown in Table 3, the survival rates of 6, 12 and 18 months in TACE group were 100.00%, 81.81% and 50.00%, respectively, and those in TACE+^{125}I group were 100.0%, 93.75% and 65.63%, respectively. The mean survival time in TACE group and TACE+^{125}I group was 19.5 and 22.9 months, respectively. There was significant difference of overall survival rate between two groups ($P < 0.05$) (Figure 4A).

Toxicities and complications

Patients in both groups presented pain and discomfort in liver area, nausea and vomiting, mild diarrhea, fever at 3-7 days after operation, transient liver function abnormalities and varying degrees of bone marrow suppression. But all of these symptoms were relieved by symptomatic treatment. The incidence of complications caused by TACE was significantly higher than that caused by ^{125}I seeds implantation, but no serious complication was found in both groups. The operation number in TACE+^{125}I group was more than that in TACE group, but the postoperative side effects and blood test abnormalities in TACE+^{125}I group were fewer instead (Figure 4B).

Discussion

Treatment via hepatic artery is mainly suitable for HCC patients. Ma et al. (2013) evaluated the relative effectiveness of three main methods via hepatic artery including TACE, transcatheter arterial embolization (TAE) and transcatheter arterial infusion (TAI) in treatment of HCC. Results found that, TACE and TAE demonstrated more effective reduction of tumor size than group TAI. TACE is still admitted the primary means for treating the advanced primary liver cancer. However, the drugs of TACE, especially the chemotherapy drugs used, often present high toxicity, unremarkable efficacy and other disadvantages, although various types of anti-tumor drugs are covered. To date, the most commonly used chemotherapy drugs for TACE clinically were adriamycin and platina (Marelli et al., 2007; Martin et al., 2012). Adriamycin belongs to non-specific cycle drugs

and used as conventional TACE drug due to its broad anti-tumor spectrum. As a third generation of platina, lobaplatin also has a broad-spectrum anti-tumor effect. It has been used as first-line chemotherapeutic agent for the treatment of a variety of tumors. In this study, we found that lobaplatin can well blend to iodized oil and become more stable emulsifier, making lipiodol depositing more thoroughly. Additionally, lobaplatin has good solubility that is relatively stable in water, ensuring its high blood drug concentration in the blood vessels within the tumor and thereby increasing the time for inactivating the tumor (McKeage, 2001; AEterna Laboratories, 2003). Studies have shown that the efficacy of lobaplatin-TACE is higher than the conventional TACE or transcatheter arterial embolization (Zhou et al., 2010; Shi et al., 2013). Our results showed that the mean survival time in TACE group was 19.5 months, higher than that in the literatures (Ho and Yang, 1992; Zhao et al., 2010; Kim et al., 2013). We believed that it may owe to lobaplatin.

From the initial application in the treatment of early prostate cancer to its applications in the treatment of systemic solid tumors, the development of ^{125}I seeds implantation is closely related to its anti-tumor properties. Its principle is to implant the seeds carrying ^{125}I directly into the lesions, making continuous low-dose irradiation on tumor cells. It can arrest the cell cycles at the radiation-sensitive G2/M phase and thereby plays a role in killing tumor cells. Furthermore, multiple seed implantations may have a "stacking effect", causing the radiation dose in lesions surged and thus inactivating tumor cells more thoroughly. More importantly, the killing radius of ^{125}I is short (1.7 cm), which almost has no effect on the normal tissues around the lesions (Nakamura et al., 2006).

The advantage of TACE combined with ^{125}I seed implantation is that some tumor residuals left by TACE treatment can be further inactivated by ^{125}I seeds. For the tumors lack of blood supply, especially for those with varied hepatic artery structure and/or neovascular and being unable to receive another TACE or for those with unsatisfactory lipiodol deposition, a combination with ^{125}I seed implantation is more necessary. Moreover, ^{125}I seed implantation can not be confined by the lesion location. It can also be carried out for the lesions close to large vessels, hepatic duct or liver edges. In this study, the partial remission rate in TACE+^{125}I group was higher than that in TACE group, and the mean survival time was also prolonged for 3.4 months as compared with that of TACE group. The difference showed statistically significant ($P < 0.05$).

Portal vein tumor thrombosis (PVTT) is a major problem in the treatment of liver cancer. Intrahepatic vascular system is vulnerable to the invasiveness of HCC (Xue et al., 2013). Studies have shown that the incidence rate of HCC complicated with intrahepatic portal vein branch tumor thrombosis could reach 30% to 60.2% and the average survival time of these patients was only 2.7 months if they were not treated (Llovet et al., 1999). For such patients, the Guidelines of NCCN recommend to use sorafenib treatment. But its effect is very short and it can only prolong the average survival time to 6.5 months (Cheng et al., 2009). In this study, since few PVTT cases

were included, no statistically significant difference was found yet. But from the comparison results (not shown), it was also of some positive significance. Three patients in TACE group died before the end of the last follow-up. Their survival times were 5.7, 7.3 and 11.8 months, with an average of 8.3months. Three of six PVTT cases died before the end of the follow-up with survival time of 8.1, 9.7 and 12.5 months, respectively. While the follow-up time for the other three cases were 14.5, 17.6 and 23.5months, and their AFP values are all reduced more than 75%, taking reference the baseline values. There were two cases with AFP returned to normal, including one case dropped to 1.16 ng/ml. From these we can see that lobaplatin-TACE combined with ^{125}I seed implantation for the treatment of hepatocellular carcinoma PVTT has certain advantages, but still need a large random sample to support.

For patients with distant metastases, TACE combined with ^{125}I seed implantation can not only control the intrahepatic lesions, but also control the extrahepatic metastases. Although the different treatments may lead to different final survivals, ^{125}I seed implantation can achieve the complete inactivation of metastases as used for the treatment of solid tumor metastases (especially for those located in lung). It can reduce the systemic tumor burden and has a positive significance for patient's quality of life and survival time.

Currently, no myelosuppression caused by radioactive ^{125}I seed implantation in the treatment of liver cancer has been reported. In this study, lobaplatin-TACE cause various degrees of platelet decline at 1 week after the operation and it was statistically significant as compared with that before the operation. However, there was no significant decrease in platelets after ^{125}I seed implantation. Some relevant literatures showed, the main side effect of adriamycin is a decline in white blood cell count but not in red blood cell RBC count or platelet count. The decreased platelet counts in our results may be associated with the pharmacological effects of lobaplatin or the synergetic effect of the two drugs, but it should be confirmed by more researches (Gabizon et al., 1989; Voegeli et al., 1990). In this study, three cases of myelosuppression grade III occurred after TACE treatment, 2 of them self-improved and one of them returned to normal after injection of prophylactic recombinant human thrombopoietin for one week.

Complications of TACE are mainly liver function abnormalities. The blood tests in our results showed that glutamate pyruvate transaminase, glutamic oxalacetictransaminase, glutamyl transpeptidase and total bilirubin were all elevated at various extents as compared with the preoperative. Among the total blood tests in follow-up time, 30 to 61 cases of liver function were elevated to varied degrees, with an average of more than 1-fold, which was statistically significant as compared with those before the operation ($P < 0.05$). For symptoms, there were 2 cases of ascites after TACE treatment, although they were all clinically controllable. It might directly result from liver hypoperfusion after embolization and the liver damage of chemotherapy. After ^{125}I implantation, the incidence of liver function

abnormality was significantly lower than single TACE, without occurrence of ascites. This indicated that, ^{125}I seed implantation had less damage to liver. TACE combined with ^{125}I seed implantation therapy reduced the frequency of TACE and thereby reduced the liver dysfunction caused by TACE, suggesting that it has a positive effect on the long-term survival of patients. Aspartate transaminase was also increased to a lesser extent after ^{125}I seed implantation, probably resulted from the damage caused by the puncture needle during the implantation process. The continuing irradiation of ^{125}I seeds can also cause liver damage, but no reports were found on the serious liver damage or other serious complications caused by ^{125}I seed implantation (Martinez-Monge et al., 1989; Zhang et al., 2006; Zhang et al., 2007; Zhang et al., 2009).

In conclusion, as a combined chemotherapy drug with TACE, lobaplatin has significant clinical efficacy. TACE combined with ^{125}I seed implantation in the treatment of advanced liver cancer can better control the lesions and protect liver function, as compared with TACE alone. It can improve the survival rate of patients and be an effective treatment modality.

Acknowledgements

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