RESEARCH ARTICLE

Impact of Low Versus Conventional Doses of Chemotherapy During Transcatheter Arterial Chemo-embolization on Serum Fibrosis Indicators and Survival of Liver Cancer Patients

Wei-Dong Kong[1], Jian-Ming Cao[1], Jian Xu[1], Bo Chen[1], Tao Yang[1], Tan-Tan Xu[1], Guang-Ming Lu[1], Jun Li[2]*, Xin-En Huang[3]*

Abstract

Objectives: To explore the impact of low- vs conventional-dose chemotherapy via transcatheter arterial chemo-embolization (TACE) on serum fibrosis indicators and treatment efficacy of hepatocellular cancer patients (HCC). Materials and Methods: Patients fulfilling the eligibility criteria were assigned to TACE in Group A (with low-dose chemotherapy) or Group B (conventional-dose chemotherapy). Four serum fibrosis related indicators, hyaluronic acid(HA), human pro-collagen type-III (hPC-III), laminin (LN), and collagen type-IV(IV-C) before TACE were compared with the values 7 days after TACE. The response rate and survival time were also compared between the two groups. Results: Fifty patients with HCC were enrolled in this study, including 25 in Group A and 25 in Group B. No significant differences were detected between the two groups in the four indicators before TACE. After TACE, the value of the four serum indicators increased significantly in Group B. However, no significant differences regarding these four indicators were found in Group A after TACE. Significant differences were demonstrated between the two groups after TACE, but median survival time and 1 or 2 year overall survival rates did not differ (P>0.05). Conclusions: Low-, compared with conventional-dose chemotherapy exerts the same impact on the variation of fibrosis related indicators and has no influence on median survival time and survival rate after TACE in HCC patients.

Keywords: Hepatocellular cancer - transcatheter arterial chemo-embolization - fibrosis indicators

Asian Pacific J Cancer Prev, **13 (9)**, 4757-4761

Introduction

Transcatheter arterial chemoembolization (TACE) is one of the main methods in treating hepatocellular cancer (HCC) (Raoul et al., 2011). Repeated TACE improves the overall survival and the overall response rate of HCC (Artinyan et al., 2008; Toyama et al., 2012). Serum albumin level, Child-Pugh class, tumor number, size, alpha-fetoprotein, alanine aminotransferase, des-gamma carboxy-prothrombin, and gamma-glutamyl transferase are correlated to treatment outcomes (Hakamada et al., 2008; Zhang et al., 2011), but no standardized protocol regarding the selection, dosage, concentration, rate of injection of the chemotherapeutic agent, and optimal retreatment strategy (Paul et al., 2011). Upper gastrointestinal hemorrhage, hepatic failure, atrophy or cirrhosis, pulmonary embolism, and cholecystitis are most common side effects (Li et al., 2012). The number of treatment sessions depends on the response of the tumor and whether serious side effects are seen (Marelli et al, 2007). In recent years, efforts have been directed to improve the delivery system of chemotherapeutic and radiotherapeutic agents to be used in TACE (Hsu et al., 2011; Tam et al., 2011). Drug-eluting beads are designed to localize a drug to the targeted tumor and minimize systemic exposure to the drug, thus decreasing the common postoperative adverse effects associated with chemoembolization with lipiodol. However, one study from a single center showed that lipiodol TACE was not inferior to TACE with drug-eluting beads in terms of response rate and was superior to the latter regarding time to progression. What is more, this study demonstrated that the median overall survival was 46 months for TACE and only 19 months for TACE with drug-eluting beads (Baroni et al., 2010). Other strategy to low the side effects of TACE is to modify the dosage of regimens. We hypothesize that low dose doxorubicin would reduce sides effects and especially the possibility of liver cirrhosis and in the mean time maintain the treatment efficacy. Because little is known how to predict which patients have liver fibrosis or cirrhosis, this study used serum fibrosis markers [hyaluronic acid (HA), human pro-collagen type-III (hPC-III), laminin (LN), collagen type-IV (IV-C)] to demonstrate the impact of chemotherapy on fibrosis.

*[1]Department of Medical Imaging, Jinling Hospital, Clinical School of Medical College, Nanjing University, [2]Department of Oncology, Meishan Hospital Shanhai Meishan CoLtd, [3]Department of Chemotherapy, Jiangsu Cancer Hospital & Research Institute, Nanjing, China *For correspondence: huangxinen06@yahoo.com.cn*

Materials and Methods

Patients eligibility

In this study, all patients shoud be admitted to the hospital and treated from August 2004 to September 2006. Other inclusion criteria were: (1) diagnosed and staged according to the Hepatocellular carcinoma diagnosis standard issued from Guangzhou Conference by Chinese Society of Liver Cancer on 2001; (2) karnofsky performance status of 60 or more; (3) age less than 75 years; (4) adequate hematological (white blood cell count > 3.5×10^9 and platelet count > 80×10^9), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine leval < 1.5 times the upper normal limit); (5) no pre-existing or concomitant malignant neoplasms or pre-operative chemotherapy and radiotherapy. All eligible patients were divide into two groups, group A received low-dose anticancer agents and group B got conventional-dose. All of our patients were first treated with TACE and without surgical operation and signed informed consent before TACE.

Embolism and chemotherapeutic agents

During TACE, a mixture of epirubicin, cisplatin 60 mg, 5-fluorouracil 1g and super emulsified lipiodol (5-15 ml) was infused. Dose of epirubicin administrated to Group A was estimated according to tumor size: 10mg to tumor diameter<5 cm; 20mg to diameter>5 cm. Dose of epirubicin to Group B was set as 50 mg.

TACE and Serological examination

Seldinger technology was used to puncture the femoral artery. TACE procedures were performed under radiographic guidelines following the steps that has been described elsewhere (Li et al., 2012). Venous blood samples of all patients were collected prior to first TACE and 1 week after TACE. Radioimmunoassay was used to examin serum fibrosis index, including HA, PCIII, C-IV and LN. Variation of hepatic function was monitored before and after TACE using serum indicatiors, eg., total bilirubin, albumin and glutamate pyruvate transaminase.

Evaluation of treatment efficacy

Patients take the CT examination 1 month after TACE, and were evaluated the short term effect based on Response criteria for solid tumor. Effectiveness or stabilization ones were proceeded the chemotherapy 2-6 times every 1-3 months, and evaluated the curative effect every time. We use the best curative effect calculate the rate of effectiveness. We observe the survival rate and the median survival time as long-term efficacy. The survival time was defined from final diagnosis to death or lost.

Efficacy endpoints Efficacy variables included response rate was defined according to RECIST criteria (Therasse et al., 2000). If a patient had a CR or PR that occurred before progression, the patient was classified as a responder. Other efficacy analyses included survival.

Safety analyses

Safety parameters included adverse events, serious adverse events, laboratory abnormalities, and deaths. Safety analyses were evaluated for all patients who received at least one TACE procedure. The WHO Toxicity Grading System was used for all adverse events.

Statistical analysis and research experience

Serological testing data were demonstrated as X±s, life span was calculated by month. Chi-square tests were conducted to compare the differences between frequencies, and t test to check the differences between means.The median survival time was estimated by Kaplan-Merier method, and survival rate were compared by Log-rank test. All statistical processing were analysed by SPSS10.0, $P\leq0.05$ was considered statistical significance. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

Treatment of TACE

We recruited 50 eligible hospitalized HCC patients, with 25 patients in group A and 25 in group B. Of all 50 patients, 38 were men and 12 were women, age of patients was arranged from 29 to 72 and the average age was 52.8. Our cases include AFP>400 U/ml pre-TACE 35 cases; merging portal vein tumor thrombus 10 cases; Child-pugh A 37 cases and Child-pugh B 13 cases; Clinical stage 1 period 5 cases, 2 period 38 cases, 3 period 7 cases; Giant mass type 42 cases and Multiple nodular type 8 cases. According to the extent of disease, there were right liver lobe 37 cases ,left liver lobe 5 cases and total liver lobes

Table 1. The Comparison of Clinical Data Between Groups with low- (A) and Conventional-dose (B) Chemotherapy During Transcatheter Arterial Chemo-embolization

		Group A (n=25)	Group B (n=25)
Gender	Man/woman	21/4	17/8
Age,years	range	29-70	33-72
	average age	53.2	55.8
Child-Pugh grading	A/B	18/7	19/6
Clinical stage	I/II/III	2/20/3	3/18/4
AFP	>400U/ml	19	16
	≤400U/ml	6	9
portal vein tumor thrombus	Yes / no	21/4	19/6
Gross tumor classification	Giant mass type/ Multiple nodular type	20/5	22/3

Table 2. Effect on the Changes of Serum Fibrosis Indicators During Transcatheter Arterial Chemo-embolization (TACE) with Low- (A) Versus Conventional-dose (B) of Chemotherapeutic in Patiens with Hepatocellular Cancer

Index (ng/ml)	Group A (n=25)			Group B (N=25)		
	Pre-TACE	Post-TACE	P value	Pre-TACE	Post-TACE	P value
HA	341.4±191.7	351.7±177.2	<0.05	334.7±112.3	414.8±156.4	<0.01
PCIII	240.1±42.5	252.6±68.1	<0.05	258.2±123.1	305.5±145.9	<0.01
LN	135.4±25.7	141.6±16.9	<0.05	137.4±20.6	161.3±29.2	<0.01
C-IV	91.3±18.1	100.2±21.4	<0.05	119.2±21.7	134.6±24.9	<0.01

HA, hyaluronic acid; PCIII, human pro-collagen type-III; LN, laminin; C-IV, collagen type-IV

8 cases. We search the comparability of such two groups though the aspects such as gender, age, AFP, portal vein tumor thrombus, Child-Pugh grading, Gross tumor classification, Clinical stage and so on (Table 1). Through the chi-square tests and t test, this two groups of data has no statistical difference excluded gender (P>0.05). The dose of epirubicin used in Group A was 10 mg 10 cases, 20mg 15 cases, and the dose of super emulsified Lipiodol were 5-12 ml with average number as 8.5 ml. While in Group B, the dose of epirubicin was 50 ml and super emulsified Lipiodol was 5-15ml with average number as 9.0ml. All 50 cases with lipiodol deposition good in tumor post-PACE, and the visualization shows most of the cases reach complete embolism on Radiographic standards except a few cases having tumor stain residue (5 in 25 of Group A and 6 in 25 of Group B). The number of TACE was 3-6 in Group A and 3-7 in Group B. Neither of the group had took a second surgery post-TACE.

Liver function tests

Each liver function index of both groups pre-TACE was in the normal range, while it rose up 17 in 25 cases and down to the normal level 8 cases in Group A one week after TACE. In Group B the transaminase of all 25 cases rose 1-5 times post-TACE.

Liver fibrosis index

The serum fibrosis indicators before and after the TACE of patients in both groups had been described particularly in Table 2. The index pre-TACE in both groups have no significant difference (P>0.05). No significant difference were found from cases in Group A either pre-TACE or post-TACE (P>0.05), while the index rose obviously in Group B (P<0.05). Compared the difference before and after TACE of each index, there were significant differences (P<0.01). While the compare of two groups post-TACE shows all index in Group B were higher than which in Group A.

Short term effect

Evaluation of curative effect have been made in all 50 cases. The recent curative effect was as follows: CR 3 cases, PR 8 cases, SD 16 cases, PD 1 case in Group A and CR 1 case, PR 7 cases, SD 10 cases, PD 6 cases in Group B.

The follow-up results and Long-term evaluation

During the follow-up, 1 in 50 cases was lost(lost rate was 2%). The last follow-up was in October 30, 2006 and the follow-up time was 8 to 32 months. At the last follow-up, survival 16 in 25 cases and death 9 in 25 cases in Group A while survival 13 in 25 cases, death 11 in 25 cases and loss 1 in 25 cases in Group B. Cases in Group A had the survival period of 10-31 months, with a 19.2 days mid-survival rate ,had TTP of 9.5 months and survival rates of 1-, 2-years were 60.9%, 40.1%, whereas in Group B the survival time was 8-28mo, the media time was 18.5 months, the TTP was 9.1 months and the 1-, 2-years survival rates were 58.8%, 39.5%. There was no remarkable difference between two groups (P>0.05).

Discussion

The difference between TAE and TACE is focused on the argument over the rationale of chemotherapeutic agents injected into the blood vessels (Marelli et al., 2007; Miraglia et al., 2007; Pleguezuelo et al., 2008). Those who support TACE suggested that TACE appears to be superior to TAE (Artinyan et al., 2008). TACE derives its anti-tumor effect by two methods. Firstly, chemotherapy allows a higher dose of chemotherapeutic agents to the tissue while systemic exposure is less extensively increased. Thus, the cytotoxic effect on tumor cells is enhanced and systemic side effects are mild. In the mean time, arterial embolization interrupts blood supply of tumors that are mostly supplied by the hepatic artery, and postpones tumor growth. This effect will be potentiated because chemotherapeutic drug will not washed out from tumor bed after embolization (Miraglia et al., 2007). Secondly, during TACE, embolotherapy and regional chemotherapy are synergic since tumor ischemia caused by embolization increases drug concentration compared to sole infusion and prolongs retention of chemotherapeutic drugs, and with repeated TACE, survival time for a patient with unresectable HCC could be rationally extended for 1 to 2 years (Huang et al., 1999). However, the best regimen and best dosage of chemotherapy is not established. In some study, adriamycine was administrated in 50mg but in others in 25 mg (Choi, 2009; Britten, 2012). No comparison regarding treatment efficacy and side effects was conducted between low- and conventional doses. Our study shows: compared with conventional-dose of chemotherapeutic agent, the value of serum fibrosis indicators measured shortly after TACE in low-dose chemotherapeutic agent group did not increase significantly. This could be interpreted as a result that risk of liver fibrosis is decreased. Liver fibrosis implys the ultra-precipitation of hepatic extracellular matrix

especially collagen, which is a repair response of injury in liver parenchyma. Now some indicators were considered to have diagnostic significance in detecting liver cirrhosis, including HA, LN, PCIII and C-IV (Collazos et al., 1993; Resino et al., 2010). As HCC mostly occurred during hepatic cirrhosis in China, the extent of hepatic cirrhosis in a clinical setting will greatly influence curative effect, complication and prognosis of treatment for HCC patients. We found in this study: if serum fibrosis indicators elevated markedly after first TACE, it suggests that chronic liver injury may occur, and will aggravate liver cirrhosis; if chronic liver injury has not been well treated, liver cirrhosis may further deteriorate. In Conclusions, low-, compared with conventional-dose chemotherapy impose same impact on the variation of fibrosis related indicators and has no influence on median survival time and survival rate after TACE in HCC patients, suggesting low dose TACE in treating HCC in China is a proper choice, but this conclusion needs to be verified by large scale randozimed clinical trials.

Acknowledgements

Dr. Xin-En Huang is supported in part by a grant from Jiangsu Provincial Administrtion of Traditional Chinese Medicine (LZ11091), and in part from a special research fund of Organization Department of Jiangsu Provincial Party Committee,Talent Work Leading Group of Jiangsu Province (333 High-level Personnel Training Project).

References

Artinyan A, Nelson R, Soriano P, et al (2008). Treatment response to transcatheter arterial embolization and chemoembolization in primary and metastatic tumors of the liver. *HPB (Oxford)*, 10, 396-404.

Britten CD, Gomes AS, Wainberg ZA, et al (2012). Transarterial chemoembolization plus or minus intravenous bevacizumab in the treatment of hepatocellular cancer: a pilot study. *BMC Cancer*, **12**, 16.

Choi SB, Kim KS, Park YN, et al (2009). The efficacy of hepatic resection after neoadjuvant transarterial chemoembolization (TACE) and radiation therapy in hepatocellular carcinoma greater than 5 cm in size. *J Korean Med Sci*, **24**, 242-7.

Collazos J, Díaz F, Genollá J (1993). Serum concentrations of laminin in cirrhosis of the liver. *Gut*, **34**, 974-6.

Gao LL, Huang XE, Zhang Q, et al (2011). 14.A Cisplatin and vinorelbine (NP) regimen as a postoperative adjuvant chemotherapy for completely resected breast cancers in China: final results of a phase II clinical trial. *Asian Pac J Cancer Prev*, **12**, 77-80.

Gong P, Huang XE, Chen CY, et al (2012). Comparison on complications of peripherally inserted central catheters by ultrasound guide or conventional method in cancer patients. *Asian Pac J Cancer Prev*, **13**, 1873-5.

Hakamada K, Kimura N, Miura T, et al (2008). Des-gamma-carboxy prothrombin as an important prognostic indicator in patients with small hepatocellular carcinoma. *World J Gastroenterol*, **14**, 1370-7.

Huang YH, Wu JC, Chau GY, et al (1999). Supportive treatment, resection and transcatheter arterial chemoembolization in resectable hepatocellular carcinoma: an analysis of survival in 419 patients. *Eur J Gastroenterol Hepatol*, **11**, 315-21.

Huang XE, Li CG, Li Y, et al (2011). Weekly TP regimen as a postoperative adjuvant chemotherapy for completely resected breast cancer in China: final result of a phase II trial. *Asian Pac J Cancer Prev*, **12**, 2797-800.

Jiang Y, Huang XE, Yan PW, et al (2010). Validation of Treatment Efficacy of a Computer-assisted Program for Breast Cancer Patients receiving Postoperative Adjuvant Chemotherapy. Asian Pacific J Cancer Prev, 11, 1059-62.

Li CG, Huang XE, Li Y, et al (2011). Phase II trial of irinotecan plus nedaplatin (INP) in treating patients with extensive stage small cell lung cancer. *Asian Pacific J Cancer Prev*, **12**, 487-90.

Li CG, Huang XE, Li Y, et al (2011). Clinical observations on safety and efficacy of OxyContin® administered by rectal route in treating cancer related pain. *Asian Pac J Cancer Prev*, **12**, 2477-8.

Li CG, Huang XE, Xu L, et al (2012). Clinical application of serum tumor associated material (TAM) from non-small cell lung cancer patients. *Asian Pac J Cancer Prev*, **13**, 301-4.

Li H, Hu Y, Li N, Zhou Y (2012). Liver fibrosis and five year survival of hepatocellular cancer cases undergoing transcatheter arterial chemo embolization using small doses. *Asian Pac J Cancer Prev*, **13**, 1589-93.

Li Y, Yan PW, Huang XE, et al (2011). MDR1 gene C3435T polymorphism is associated with clinical outcomes in gastric cancer patients treated with postoperative adjuvant chemotherapy. *Asian Pac J Cancer Prev*, **12**, 2405-9.

Liu W, Li SY, Huang XE, et al (2012). Inhibition of tumor growth in vitro by a combination of extracts from rosa roxburghii tratt and fagopyrum cymosum. *Asian Pac J Cancer Prev,* **13**, 2409-14.

Malenstein H, Maleux G, Vandecaveye V, et al (2011). A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. *Onkologie*, **34**, 368-76.

Marelli L, Stigliano R, Triantos C, et al (2007). Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol*, **30**, 6-25.

Miraglia R, Pietrosi G, Maruzzelli L, et al (2007). Efficacy of transcatheter embolization/chemoembolization (TAE/TACE) for the treatment of single hepatocellular carcinoma. *World J Gastroenterol,* **13**, 2952-5.

Paul B, Gamanagatti S, Sreenivas V, et al (2011). Trans-arterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma: experience from a Tertiary Care Centre in India. *Indian J Radiol Imaging*, 21, 113-20.

Pleguezuelo M, Marelli L, Misseri M, et al (2008). TACE versus TAE as therapy for hepatocellular carcinoma. *Expert Rev Anticancer Ther*, **8**, 1623-41.

Raoul JL, Sangro B. Forner A, et al (2011). Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev*, **37**, 212-20.

Resino S, Bellón JM, Asensio C (2010). Can serum hyaluronic acid replace simple non-invasive indexes to predict liver fibrosis in HIV/Hepatitis C coinfected patients? *BMC Infect Dis*, **10**, 244.

Scartozzi M, Baroni GS, Faloppi L, et al (2010). Trans-arterial chemo-embolization (TACE), with either lipiodol (traditional TACE) or drug-eluting microspheres (precision TACE, pTACE) in the treatment of hepatocellular carcinoma: efficacy and safety results from a large mono-institutional analysis. *J Exp Clin Cancer Res*, **29**, article 164.

Shu J, Li CG, Liu YC, et al (2012).Comparison of Serum Tumor Associated Material (TAM) with Conventional Biomarkers

in Cancer Patients. *Asian Pac J Cancer Prev*, **13**, 2399-403.
Tam KY, Leung KC, Wang YX, et al (2011). Chemoembolization agents for cancer treatment. *Eur J Pharm Sci*, **44**, 1-10.
Therasse P, Arbuck SG, Eisenhauer EA, et al (2000). New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*, **92**, 205-16.
Toyama T, Nitta N, Ohta S, et al (2012). Clinical trial of cisplatin-conjugated gelatin microspheres for patients with hepatocellular carcinoma. *Jap J Radiol*, **30**, 62-8.
Xu JW, Li CG, Huang XE, et al (2011). Ubenimex capsule improves general performance and chemotherapy related toxicity in advanced gastric cancer cases. *Asian Pac J Cancer Prev*, **12**, 985-7.
Xu HX, Huang XE, Li Y, et al (2011). A clinical study on safety and efficacy of Aidi injection combined with chemotherapy. *Asian Pac J Cancer Prev*, **12**, 2233-6.
Xu HX, Huang XE, Qian ZY, et al (2011). Clinical observation of Endostar® combined with chemotherapy in advanced colorectal cancer patients. *Asian Pac J Cancer Prev*, **12**, 3087-90.
Xu T, Xu ZC, Zou Q, Yu B, Huang XE (2012). P53 Arg72Pro polymorphism and bladder cancer risk--meta-analysis evidence for a link in Asians but not Caucasians. *Asian Pac J Cancer Prev*, **13**, 2349-54.
Yan PW, Huang XE, Jiang Y, et al (2010). A clinical comparison on safety and efficacy of Paclitaxel/Epirubicin (NE) with Fluorouracil/Epirubicin/Cyclophosphamide (FEC) as postoperative adjuvant chemotherapy in breast cancer. *Asian Pac J Cancer Prev*, **11**, 1115-8.
Yan PW, Huang XE, Yan F, et al (2011). Influence of MDR1 gene codon 3435 polymorphisms on outcome of platinum-based chemotherapy for advanced non small cell lung cancer. *Asian Pac J Cancer Prev*, **12**, 2291-4.
Yu DS, Huang XE, Zhou JN, et al (2012). A Comparative Study on the Value of Anal Preserving Surgery for Aged People with Low Rectal Carcinoma in Jiangsu, China. *Asian Pac J Cancer Prev*, **13**, 2339-40.
Zhang LQ, Huang XE, Wang J, (2011). The cyclin D1 G870A polymorphism and colorectal cancer susceptibility: a meta-analysis of 20 populations. Asian Pac J Cancer Prev,12(1):81-5.
Zhang XZ, Huang XE, Xu YL, et al (2012). A Phase II Study on Voriconazole in Treating Chinese Patients with Malignant Hematological Disorder and Invasive Aspergillosis. *Asian Pacific J Cancer Prev*, **13**, 2415-8.
Zhou JN, Huang XE, Ye Z, et al (2009). Weekly paclitaxel/ Docetaxel combined with a paltinum in the treatment of advanced non-samll cell lung cancer: a study on efficacy, safety and pre-medication. *Asian Pac J Cancer Prev*, **10**, 1147-50.