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Efficacy of Transcatheter Arterial Infusion Alone or Combined with Transcatheter Arterial Chemoembolization on Advanced Hepatocellular Carcinoma

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Abstract

Objective: Interventional therapy for advanced hepatocellular carcinoma (HCC) is still controversial. This retrospective study was to evaluate the efficacy of transcatheter arterial infusion (TAI) alone or combined with transcatheter arterial chemoembolization (TACE) on advanced HCC.

Methods: The study population consisted of 132 advanced HCC patients with Child-pugh A/B. Tumor in all patients was involved with main trunk of portal vein and/or inferior vena cava, or local lymph node metastasis, or distant metastasis. TAI alone or combined with TACE were performed in 65 patients with advanced HCC (interventional treatment group), 67 patients were treated with traditional Chinese herbal drug (Chinese herb group). The prime end point was overall survival (OS), and prognostic factors were analysed.

Results: The median OS was 205 days [95% confidence interval (CI), 155-255 days] in interventional treatment group and 127 days (95% CI, 70-184 days) in Chinese herb group (P <0.05). The 6-month, 1-year, and 2-year OS rates were 58.9%, 29.1%, 7.7% in interventional treatment group, and 33.3%, 12.3%, 1.8% in Chinese herb group. The portal vein thrombosis, ECOG performance status were independent prognostic factors for OS.

Conclusion: Interventional treatment could greatly prolong the OS of advanced HCC patients.

Keywords: Liver neoplasm; Chemoembolization; Transcatheter arterial infusion; Sorafenib

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world, and the third commonest cause of cancer mortality worldwide, with more than 80% of cases occurring in Asia [1,2]. About 110 000 persons die each year from HCC in China, which accounts for 45% of the deaths from HCC worldwide [3]. Treatment of liver cancer is still a very difficult problem; surgical resection is the main curative treatment. Unfortunately, only around 20% of HCC patients may benefit from surgical therapy.

Many patients with locally advanced or metastatic cancer need receive systemic treatment. Many pharmacologic treatments have been tested against HCC; most of them belong to three categories: chemotherapy, hormone therapy, and immunotherapy. Neither single agent nor combination chemotherapy have demonstrated a clear reproducible advantage in terms of overall survival [4,5]. According to the Barcelona Clinic Liver Cancer staging system, the recommended treatment strategy for advanced HCC defined as presence of macroscopic vascular invasion, extrahepatic spread is sorafenib [6]. However, at present, the majority of HCC patients in China cannot afford the high cost of treatment of sorafenib. Advanced HCC patients in China mainly receive interventional or Chinese herbal drug treatment. Thus, in order to evaluate the efficacy of interventional treatment of advanced HCC patients with local advanced or metastatic cancer, we compared survival of interventional treatment group with that of Chinese herbal drug group. All patients were admitted to our hospital in last 3 years.

Materials and Methods

Patients

We retrospectively studied consecutive records of patients who were admitted to our hospital from January 2007 to November 2009. A total of 132 advanced HCC patients with stage IIIa were diagnosed by the criteria of Diagnosing and Staging National Standards of China (2001) for HCC [7]. All patients met the following criteria: (1) pathologically proven HCC; (2) an alpha-fetoprotein (AFP) level ≥ 400 ng/mL together with a typical imaging findings on dynamic computed tomography (CT), magnetic resonance imaging (MRI), or digital subtraction angiography (DSA); (3) AFP < 400 ng/mL together with two typical imaging findings. All patients with Child-pugh A/B had main trunk of **portal** vein and/or inferior vena cava thrombosis, or local lymph node metastasis, or distant metastasis. Of the 132 patients, 116 were men and 16 women; 87 had a serum AFP level of > 400 mg/L; 117 had positive hepatitis B virus infection; 89 had portal vein trunk and/or inferior vena cava thrombosis, 56 had local lymph node metastasis, and 44 had distant metastasis; 94 were at Child-pugh grade A, 38 at Child-pugh grade B. The median **age** of the **patients** was 50 **years** (range, 16-83 years). Of the 132 patients, 65 received transcatheter arterial infusion (TAI) alone or combined with transcatheter arterial chemoembolization (TACE), 67 received Chinese herbal drug. No

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significant differences in baseline demographics were noted between the two groups (Table 1).

Treatment procedure

The interventional treatment group received TAI alone or combined with TACE according to a standard protocol. Patients had fasted 8 hours before interventional treatment. 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. Patients with complete occlusion of the main portal vein or lack of arterial blood supply received TAI alone; while patients without complete occlusion of the main portal vein received TAI combined TACE. In TAI protocol, oxaliplatin (150mg to 200mg) and floxuridine (1,000 mg) or gemcitabine (1,600 mg) were injected into the celiac trunk artery, the common hepatic artery and proper hepatic artery in turn at a ratio of 50: 25: 25.

In TACE protocol, 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 20 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. This was followed by embolization with small gelatin-sponge pellets 1 mm in diameter. Chemoembolization was repeated in 30 to 45 days. Chinese herb group received Chinese herbal drugs or combined with support treatment.

Statistical analysis

The primary study endpoint was overall survial. Only 1.5 percent of the patients were lost to follow-up. 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. 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.

Item	Interventional treatment group	Chinese herb group
Sex		
Male	56	60
Female	9	7
Age (years)		
Median	51	51
Range	25-75	16-83
Serum hepatitis B surface antigen		
Positive	58	59
Negative	7	8
Serum AFP (ng/mL)		
<20	18	15
21-400	6	6
≥400	41	46
Child-Pugh Classification		
A	51	43
B	14	24
Portal vein thrombosis		
Positive	45	44
Negative	20	23
ECOG performance status		
1	40	29
2	22	31
3	3	7
Tumor burden (tumor/non-tumor)		
≥50%	41	36
<50%	24	21
The number of tumor		
1	37	30
≥2	28	37
Abdominal lymph node metastasis		
Positive	27	29
Negative	38	38
Distant metastasis		
Positive	18	26
Negative	37	41

AFP, alpha-fetoprotein; ECOG, the Eastern Cooperative Oncology Group

Table 1: General data of advanced HCC patients in interventional treatment group and Chinese herb group.

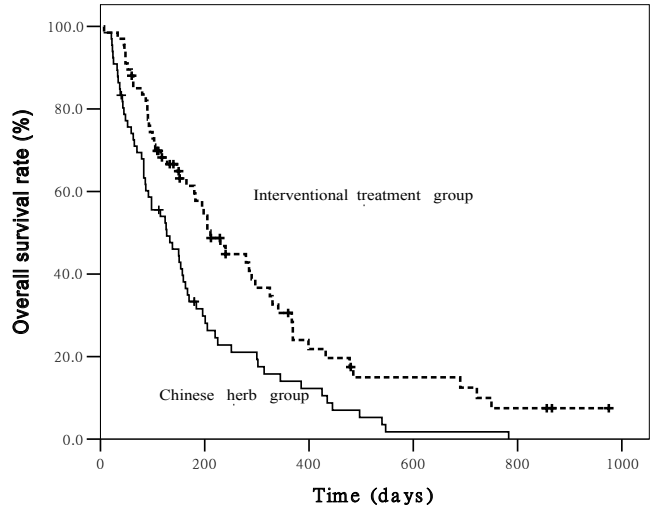

Figure 1: Overall survival curves of advanced HCC patients in interventional treatment group and Chinese herb group (log-rank test, P<0.05).

Results

Overall survival

Among the 132 patients, 2 patients was lost to follow-up during the first year. At the end of study, 50 patients in interventional treatment group and 62 patients in Chinese herb group were died. A total of 65 patients of interventional treatment group received a total of 101 courses (median, 1 courses; range, 1-4 courses) of TACE/TAI.

The median overall survival (OS) was 205 days [95% confidence intervals (CI), 155- 255 days] for interventional treatment group and 127 days (95% CI, 70-184 days) for Chinese herb group. The median OS was significantly better in interventional treatment group than in Chinese herb group ($P = 0.002$). The 6-month, 1-year, and 2-year OS

Variable	Interventional treatment group	Chinese herb group	P
Tumor nodules			
1	198±29.6	133±43.1	0.454
≥2	325±112.4	151±45.1	0.002
Tumor diameter			
<10cm	325±100.8	159±19.4	0.004
≥10cm	182±32.0	98±27.3	0.385
The tumor-to-liver ratio			
≥50%	180±33.2	133±37.9	0.489
<50%	367±60.9	138±48.7	0.003
Portal vein thrombosis			
positive	165±37.4	83±5.2	0.028
negative	240±52.6	170±18.1	0.067
Child-Pugh classification			
A	211±51.6	154±20.2	0.005
B	128±45.8	126±45.4	0.798
ECOG performance status			
0-1	325±76.5	154±20.4	0.002
2	115±21.1	98±28.6	0.485
3	95±26.1	150±96.2	0.524

Table 2: Univariate prognostic analysis of advanced HCC patients.

Variable	B	SE	Wald	Sig.	Exp(B)
Tumor nodules	-0.015	0.120	0.015	0.903	0.985
Tumor diameter	0.009	0.035	0.073	0.786	1.009
The tumor-to-liver ratio	0.158	0.286	0.305	0.581	1.171
Portal vein thrombosis	0.496	0.201	6.067	0.014	1.643
Child-pugh classification	0.147	0.237	0.386	0.534	1.158
ECOG PS	0.511	0.168	9.248	0.002	1.668

Table 3: Multivariate prognostic analysis of advnced HCC patients.

rates were 58.9%, 29.1%, 7.7% in interventional treatment group, and 33.3%, 12.3%, 1.8% in Chinese herb group (Figure 1).

Of the interventional treatment group, 47 patients received TACE, 18 received TAI; the median OS was 205 days (95% CI, 70-184 days) in TACE subgroup and 198 days (95% CI, 76-320 days) in TAI subgroup. There was no statistically significant difference in the median OS between TACE and TAI subgroup ($P = 0.981$).

Of the interventional treatment group, the median OS was 165 days 95% CI, 71-259 days in patients with main trunk of portal vein / inferior vena cava thrombosis, 230 days (95% CI, 171-289 days) in patients with local lymph node metastasis, 367 days (95% CI, 169-565 days) in patients with distant metastasis and 152 days 95% CI, 62-242 days in patients with main trunk of portal vein / inferior vena cava thrombosis and distant metastasis. There was no statistically significant difference among interventional treatment subgroup described above in terms of the median OS ($P = 0.437$).

Prognosis

Univariate analysis showed that tumor nodules, tumor diameter, the tumor-to-liver ratio, portal vein thrombosis, Child-Pugh classification, ECOG performance status (ECOG PS) were associated with OS (Table 2). With multivariate analysis, the portal vein thrombosis and ECOG performance status were independent prognostic factors of all patients (Table 3).

Discussion

Advanced HCC patients, especially those with local advanced or metastatic cancer, need receive systemic treatment according to the Barcelona Clinic Liver Cancer staging system. Many pharmacologic treatments have been tested against HCC, but only sorafenib has been proven to be able to improve survial. In view of the high cost of sorafenib currently, many patients with advanced HCC in China cannot afford the sorafenib treatment. Two randomized-controlled trials published in 2002, one conducted in Barcelona and the other in Hong Kong, followed by a systematic meta-analysis showed that TACE has a significant and positive impact on survival in well-selected patients with preserved liver function [8,9,10], as determined the status of TACE for unresectable HCC. TAI is mainly used for HCC patients with major portal vein thrombosis or lack of arterial blood supply. Traditional TACE was mainly used in moderate stage HCC or advance HCC without distant metastasis. Thus, the role of TACE/TAI for advanced HCC patients with local advanced or metastatic cancer has remained controversial.

The results that median OS was 205 days for interventional treatment group and 127 days for Chinese herb group showed that patients whether having the big vascular invasion, local lymph node metastasis, or distant metastasis can benefit from interventional treatment. Patients with ECOG PS 0-3 and Child-Pugh status A/B were enrolled into this study, but patients were enrolled in the randomized phase III trial of sorafenib versus placebo with ECOG PS 0-2, Child-Pugh status A. Despite the lower level of evidence, the result of this study is exciting. Further study with high level of evidence to determine the efficacy of interventional treatment for advanced HCC patients with local advanced or metastatic cancer should be carried out.

There is no standard chemotherapy regimen used in TACE, doxorubicin-based chemotherapy regimen has demonstrated greater toxicity, and there are few agents effective in the treatment of HCC. Our previous studies have already found that oxaliplatin combined with floxuridine regimen used in TACE demonstrated less toxicity [11,12]. Simple local chemoembolization has limited efficacy for main trunk of portal vein and/or inferior vena cava thrombosis, or local lymph node metastasis, or distant metastasis. The major controversy exists regarding whether TACE is suitable for such patients. TAI play the role of systemic treatment while maintaining high local drug concentration. Thus, interventional therapy procedure used in this study, which is diffferent from traditional chemoembolization, consisted of intraarterial chemotherapy with gemcitabine or floxuridine and chemoembolization with oxaliplagtin, lipiodol and/or gelatin sponge. Subgroup analyses showed that no significant difference in outcomes was found between TACE and TAI. This conclusion seems to be a challenge to traditional chemoembolization. In fact, traditional chemoembolization was mainly used in moderate stage HCC, but the tumor of patients in this study was already involved with main trunk of portal vein and/or inferior vena cava, or local lymph node metastasis, or distant metastasis. Prognosis analysis show that local lymph node metastasis, or distant metastasis is not prognostic factor for OS, but the portal vein thrombosis and ECOG PS were independent prognostic factors of all patients. That is to say hepatic primary tumor with the resulting physical performance status is key to survival. It is reported that more than 60% cause of death of patients with advanced HCC was liver failure [13], and intrahepatic tumor progression is the main reason for liver failure. Thus, active treatment on hepatic primary tumor for patients with advanced HCC can delay the occurrence of liver failure, improve survival. TACE procedure based on intraarterial chemotherapy can achieve better efficacy for advanced HCC. Moreover, a recent randomized clinical study, which confirmed the role of transcatheter arterial infusion chemotherapy for HCC, gave us further confidence [14].

With the development of Evidence-Based Medicine, comprehensive treatment paly more and more important role in interventional treatment of HCC. Many reports showed that interventional comprehensive treatment modalities such as TACE combined with either immune therapy or radiation therapy or Chinese medicine, etc. can further improve survival for HCC patients [15,16,17,18,19]. The preliminary study results suggest that TACE combined with sorafenib can further enhance the clinical efficacy [20]. TACE combined with sorafenib modality might be a potential application for advanced HCC patients with local advanced or metastatic cancer.

In a summary, TAI alone or combined with TACE can improve survival of advanced HCC patients with local advanced or metastatic cancer and play an important role in comprehensive treatment. The portal vein thrombosis and ECOG PS were independent prognostic factors for OS.

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