RESEARCH ARTICLE

Application of Lobaplatin in Trans-catheter Arterial Chemoembolization for Primary Hepatic Carcinoma

Nan Wang[1], Yin-Zhang Lv[1], An-Hui Xu[1], Yan-Rong Huang[1], Ling Peng[1], Jia-Rui Li[2]*

Abstract

Objective: To explore the efficiency of single application of lobaplatin in tran-scatheter arterial chemoembolization (TACE) for patients with a primary hepatic carcinoma who were unable or unwilling to undergo surgery. Methods: 173 patients with primary hepatic carcinoma diagnosed by imaging or pathology were randomly divided into experimental and control groups and respectively treated with lobaplatin and pirarubicin hydrochloride as chemotherapeutic drugs for TACE. The amount of iodipin was regulated according to the tumor number and size, and then gelatin sponge or polyvinyl alcohol particles were applied for embolisms. The efficiency of treatment in the two groups was compared with reference to survival time and therapeutic response. Results: The experimental group (single lobaplatin as chemotherapy drug) was superior to control group (single pirarubicin hydrochloride as chemotherapy drug) in the aspects of survival time and therapeutic response, with statistical significance. Conclusions: Single lobaplatin can be as a chemotherapy drug in TACE and has better efficiency in the aspects of mean survival time and therapeutic response, deserving to be popularized in the clinic.

Keywords: Tran-scatheter arterial chemoembolization - primary hepatic carcinoma - lobaplatin - survival rate

Asian Pac J Cancer Prev, **15 (2)**, 647-650

Introduction

Hepatocellular carcinoma (HCC) ranks the fifth in global tumors. About 0.5-1.0 million people are diagnosed as newly-increased HCC patients every year, most of which are Chinese (El-Serag et al., 2007; Gomes et al., 2013). At present, HCC has been topped the second place in tumor-caused deaths (Huang et al., 2007). Tran-scatheter arterial chemoembolization (TACE) has been considered as the optimal method for unresectable hepatic carcinoma, and its selection for chemotherapy regimens during operation is closely associated with efficiency. As the third generation of platinum anti-tumor drug, lobaplatin (LBP) exerts definite effects in the treatment of various tumors (Yang et al., 2009; Ali et al., 2013). In this study, single LBP was selected as the chemotherapy drug in TACE, and its influence on the efficiency of primary hepatic carcinoma in TACE was evaluated by survival time and therapeutic response under the precondition of other chemotherapy drugs as a control.

Materials and Methods

General data

173 patients with primary hepatic carcinoma undergoing TACE were selected in Radiology Department of our hospital from Mar., 2011 to Jul., 2012, in which males and females were respectively 153 and 20 cases, with mean age of 49.8 years old. All the patients with primary hepatic carcinoma diagnosed by imaging or pathology were unable or unwilling to undergo the operation, but got the informed consent form and operation consent form before enrollment and were approved by Ethics Committee of our hospital; those with severe liver dysfunction, arteriovenous fistula, tumor embolus in portal veins and distal metastasis were excluded. The patients were randomly divided into experimental group given 131 times of TACE with LBP as the chemotherapy drug and control group given 119 times of TACE with pirarubicin hydrochloride as the chemotherapy drug. There was no significant difference regarding the general data of patients between two groups (P>0.05) (Table 1).

TACE method

Under local anesthesia, 5F Yashrio, Cobra or HR catheter was placed for super-selection to tumor feeding arteries after Seldinger method was used to conduct the femoral arterial puncture intubation. SP microtubules were applied if necessary. After that, the emulgator mixed with lipiodol and chemotherapy drugs was injected. The chemotherapy drug in experimental group was LBP (specification: 50 mg/bottle, Hainan Changan

[1]*Invasive Technology Department, Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science & Techonology, Wuhan,* [2]*Invasive Technology Department, The First Hospital of Jilin University, Changchun, China *For correspondence: Lirui1971@sina.com*

Table 1. Comparison on the General Data and Liver Conditions of 173 Patients with Hepatic Carcinoma Before TACE

Item	Experimental group (n=90)	Control group (n=83)		*P*
Gender (M/F)	79/11	74/9	x^2=0.08	>0.05
Age (years old)	50.2±11.8	49.4±10.7	u =1.96	>0.05
Tumor size (cm)	7.02±3.01	6.94±3.14	u =0.93	>0.05
Number (single/multiple)	70/20	62/21	x^2=0.23	>0.05
ALT (U/L)	68.51±43.28	69.72±41.98	u=2.17	>0.05
AST (U/L)	70.28±48.22	72.64±51.04	u=1.38	>0.05
TBIL (μmol/L)	18.84±8.16	18.24±6.98	u=0.38	>0.05
DBIL (μmol/L)	4.98±3.64	4.67±2.97	u=2.37	>0.05
ALB (g/L)	37.28±6.18	38.25±6.67	u=1.23	>0.05
A/G ratio	2.01±0.28	1.98±0.38	u=0.57	>0.05
Distal metastasis	7/83	6/77	x^2=0.02	>0.05
Portal tumor embolus (yes/no)	72/18	69/14	x^2=0.28	>0.05
AFP (normal/abnormal)	13/77	11/72	x^2=0.05	>0.05

International Pharmaceutical Co., Ltd.), and its dose was regulated by the operator according to the pathological condition of patients, usually being 20-50 mg. The chemotherapy drug in control group was pirarubicin hydrochloride (specification: 10 mg/bottle, Shenzhen Main Luck Pharmaceuticals Inc.), and its dose was also regulated by the operator according to the pathological condition of patients, usually being 5-10 mg, while that of lipiodol was decided by the manipulator, being 1.0-1.5 mL/cm in general, and the maximum was no more than 25 mL. There still was tumor stain if the scheduled dose was injected, then gelatin sponge or PVA particles could be used for embolism.

Comparison on survival time and therapeutic response

Imageological examination was performed 1 month after operation every time to confirm the changes of tumor size. Response evaluation criteria in solid tumors were adopted to evaluate the response of tumors to the drugs. Complete response (CR): all lesions disappeared in the targeted area; partial response (PR): the maximum diameter was decreased to 30%-99% in the targeted area; stable disease (SD): it was between PR and progressive disease (PD); PD: the maximum diameter was increased over 20% in the targeted area. Clinical response rate (RR) = (CR+PR) / total number of cases×100%. For the patients undergoing TACE many times, the therapeutic response was assessed according to the final efficiency of multiple treatments.

Statistical data analysis

SPSS16.0 statistical software was applied to analyze the data, and Kaplan-Meier survival curve to achieve 3, 6, 9 and 12-month survival rates of patients in two groups.

Table 3. Comparison on the Clinical Efficiency of Two Groups [n(%)]

Groups	n	CR	PR	SD	PD	RR/%
Experimental group	80	0(0.0)	23(28.8)*	36(45.0)	21(26.3)	28.8*
Control group	74	0(0.0)	11(14.9)	33(44.6)	30(40.5)	14.9

Compared with control group, *P<0.05

The mean survival time was calculated by Kaplan-Meier method and tested by Log-rank test. The therapeutic response was RXC table with unordered grouping variables but ordered index variables, and nonparametric test with rank conversion was used. All inspection levels of hypothesis testing were set α=0.05.

Results

Comparison on survival rates and mean survival time

The 3, 6, 9 and 12-month survival rates of patients in experimental group and control group were respectively 94.4%, 86.7%, 80.0%, 74.4% and 90.4%, 80.7%, 73.5%, 61.4%. The significant difference was presented by comparison to 12-month survival rates of two groups (X^2=3.9791, P<0.05) (Table 2).

Clinical efficiency

The clinical efficiency of 10 and 9 cases respectively in experimental group and control group was unable to be evaluated due to the deaths, loss of visit, poor constitution and rejection to further consultation, therefore the final cases were 80 and 74 cases respectively in experimental group and control group.

In experimental group, there was no one being CR, but PR 23, SD 36 and PD 21; in control group, there was also no one being CR, but PR 11, SD 33 and PD 30. RR in experimental group was significantly higher than in control group (P<0.05) (Table 3).

Discussion

The incidence and mortality of HCC are relatively higher in our country. The causes of the latter lie in most patients are at the milled-advanced stage when diagnosed and miss the opportunities of receiving radical operation, or the postoperative recurrence rate is also higher even if they have opportunities to receive radical operation. TACE, the recognized optimal method for unresectable hepatic carcinoma at present (Giunchedi et al., 2013; Giunchedi et al., 2013; Hao et al., 2013), can not only reduce the intraoperative hemorrhage and postoperative complications before radical operation, but also has a certain effect on the patient waiting for the liver transplantation or those with recurrence after liver

Table 2. Comparison on Survival Rates and Mean Survival Time of Two Groups

Groups	Accumulated survival rate (%)				Mean survival	95%CI of mean
	3 months	6 months	9 months	12 months	time (month)	survival time
Experimental group (n=90)	85(94.4)	78(86.7)	72(80.0)	67(74.4)*	10.902	10.348-11.455
Control group (n=83)	75(90.4)	67(80.7)	61(73.5)	50(60.2)	10.614	10.008-11.220

Compared with control group, *P<0.05

transplantation (Zhou et al., 2010; Agnello et al., 2013; Cescon et al., 2013). There is no unified notion with regard to the variety and doses of chemotherapy drugs in TACE. In the variety of chemotherapy drugs, there are various kinds of drugs that can be selected, such as epirubicin hydrochloride, mitomycin, hydroxycamptothecine, 5-fluorouracil, platinum chemotherapy drugs and sapylin.

As the third generation of platinum anti-tumor drug, LBP can obstruct the process of DNA replication and transcription by forming Pt-GG and Pt-AG intrachain cross-linking so as to interfere the running of tumor cell cycles (Mckeage et al., 2001; Liu et al., 2013). Characterized by good water solubility, broad anti-tumor spectrum, strong anti-tumor activity, no achiasmate drug resistance with other platinum-based drugs and low toxicity, it exerts definite effects in the treatment of various tumors, such as breast cancer (Engel et al., 2012; Deng et al., 2013), lung cancer (Xie et al., 2012), esophageal carcinoma, gastrointestinal cancer (Li et al., 2013) and malignant pleural effusion and ascites. In terms of primary hepatic carcinoma, the in-vitro experimental studies have demonstrated that LBP has an inhibitory effect on hepatocellular carcinoma cells, and can be recommended to treat primary hepatic carcinoma in clinic (Qian et al., 2009; Wu et al., 2010; Wang et al., 2012). By applying LBP in TACE for hepatic carcinoma, the research results made by Shi et al. revealed that the efficiency of epirubicin hydrochloride combined with LBP and mitomycin was superior to that of single epirubicin hydrochloride in the treatment of unresectable hepatic carcinoma with good liver function (Shi et al., 2009; Shi et al., 2013).

By referring to the doses used in systemic chemotherapy, traditional TACE performs embolization after intra-arterial infusion plus chemotherapy drugs in terms of chemotherapy drug doses (Cui et al., 2012; Kong et al., 2012; Li et al., 2013; Minami et al., 2013; Murata et al., 2013; Wang et al., 2013). It is still controversial with regard to chemotherapy drug doses at present. There is a new method to reduce the variety and doses of chemotherapy drugs, namely small dose of TACE, which includes single-small dose of chemotherapy drugs only through the transarterial embolization and mixed lipiodol emulsion. In addition, gelatin sponge and PVA particles can be replenished if necessary. The previous research studies made by our department revealed that there was no significant difference between small and routine doses of TACE regarding the survival rates, and small dose of TACE had less damage on the liver function and postoperative adverse reactions were less (Hu et al., 2004). Thereby, it is more important to select proper chemotherapy drugs and apply appropriate doses when TACE is used in a small dose. In this study, 173 patients with primary hepatic carcinoma diagnosed by imaging or pathology were randomly divided into two groups, and respectively treated with single LBP and pirarubicin hydrochloride. Except for the used chemotherapy drugs, other therapeutic regimens were the same and the difference had no statistical significance about the patents' general data between two groups. The research results showed that single LBP as the chemotherapy drug was superior to pirarubicin hydrochloride during operation in the aspects of survival time and therapeutic response, with statistical significance, suggesting that single LBP can be as a chemotherapy drug in TACE and has better efficiency in the aspects of mean survival time and therapeutic response, deserving to be popularized in clinic.

The disadvantages of this study lie in shorter follow-up time and deficiency of long-term statistical data. Besides, how to control LBP dose is also worthy of being studied further.

References

Agnello F, Salvaggio G, Cabibbo G, et al (2013). Imaging appearance of treated hepatocellular carcinoma. *World J Hepatol*, **5**, 417-24.

Ali I, Wani WA, Saleem K, et al (2013). Platinum compounds: a hope for future cancer chemotherapy. *Anticancer Agents Med Chem*, **13**, 296-306.

Cescon M, Cucchetti A, Ravaioli M, et al (2013). Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol*, **58**, 609-18.

Cui L, Liu XX, Jiang Y, et al (2012). Comparative study on transcatheter arterial chemoembolization, portal vein embolization and high intensity focused ultrasound sequential therapy for patients. *Asian Pac J Cancer Prev*, **13**, 6257-61.

Deng QQ, Huang XE, Ye LH, et al (2013). Phase II trial of Loubo (R) (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev*, **14**, 413-7.

El-Serag HB, Rudolph KL (2007). Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*, **132**, 2557-76.

Engel JB, Martens T, Hahne JC, et al (2012). Effects of lobaplatin as a single agent and in combination with TRAIL on the growth of triple-negative p53-mutated breast cancers in vitro. *Anticancer Drugs*, **23**, 426-36.

Giunchedi P, Maestri M, Gavini E, et al (2013). Transarterial chemoembolization of hepatocellular carcinoma. Agents and drugs: an overview. Part 1. *Expert Opin Drug Deliv*, **10**, 679-90.

Giunchedi P, Maestri M, Gavini E, et al (2013). Transarterial chemoembolization of hepatocellular carcinoma--agents and drugs: an overview. Part 2. *Expert Opin Drug Deliv*, **10**, 799-810.

Gomes MA, Priolli DG, Tralhao JG, et al (2013). Hepatocellular carcinoma: Epidemiology, biology, diagnosis, and therapies. *Rev Assoc Med Bras*, **59**, 514-24.

Hao YX, Wang JP, Zhao LF (2013). Associations Between Three Common MicroRNA Polymorphisms and Hepatocellular Carcinoma Risk in Chinese. *Asian Pac J Cancer Prev*, **14**, 6601-4.

Hu DY, Li Z, Wang N, et al (2004). Comparative study of low-dosage and routine dosage chemotherapeutic drugs on liver cancer through transcatheter arterial chemoembolization. *J Clin Radiol*, **23**, 502-6.

Huang XE, Wei GL, Huo JG, et al (2013). Intrapleural or intraperitoneal lobaplatin for treatment of patients with malignant pleural effusion or ascites. *Asian Pac J Cancer Prev*, **14**, 2611-4.

Huang ZJ, Zhou MG, Wang LJ (2007). Study on the geographic distribution of liver cancer mortality and HBsAg carrier rate in China. *Disease Surveillance*, **22**, 242-5.

Kong WD, Cao JM, Xu J, et al (2012). Impact of low versus conventional doses of chemotherapy during transcatheter

arterial chemo-embolization on serum fibrosis indicators and survival of liver cancer patients. *Asian Pac J Cancer Prev*, **13**, 4757-61.

Li C, Zhang Y, Zhou J, et al (2013). Therapeutic effect and tolerability of gelatin sponge particle-mediated chemoembolization for colorectal liver metastases: a retrospective study. *World J Surg Oncol*, **11**, 222.

Li KW, Li X, Wen TF, et al (2013). The effect of postoperative TACE on prognosis of HCC: an update. *Hepatogastroenterology*, **60**, 248-51.

Liu D, He C, Wang AZ, et al (2013). Application of liposomal technologies for delivery of platinum analogs in oncology. *Int J Nanomedicine*, **8**, 3309-19.

Mckeage MJ (2001). Lobaplatin: a new antitumour platinum drug. *Expert Opin Investig Drugs*, **10**, 119-28.

Minami Y, Kudo M (2013). Therapeutic response assessment of transcatheter arterial chemoembolization for hepatocellular carcinoma: ultrasonography, CT and MR imaging. *Oncology*, **84**, 58-63.

Murata S, Mine T, Ueda T, et al (2013). Transcatheter arterial chemoembolization based on hepatic hemodynamics for hepatocellular carcinoma. *ScientificWorldJournal,* **2013**, 1-8.

Qian J, Qin SK, Yang AZ, et al (2009). Experimental research about different inhibition of platinum complexes in human hepatocellular carcinoma cell line. *Chin Clin Oncol*, **14**, 414-7.

Shi M, Chen JA, Lin XJ, et al (2009). Prospective Randomized Controlled Study of Transarterial Chemoembolization with Doxorubicin versus Doxorubicin/Lobaplatin/Mitomycin Combination for Unresectable Hepatocellular Carcinoma. *Chin J Clin Oncol*, **36**, 9-13.

Shi M, Lu LG, Fang WQ, et al (2013). Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma: single-blind, randomized trial. *J Natl Cancer Inst*, **105**, 59-68.

Wang Y, Zheng WL, Ma WL (2012). Lobaplatin inhibits the proliferation of hepatollular carcinoma through p53 apoptosis axis. *Hepat Mon*, **12**, e6024.

Wang SY, Zhu WH, Vargulick S, et al (2013). Nausea and vomiting after transcatheter arterial chemoembolization for hepatocellular carcinoma: incidence and risk factor analysis. *Asian Pac J Cancer Prev*, **14**, 5995-6000.

Wu Q, Qin SK, Teng FM, et al (2010). Lobaplatin arrests cell cycle progression in human hepatocellular carcinoma cells. *J Hematol Oncol,* **3**, 43.

Xie CY, Xu YP, Jin W, et al (2012). Antitumor activity of lobaplatin alone or in combination with antitubulin agents in non-small-cell lung cancer. *Anticancer Drugs*, **23**, 698-705.

Yang LQ, Qin SK (2009). Progression of lobaplatin as the third generation platinum drug. *Chin Clin Oncol*, **14**, 1134-9.

Zhou B, Shan H, Zhu KS, et al (2010). Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. *J Vasc Interv Radiol*, **21**, 333-8.