Hepatitis Monthly 2009; 9(4): 253-260

ORIGINAL ARTICLE

Comparison of Intra-Arterial Chemotherapy with Gemcitabine or Floxuridine Followed by TACE with Oxaliplatine

Hao Ming-Zhi [1], Chen Qiang [2]*, Lin Hai-Lan [1], Wu Hui [2], Chen Qi-Zhong [1], Li Jian-Cheng [3], Zheng Jian-Xiong [1], Ye Yun-Bin [2]

[1] Department of Interventional Radiology, Fujian Provincial Tumor Hospital, Fuzhou 350014, Fujian, P. R. China
[2] Department of Medical Oncology, Fujian Provincial Tumor Hospital, Fuzhou 350014, Fujian, P. R. China
[3] Department of Radiation Oncology, Fujian Provincial Tumor Hospital, Fuzhou 350014, Fujian, P. R. China

Background and Aims: **To investigate the efficacy and safety of a gemcitabine plus oxaliplatin combination regimen and a floxuridine plus oxaliplatin combination regimen used in transcatheter arterial chemoembolization for patients with inoperable hepatocellular carcinoma (HCC).**

Methods: **From October 2005 to October 2008, 122 chemonaïve patients with newly diagnosed, inoperable HCC were randomized into a gemcitabine plus oxaliplatin combination regimen group (GO group) or a floxuridine plus oxaliplatin combination regimen group (FO group). The GO group was treated with 1,600 mg of gemcitabine and 200 mg of oxaliplatin, and the FO group was treated with 1,000 mg of floxuridine and 200 mg of oxaliplatin. Both groups were treated with glutin and iodolipol as the embolic agent in the transcatheter arterial chemoembolization (TACE).**

Results: **The progression-free survival, the median survival period, and the median time to progress had no significant difference between the two groups. However, there was a significant difference in the incidence of grade 3/4 thrombocytopenia between the two groups (P = 0.002). Grade 3/4 hematologic toxicity was observed only in the GO group. One patient (1.7%) with grade 3/4 leukopenia and 6 patients (10%) with grade 3/4 thrombocytopenia were observed. A multivariate analysis revealed that the Eastern Cooperative Oncology Group (ECOG) scores and portal vein thrombosis were the only independent prognostic factors that affected progression-free survival.**

Conclusions: **The floxuridine plus oxaliplatin combination regimen was tolerated better than the gemcitabine plus oxaliplatin combination regimen used in TACE.**

Keywords: **Hepatocellular Carcinoma, Transcatheter Arterial Chemoembolization, Gemcitabine, Floxuridine, Oxaliplatin, Oxaliplatin Lipiodol Emulsion**

Trial Registration No.: **ChiCTR-TRC-00000345**

Introduction

Hepatocellular carcinoma (HCC) is the fifth-most common cancer in the world, with more than 80% of cases occurring in Asia [(1)]. The most common causes of HCC are hepatitis B and C viral infections. Chronic hepatitis B viral infection is prevalent in Asian countries and accounts for most cases of HCC. In contrast, chronic hepatitis C viral infection is more common in Western countries. Surgical resection is the main curative treatment. Unfortunately, only around 20% of patients, mostly diagnosed by regular screening, may benefit from

**** Correspondence:***
Chen Qiang, M.D.
Department of Medical Oncology, Fujian Provincial Tumor Hospital, No. 91, Fengban maluding, Fuma Road, Fuzhou 350014, Fujian Province, P. R. China.

Tel/Fax: *+86 0591 8366 0063*

E-mail: *cqiang8@pub5.fz.fj.cn*

Received: *30 Jul 2009* ***Revised:*** *10 Oct 2009*
Accepted: *12 Oct 2009*

Hepat Mon 2009; 9 (4): 253-260

surgical therapy. The prognosis still remains poor because of the advanced stage of cancer and associated hepatic impairment at diagnosis and because of the high intrahepatic recurrence rate, 79%–80%, 5 years after hepatic surgery [2], resulting from either intrahepatic metastases from the primary tumor or multicentric occurrence.

Transcatheter arterial embolization has been applied to most inoperable HCC since 1974 using gelatin sponge particles and anticancer agents. In the mid-1990s lipiodol was introduced to enhance the therapeutic effect [3-5]. Transcatheter arterial chemoembolization (TACE), which has shown a survival benefit, is now the treatment of choice for inoperable HCC [6, 7].

There is no standard chemotherapy regimen used in TACE because there are few agents effective in the treatment of HCC. A phase-II study of gemcitabine plus oxaliplatin in advanced HCC showed that 4 objective responses were observed in 26 patients, one leading to a surgical resection of the tumor [8]. Another phase-II study showed the clinical activity of gemcitabine alone and of the 5-fluorouracil/oxaliplatin combination in patients with HCC [9, 10]. Some clinical studies have shown that intra-arterial administration of gemcitabine in pancreatic cancer has a major advantage related to reduced toxicity because increasing the dose through this administration route will eventually result in pancreatic cellular drug target delivery prior to systemic availability [11-13]. The clinical results encouraged us to investigate whether this approach benefits HCC patients. We found that oxaliplatin had good stability of physical and chemical properties in oxaliplatin lipiodol emulsion by high-performance liquid chromatography. This background led us to conduct the current study to evaluate the efficacy and safety of intra-arterial chemotherapy with gemcitabine or floxuridine followed by TACE with oxaliplatin for patients with inoperable HCC.

Materials and Methods

Selection of Patient

From October 2005 to October 2008, 122 chemonaïve (no intra-arterial or systemic chemotherapy) male and female patients over 18 years of age with inoperable HCC were considered for recruitment to the study. All patients were admitted to our hospital. The diagnosing criteria of HCC was made according to the Diagnosing and Staging National Standards of China (2001) for HCC [14]. The criteria for inclusion and exclusion of patients is shown in Table 1.

Randomization

Randomization to either the TACE with gemcitabine plus oxaliplatin combination group (GO group) or the TACE with floxuridine plus oxaliplatin combination group (FO group) was performed without stratification by drawing consecutively numbered sealed envelopes. The protocol was approved by the ethics committee of

Table 1. Criteria for inclusion and exclusion of patients.

Inclusion criteria	Exclusion criteria
• Men and women >18 years of age	• Prior systemic anticancer therapy or local tumor therapy (PEI, cryotherapy, RFA, TACE, etc.)
• HCC diagnosed by high serum alpha-fetoprotein (AFP ≥ 400 ng/ml) with typical imaging findings, or needle liver biopsy when AFP < 400ng/ml	• Significant cardiovascular disease such as myocardial infarction < 6 months previously, chronic heart failure or unstable coronary artery disease
• Impossible to resect	• Infiltrative or diffuse HCC
• Total bilirubin < 3 × upper limit of normal	• Patients with other malignant tumor within the past 5 years prior to treatment
• Child-Pugh stage A or B	• Pregnant or breastfeeding patients
• No intra-arterial or systemic chemotherapy	• Patients with uncontrolled infections or HIV seropositive patients
• INR/PTT < 1.5 × upper limit of normal	• Prior organ transplant
• Written informed consent	• Patients with hemorrhage/bleeding event
• No extrahepatic metastasis	• Mental conditions rendering the patient incapable to understand the nature, scope, and consequences of the study
• Tumor-to-liver volume ratio(TTLVR)<70%	

Fujian Provincial Tumor Hospital. Written informed consent was obtained.

Treatment procedure

The two groups received TACE according to a standard protocol. Patients had fasted 8 hours before TACE. Intravenous triopisetron (5 mg) was given before the procedure. The femoral artery was catheterized under local anesthesia. Hepatic arteriography and superior mesenteric arterial portovenography were performed to define the sizes and locations of tumor nodules and to identify occlusion of the main portal vein. The right or left hepatic artery feeding the tumor was superselectively catheterized. Using the pumping method, the emulsion of anticancer agent and lipiodol was prepared by mixing oxaliplatin with lipiodol in a ratio of 100 mg to 10 ml. Various amounts of the emulsion, up to a maximum of 40 mL of lipiodol (containing 200 mg of oxaliplatin) were injected slowly under fluoroscopic monitoring according to the size of the tumor and the arterial blood flow. The aim was to deliver a sufficient amount of the emulsion to the tumor areas without retrograde flow. If the tumor involved both lobes of the liver, or if superselective catheterization was not possible, the emulsion was injected into the proper hepatic artery distal to the origin of the gastroduodenal artery. Floxuridine (1,000 mg) in the FO group and gemcitabine (1,600 mg) in the GO group were injected into the common hepatic artery before lipiodol embolization. If possible, remanent oxaliplatin were injected into the common heptic artery after lipiodol embolization. This was followed by embolization with small gelatin-sponge pellets 1 mm in diameter. Chemoembolization was repeated in 30 to 45 days and was withheld or discontinued whenever vascular contraindications, poor hepatic function, severe adverse effects, or progressive disease developed with a diffuse growth pattern.

Assessment of outcome

The primary end points for this study were progression-free survival (PFS), defined as the interval from the onset of treatment to death or disease progression, and the time to progress (TTP), defined as the interval from the onset of treatment to disease progression. The secondary end points included overall survival (OS), hematological toxicity, neurotoxicity, and liver function. The patients were followed monthly at the outpatient clinic. Follow-up assessments included serum biochemistry, serum alpha-fetoprotein (AFP) level, and CT or MRI and were repeated every month in the first trimester, then every three months. Hematological toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 3.0) [15]. Neurotoxicity was assessed by Levi's grading standards. Follow-up was continued through January 15, 2009. All patient deaths were the end point irrespective of the cause of death. TACE-related death was designated as death within 30 days after the initial therapy.

Statistical Analysis

Comparison between the two groups was made on an intention-to-treat basis. The frequency of each variable was analyzed by the chi-squared test, and comparisons between group means were performed using Student's *t* tests. Univariate analysis for baseline variables to identify predictors of survival was performed by estimating the survival rate according to the Kaplan-Meier method and compared with the use of a log-rank test. The survival curves of the two groups were then compared with stratification according to statistically significant prognostic factors. Finally, all of the significant prognostic factors identified from the univariate analysis were put into a Cox proportional hazards model for multivariate analysis. The level of significance was set at $P < 0.05$. The statistical analysis was performed with the SPSS 13.0 computer software program.

Results

Patient characteristics

From October 2005 to October 2008, 122 chemonaïve patients with newly diagnosed, inoperable HCC were randomized into the GO and FO groups. One hundred and thirteen patients (92.6%) had positive serology test results for hepatitis B surface antigen. Multiple tumors were present in 49 patients (40.2%), and 31 patients (25.4%) had portal vein thrombosis. Baseline characteristics were well balanced between the two groups (Table 2).

Progression-free survival

The PFS rates at 6 months, 1 year, and 2 years were 43.3%, 21.1%, and 11.5%, respectively, in the GO group, and 61.3%, 26.1%, and 11.6%, respectively, in the FO group. The median TTP was 6 months (95% confidence interval [CI], 4.9-7.1 months) in the GO group and 8 months (95% CI, 6.6-9.4 months) in the FO group ($P = 0.321$; Fig. 1).

By univariate analysis, Eastern Cooperative Oncology Group (ECOG) scores, portal vein thrombosis, and Cancer of the Liver Italian Program (CLIP) scores were associated with PFS. Additionally, the multivariate Cox's proportional hazard analysis

Table 2. Baseline characteristics of the study patients.

	GO group (n = 60)	FO group (n = 62)	P
Age (years) *	51.61±1.156	51.80±1.279	0.368
Sex (male/female)	56/4	53/9	0.241
Serum hepatitis B surface antigen (positive/negative)	56/4	57/5	1.000
Serum AFP (ng/mL) <20 21-400 ≥400	 12 11 37	 18 10 34	0.511
Child-Pugh Classification (A/B)	56/4	55/7	0.530
Portal vein thrombosis (positive/negative)	17/43	14/48	0.466
Number of tumors 1 ≥2	 34 26	 39 23	0.482
CLIP score 0-1 2-3 ≥4	 9 44 7	 18 33 11	0.066
ECOG performance status rating (0/1/2)	9/45/6	12/43/7	0.772
BCLC staging (stage B/ stage C)	43/17	48/14	0.466
Times of TACE(1/2/≥3)	22/4/34	28/5/29	0.290

AFP: alpha-fetoprotein; CLIP: Cancer of the Liver Italian Program; ECOG: The Eastern Cooperative Oncology Group; BCLC: Barcelona Clinic Liver Cancer staging. *Values are means with standard error.

Table 3. Multivariate prognostic analysis for PFS of patients with hepatocellular carcinoma after TACE.

	B	SE	Wald	Sig.	Exp(B)
ECOG scores	1.014	0.187	29.306	0.001	2.757
portal vein thrombosis	0.476	0.224	4.525	0.033	1.610
CLIP scores	0.084	0.091	0.846	0.358	1.087

Table 4. Comparison of TTP between the GO and FO groups stratified by ECOG scores and portal vein thrombosis.

	GO group	FO group	P
Portal vein thrombosis			
positive	5 (1.509)	6 (2.806)	0.643
negative	6 (1.363)	9 (0.35)	0.396
ECOG scores			
0	15(2.337)	9 (3.868)	0.222
1	6(0.469)	8(0.327)	0.084
2	1.3(0.204)	2.7(0.914)	0.104

Values are median TTP in months with standard errors in parentheses.

demonstrated that ECOG scores and portal vein thrombosis were the independent prognostic factors that affected PFS. Higher ECOG scores and portal vein thrombosis were associated with worse outcomes of shorter PFS. The multivariate prognostic analysis of patients with hepatocellular carcinoma after TACE

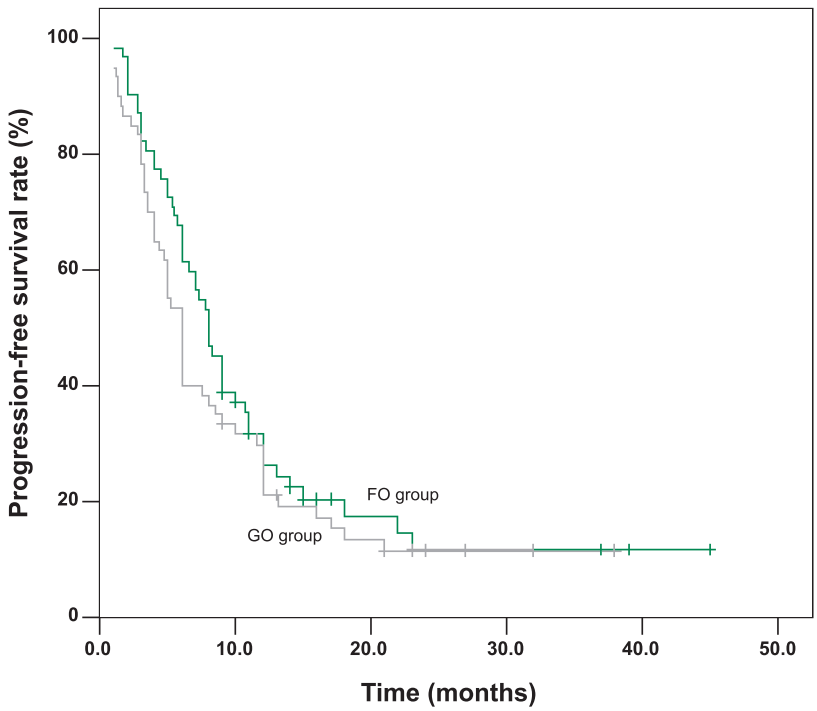

Figure 1. Progression-free survival in patients of the GO and FO groups (log-rank test, P = 0.321).

is presented in Table 3.

A comparison of TTP between the two groups, stratified according to each of the independent prognostic factors, revealed that the TTP of all patients treated with TACE did not differ significantly by any subgroup (Table 4).

Overall survival

One hundred and twenty-two patients treated with TACE received a total of 276 courses of chemoembolization, with each patient receiving a median of 2 courses (range 1-5). The median survival period was 15 months (95% CI, 11.6-18.4 months) for all patients. Two patients in the GO group were lost and could not be contacted after a follow-up of 6 months and 32 months. At the time of the final analysis, 36 patients from the GO group and 33 patients from the FO group had died. The main causes of death were tumor progression (31 in the GO group and 32 in the FO group), hepatic failure (3 in the GO group and 1 in the FO group), and gastrointestinal bleeding (2 in the GO group). TACE related death was not found in all patients. There was no significant difference between the GO group and the FO group in OS. The estimated 6-month, 1-year, and 2-year survival rates were 81.7%, 49.1%, and 32.5%, respectively, in the GO group, and 85.5%, 59.1%, and 38.8%, respectively, in the FO group. The median survival period was 12 months (95% CI, 8.2-15.8 months) for the GO group and 19 months (95% CI, 13.2-24.8 months) for the FO group (P = 0.421) (Fig. 2).

Table 5. Comparison of liver function as assessed by serum ALB, TBIL, AST, and ALT.

	GO group	FO group	P
ALB			
3 days pre-TACE	34.986(0.427)	34.164(0.539)	0.228
7 days post-TACE	29.656(0.448)	29.458(0.480)	0.763
TBIL			
3 days pre-TACE	21.999(1.475)	19.517(0.906)	0.166
7 days post-TACE	31.172(5.497)	26.101(1.850)	0.407
ALT			
3 days pre-TACE	54.87(3.437)	62.68(6.056)	0.247
7 days post-TACE	115.47(12.299)	94.55(9.943)	0.198
AST			
3 days pre-TACE	66.84(4.190)	76.48(6.945)	0.222
7 days post-TACE	82.72(5.777)	110.75(16.841)	0.097

Values are means, with standard errors in parentheses.
ALB: albumin; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

By univariate analysis, ECOG scores, CLIP scores, Child-Pugh classification, portal vein thrombosis, and times of TACE were associated with survival. In addition, the multivariate Cox's proportional hazard analysis demonstrated that ECOG scores

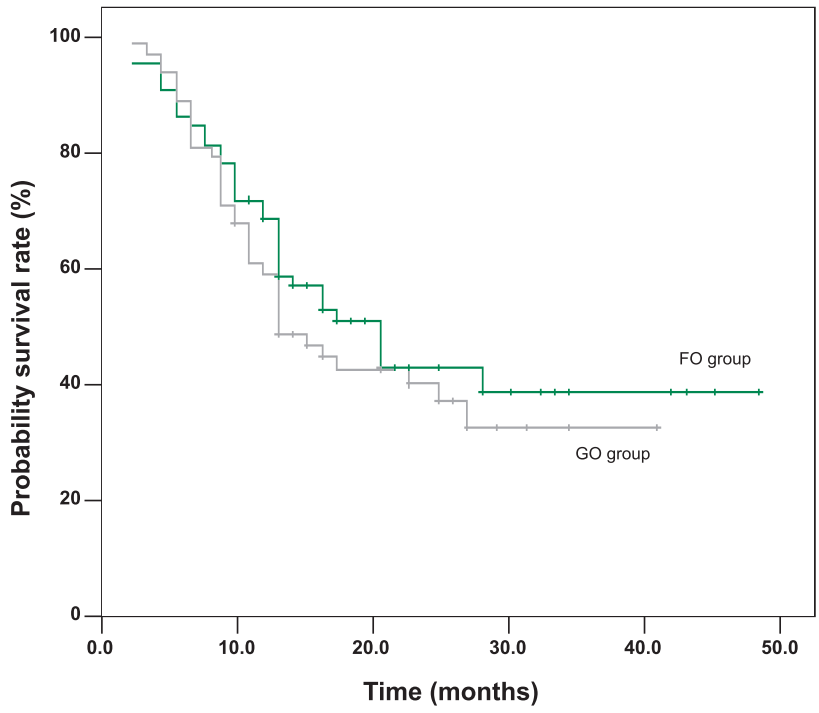

Figure 2. Probability of survival in patients of the GO group and patients of the FO group (log-rank test, P=0.421).

and times of TACE were the only independent prognostic factors that affected survival (P = 0.000, P = 0.000).

Safety

There was no significant difference in the liver function between the two groups as assessed by serum albumin (ALB) levels, serum total bilirubin (TBIL) levels, serum aspartate aminotransferase (AST) levels, or serum alanine aminotransferase (ALT) levels in the three days before the first TACE and seven days after the first TACE (Table 5). Grade 3/4 hematologic toxicity was observed only in the GO group. One patient (1.7%) with grade 3/4 leukopenia and 6 patients (10%) with grade 3/4 thrombocytopenia were in the GO group. There was a significant difference in the incidence of grade 3/4 thrombocytopenia between the two groups (P = 0.002). No grade 3/4 neurotoxicity was noted. Three patients (5%) with grade 1/2 neurotoxicity were in the GO group, and 2 patients (3.2%) with grade 1/2 neurotoxicity were in the FO group (Fisher's exact test, P = 0.677).

Discussion

Hepatocellular carcinoma is a common malignant tumor in Asia. Hepatic resection offers a chance of cure for a minor proportion of patients with early tumor detection and preserved liver functions. Because of the shortage of organ donors, the role of liver transplantation in treatment remains limited. The majority of the patients with unresectable hepatocellular carcinoma are treated by various palliative therapies. TACE is the most common treatment for inoperable HCC that cannot be treated with percutaneous interventions, with proven improvement on survival in selected patients with well-preserved liver function [7, 16]. The rationale for TACE is the almost complete arterial blood supply of the tumor compared to normal liver parenchyma, where the arterial flow is only 25% and the portal flow is responsible for the 75% of the inflow [17]. The goal of TACE is to deliver a high dose of chemotherapeutic drug and embolizing agent to the HCC, which will cause tumor necrosis and tumor control, and preserve as much normal liver parenchyma as possible. Although many chemotherapy agents (cisplatin, mitomycin,doxorubicin, floxuridine, *etc.*) have been used in TACE, there is no standard chemotherapy regimen because few cytotoxic chemotherapy agents are effective in the treatment of HCC. Thus, new active and well-tolerated chemotherapy regimens for TACE are urgently required to improve the survival rates of patients with unresectable HCC. Phase-II studies of new cytotoxic agents, such as irinotecan, topotecan, paclitaxel, and raltitrexed, have yielded disappointing results [18-21]. A phase-II study showed the clinical activity of gemcitabine alone and of the 5-fluorouracil/oxaliplatin combination in patients with HCC [9, 10]. A phase-II study of gemcitabine plus oxaliplatin in advanced HCC patients produced 4 objective responses in 26 patients, one leading to a surgical resection of the tumor [8]. This background led us to conduct the current study to evaluate the efficacy of gemcitabine/oxaliplatin and floxuridine/oxaliplatin combination chemotherapy regimens in TACE.

In an Asian trial with cisplatin used in TACE, the estimated 1-year and 2-year survival rates were 57% and 31%, respectively [7]. Another Asian trial, which was conducted to evaluate retrospectively the effects of three kinds of regimens (doxorubicin and mitomycin C, cisplatin and mitomycin C, and cisplatin and pirarubicin) used in TACE in patients with unresectable HCC, showed no significant differences in survival among the three groups [22]. In our study, the estimated 1-year and 2-year survival rates were 49.1% and 32.5%, respectively, in the GO group, and 59.1% and 38.8%, respectively, in the FO group. No significant difference was observed between the two groups in terms of baseline characteristics; the median TTP, PFS rate, and OS rate were the same in the two groups. A comparison of TTP between the two groups, stratified by portal vein thrombosis and ECOG scores, showed no significant difference. Liver toxicity was difficult to assess because many patients presented with impaired liver function at baseline. Thus, it was difficult to differentiate the etiologies of elevated transaminases due to the toxicity of chemotherapy, postembolization syndrome following TACE, or disease progression. A comparison of liver function as assessed by serum ALB, serum TBIL, serum AST, and serum ALT, which were tested three days before the first TACE and seven days after the first TACE, showed no significant differences between the two groups. The outcome of OS in this study is similar to the results of similar study in Asia.

In the current study, grade 3/4 hematologic toxicity was only observed in the GO group; one patient (1.7%) had grade 3/4 leukopenia, and 6 patients (10%) had grade 3/4 thrombocytopenia. Our data on grade 3/4 thrombocytopenia are similar to data reported in a phase-II study of gemcitabine treatment of patients with advanced hepatocellular carcinoma [10]. Hematologic toxicity was more serious in the GO group than in the FO group.

The prognosis of HCC is correlated with factors

related to the extent of the tumor and with hepatic function [23, 24]. In our study, the prognostic factors related to PFS were ECOG scores, portal vein thrombosis, and CLIP scores. A multivariate analysis revealed that the difference in the ECOG scores and portal vein thrombosis were statistically significant. ECOG scores and times of TACE were the independent prognostic factors that affected overall survival.

In our study, among 122 patients, 31 patients had portal vein thrombosis. That means that 25% of the patients had no indication of chemoembolization according to Barcelona Clinic Liver Cancer (BCLC) staging. However, according to the Guidelines of Diagnosis and Treatment of Primary Liver Cancer (2009) by the Chinese Society of Liver Cancer, portal vein thrombosis, not portal trunk thrombosis, is considered an indication for chemoembolization. In our study, the TTPs of patients with portal vein thrombosis (BCLC stage C) were 5 months in the GO group and 6 months in the FO group. The TTPs of patients in Sorafenib 11849 Trial, which was implemented in Asians, were 84 days in the sorafenib group and 41.5 days in the placebo group. The TTP results in our study are better than those of Sorafenib 11849 Trial [25].

Although we found the median TTP, overall survival did not differ significantly between the two groups. The floxuridine plus oxaliplatin combination regimen showed better tolerability. ECOG scores and portal vein thrombosis were the only independent prognostic factors that affected PFS. Adjuvant sorafenib could greatly improve the efficacy of TACE for HCC; further studies are required to test this possibility.

Acknowledgements

We thank Dr. Stephen P. Brooks for revising the manuscript.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001;**94**(2):153-6.
2. Imamura H, Matsuyama Y, Tanaka E, *et al.* Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol*. 2003;**38**(2):200-7.
3. Konno T, Maeda H, Iwai K, *et al.* Effect of arterial administration of high-molecular-weight anticancer agent SMANCS with lipid lymphographic agent on hepatoma: a preliminary report. *Eur J Cancer Clin Oncol*. 1983;**19**(8):1053-65.
4. Ohishi H, Uchida H, Yoshimura H, *et al.* Hepatocellular carcinoma detected by iodized oil. Use of anticancer agents. *Radiology*. 1985;**154**(1):25-9.
5. Yumoto Y, Jinno K, Tokuyama K, *et al.* Hepatocellular carcinoma detected by iodized oil. *Radiology*. 1985;**154**(1):19-24.
6. Llovet JM, Real MI, Montana X, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002; **359**(9319):1734-9.
7. Lo CM, Ngan H, Tso WK, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;**35**(5):1164-71.
8. Taieb J, Mansourbakht T, Ducreux M, *et al.*, editors. Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma (AHCC): results of a phase II study. *Journal of Clinical Oncology* ASCO Annual Meeting Proceedings (Post-Meeting Edition); 2004.
9. Bearz A, Sorio R, Tommasi G, *et al.* Oxaliplatin and 5-fluorouracil in hepatocarcinoma. *Proc Am Soc Clin Onco*. 2001;**20**:148b.
10. Yang TS, Lin YC, Chen JS, Wang HM, Wang CH. Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer*. 2000;**89**(4):750-6.
11. Horiuchi H, Ishikawa H, Hiraki M, *et al.* [Intra-arterial chemotherapy with gemcitabine (GEM) for unresectable pancreatic cancer]. *Gan To Kagaku Ryoho*. 2002;**29**(12):2065-9.
12. Vogl TJ, Heller M, Zangos S, *et al.* [Transarterial chemoperfusion of inoperable pancreas carcinoma and local recurrence]. *Rofo*. 2003;**175**(5):695-704.
13. Shamseddine AI, Khalifeh MJ, Mourad FH, *et al.* Comparative pharmacokinetics and metabolic pathway of gemcitabine during intravenous and intra-arterial delivery in unresectable pancreatic cancer patients. *Clin Pharmacokinet*. 2005;**44**(9):957-67.
14. Yang BH. [The Diagnosing and Staging National Standards for hepatocellular carcinoma]. *Zhonghua Ganzangbing Zazhi*. 2001;**9**(6):324-9.
15. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* 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*. 2000;**92**(3):205-16.
16. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology*. 2003;**37**(2):429-42.
17. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol*. 1954;**30**(5):969-77.
18. Wall JG, Benedetti JK, O'Rourke MA, Natale RB, Macdonald JS. Phase II trial to topotecan in hepatocellular carcinoma: a Southwest Oncology Group study. *Invest New Drugs*. 1997;**15**(3):257-60.
19. O'Reilly EM, Stuart KE, Sanz-Altamira PM, *et al.* A phase II study of irinotecan in patients with advanced hepatocellular carcinoma. *Cancer*. 2001;**91**(1):101-5.
20. Rougier P, Ducreux M, Kerr D, *et al.* A phase II study of raltitrexed ('Tomudex') in patients with hepatocellular carcinoma. *Ann Oncol*. 1997;**8**(5):500-2.
21. Chao Y, Chan WK, Birkhofer MJ, *et al.* Phase II and pharmacokinetic study of paclitaxel therapy for unresectable hepatocellular carcinoma patients. *Br J Cancer*. 1998;**78**(1):34-9.
22. Ueno K, Miyazono N, Inoue H, Nishida H, Kanetsuki I, Nakajo M. Transcatheter arterial chemoembolization therapy using iodized oil for patients with unresectable

hepatocellular carcinoma: evaluation of three kinds of regimens and analysis of prognostic factors. *Cancer*. 2000;**88**(7):1574-81.
23. Okuda K, Ohtsuki T, Obata H, *et al*. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer*. 1985;**56**(4):918-28.
24. Nomura F, Ohnishi K, Tanabe Y. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. *Cancer*. 1989;**64**(8):1700-7.
25. Cheng AL, Kang YK, Chen Z, *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;**10**(1):25-34.