·Clinical Research·

Efficacy of transcatheter arterial chemoembolization combined with cytokine-induced killer cell therapy on hepatocellular carcinoma: a comparative study

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[Abstract] Background and Objective: Cytokine-induced killer (CIK) cells have high anti-tumor activity for hepatocellular carcinoma (HCC). Whether CIK cell therapy can eradicate residual cancer cells and prevent or postpone tumor relapse after transcatheter arterial chemoembolization (TACE) should be testified. This study was to evaluate the efficacy of CIK cell therapy combined with TACE on HCC. **Methods:** A total of 146 consecutive patients with unresectable HCC were divided into combination group (72 patients treated with CIK cell therapy combined with TACE) and TACE group (74 patients treated only with TACE). The progression-free survival (PFS) and overall survival (OS) were analyzed. **Results:** The 6-month, 1-year, and 2-year PFS rates were 72.2%, 40.4%, 25.3% in combination group, and 34.8%, 7.7%, 2.6% in TACE group. The median time to progression was 11 months [95% confidence interval (CI), 8–14 months] in combination group and 5 months (95% CI, 4–7 months) in TACE group. The estimated 6-month, 1-year, and 2-year OS rates were 90.3%, 71.9%, 62.4% in combination group, and 74.6%, 42.8%, 18.8% in TACE group. The median OS was 31 months (95% CI, 27–35 months) in combination group and 10 months (95% CI, 7–13 months) in TACE group. The times of TACE, ECOG performance status, and CIK cell therapy were independent prognostic factors for PFS and OS. **Conclusion:** Adjuvant immunotherapy with CIK cells could greatly improve the efficacy of TACE on HCC, and plays an important role in prolonging the PFS and OS of HCC patients after TACE.

Key words: Liver neoplasm, chemoembolization, cytokine-induced killer, progression-free survival, overall survival

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with more than 80% of the cases occurred in Asia[1]. HCC become the second most common cause of cancer death in China. Treatment of HCC remains a critical issue, particularly in China, as it is estimated that Chinese patients account for 40% of HCC cases worldwide. Surgical resection is the main curative treatment. Unfortunately, only around 20% of HCC patients may benefit from surgical therapy. Most patients are diagnosed too late, already presenting with advanced disease. Transcatheter arterial chemoembolization (TACE), which has shown a survival benefit, is now widely adopted for unresectable HCC[2,3]. However, the recurrence rate after TACE is still high and the long-term survival is unsatisfactory. It is a challenge to enhance the efficacy of TACE and reduce recurrence after TACE. It is well known that improving the overall therapeutic effects on HCC depends on the combined therapies.

Cytokine-induced killer (CIK) cells are the major histocompatibility complex-unrestricted cytotoxic lymphocytes and generated by incubating peripheral blood monocytes (PBMC) with various types of cytokines such as CD3 monoclonal antibody, interleukin-2 (IL-2), IL-l and interferon-gamma (IFN-γ)[4]. The high anti-tumor activity of CIK cells is mainly due to the high proliferation of $CD3^+$ $CD56^+$ cells[5,6]. Some reports indicated that CIK cell therapy can be used as an efficient adjuvant anticancer immunotherapy to eradicate residual cancer cells and prevent or postpone tumor relapse[7-9]. In the present nonrandomized study, we compared therapeutic efficacy of TACE alone or in combination with CIK cell therapy on HCC in terms of progression-free survival (PFS) and overall survival (OS).

Materials and Methods

Selection of patients

From May 2005 to September 2008, 146 HCC patients over

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18 years old were enrolled according to inclusion and exclusion criteria (Table 1). The diagnosing criteria of HCC was made according to the Diagnosing and Staging National Standards of China (2001) for hepatocellular carcinoma[10]. According to the wishes of patients, they were divided into combination group (72 patients were treated with CIK cell therapy combined with TACE) and TACE group (74 patients were treated only with TACE). No significant differences in baseline demographics were noted between the two groups (Table 2).

Table 1 Criteria for inclusion and exclusion of HCC patients

Inclusion criteria	Exclusion criteria
Men and women >18 years of age	Infiltrative or diffuse HCC
HCC diagnosed by high level of serum AFP (≥ 400 ng/mL) with typical imaging findings, or confirmed by needle liver biopsy while AFP < 400 ng/mL	Significant cardiovascular disease such as myocardial infarction occurred within recent 6 months, chronic heart failure or unstable coronary artery disease
Patients had unresectable HCC or refused resection	Systemic chemotherapy or angiogenesis inhibitor therapy before disease progression
Total bilirubin < 3 × upper limit of normal	Patients with other malignant tumor within the past 5 years before treatment
Child-Pugh stage A or B	Pregnant or breastfeeding patients
No extrahepatic metastasis	Patients with uncontrolled infections or HIV-seropositive patients
INR/PTT < 1.5 × upper limit of normal	History of organ transplantation
Written informed consent	Patients with hemorrhage/bleeding event
Newly diagnosed or had postoperative recurrence	Mental conditions rendering the patient incapable to understand the nature, scope, and consequences of the study

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; HIV, human immunodeficiency virus; INR/PTT, international normalized ratio/prothrombin time.

Table 2 Baseline characteristics of the patients

Characteristic	Combination group	TACE group
Total cases	72	74
Median age (years)	53	51
Gender		
Male	65	64
Female	7	10
Serum hepatitis B surface antigen		
Positive	68	68
Negative	4	6
Serum AFP		
≤ 20 ng/mL	20	17
21–399 ng/mL	17	12
≥ 400 ng/mL	35	45
Child-Pugh classification		
A	65	66
B	7	8
Portal vein thrombosis		
Positive	13	22
Negative	59	52
Arteriovenous fistula		
Positive	12	18
Negative	60	56
BCLC stage		
A	7	5
B	6	4
C	59	65
ECOG performance status		
0–1	66	61
2–3	6	13
Times of TACE		
1	18	29
≥ 2	54	45

TACE, transcatheter arterial chemoembolization; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer Staging; ECOG, the Eastern Cooperative Oncology Group.

Treatment procedure

The two groups received TACE according to a standard protocol. Patients fasted for 8 h before TACE. Intravenous injection of 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 size and location of tumor nodules and to identify occlusion of the main portal vein. The right or left hepatic artery feeding the tumor was superselectively catheterized. By the pumping method, oxaliplatin was mixed with lipiodol in a ratio of 100 mg to 10 mL to make into an emulsion. 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 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) or gemcitabine (1 600 mg) was injected into the common hepatic artery before lipiodol embolization. If possible, remanent oxaliplatin were injected into the common heptic artery after lipiodol embolization, followed by embolization with small gelatin-sponge pellets of 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 events, or progressive disease with a diffuse growth pattern developed.

CIK cells were isolated and cultured according to a standard protocol. Using a blood cell separator, (2–4) × 10^9 PBMC cells from each patient were obtained in a total volume of 50–60 mL. Cells were resuspended in phosphate buffered saline (PBS)

without calcium and magnesium. Cell concentration was adjusted to 1.0 × 10^6/mL in RPMI-1640 medium. PBMC cells were incubated with 1000 U/mL rhIFN-γ for 24 h, then added with 50 ng/mL anti-CD3 mAb, 100 U/mL rhIL-1α, and 500 U/mL rhIL-2. Fresh rhIL-2 and fresh RPMI-1640 medium were replenished every 3 days. $CD3^+$ $CD56^+$, the major immunophenotype of CIK cells, was examined 10 days after incubation. when the cell number reached more than 1 × 10^{10}. CIK cells were collected within 24 h before TACE, then centrifuged at 1 000 rpm to remove the medium, washed with normal saline (NS) for 3 times and resuspended in 100 mL NS, and transfused back into HCC patients in combination group via the vein on days 10, 13, 15, 18, respectively, according to protocol. Successive 4 times of transfusion was a course of treatment. The number of transfused CIK cells per patient was (1-5) × 10^{10} in one course of treatment. A maximum of 4 courses of treatment was given in one patient every year. No patient accepted extra cytokine treatment.

Assessment of outcome

The primary end points were progression-free survival (PFS) and time-to-progression (TTP); the second end point was overall survival (OS). TTP was defined as the interval from the beginning of treatment to death or disease progression. The patients were followed monthly at the outpatient clinic till March 15, 2009. Serum biochemistry, serum alpha-fetoprotein (AFP) detection, and CT or MRI were repeated every month in the first trimester, then every two months. 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

Intergroup comparison was made on an intention-to-treat basis. The frequency of each variable was analyzed by the Chi-square test and comparisons of group means were performed using the Student's *t* test. 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 using the log-rank test. The PFS and OS curves of the two groups were then compared with stratification according to significant prognostic factors. All the significant prognostic factors related to PFS and OS identified from univariate analysis were put into a Cox proportional hazards model for multivariate analysis. The level of significance was set at $P < 0.05$. Statistical analysis was performed with the SPSS13.0 software.

Results

Patient characteristics

All patients received a total of 279 courses of TACE (median, 2 courses; range, 1–4 courses) before disease progression, and the 72 patients of combination group received a total of 111 courses of CIK cell transfusion (median, 1 course; range, 1–3 courses) before disease progression. One patient in the TACE group were lost and could not be contacted after a follow-up of 32 months. At the time of the final analysis, 40 patients in TACE group and 28 patients in combination group had died. According to RECIST (Response Evaluation Criteria in Solid Tumors), the short-term responses of the two groups were similar. No patient reached complete remission (CR); 13 (18.0%) patients in combination group and 11 (14.9%) in TACE group reached partial remission (PR); 59 (81.9%) patients in combination group and 63 (85.1%) in TACE group had stable disease (SD).

Progression-free survival

The 6-month, 1-year, and 2-year PFS rates were 72.2%, 40.4%, 25.3% in combination group, and 34.8%, 7.7%, 2.6% in TACE group. The median TTP was 11 months [95% confidence interval (CI), 8–14 months] for combination group and 5 months (95% CI, 4–7 months) for TACE group (Figure 1). The PFS was significantly better in combination group than in TACE group ($P < 0.001$). The median PFS increased by 6 months (120% improvement), from 5 months (TACE group) to 11 months (combination group).

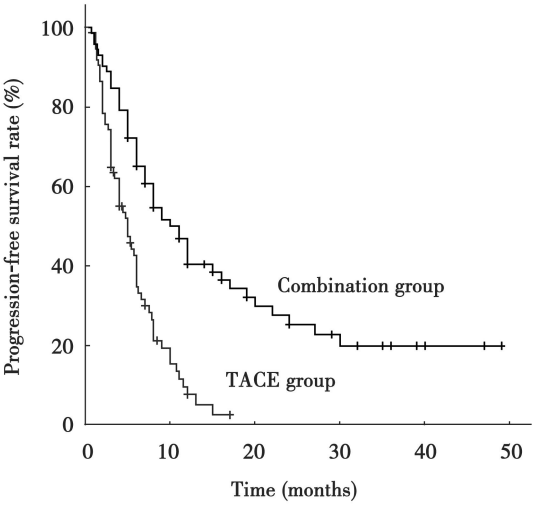

Figure 1 Progression-free survival curves of hepatocellular carcinoma (HCC) patients (n =146) received transcatheter arterial chemoembolization (TACE) combined with cytokine-induced killer (CIK) cell therapy (combination group) (n=72) and TACE alone (TACE group) (n=74) (log-rank test, $P < 0.001$)

By univariate analysis, portal vein thrombosis, Child-Pugh classification, ECOG performance status, BCLC stage, CIK cell therapy, and times of TACE before disease progression were associated with PFS. Meanwhile, multivariate Cox proportional hazard analysis demonstrated that ECOG performance status, CIK cell therapy, and times of TACE before disease progression were the independent prognostic factors that affected PFS (Table 3).

Of the 74 patients in TACE group, 63 (85.1%) had disease progression, 11 (14.9%) had extrahepatic metastasis. Of the 72 patients in combination group, 51(70.8%) had disease progression, 10(13.9%) had extrahepatic metastasis. The difference in disease progression was not significant between the two groups (P = 0.769).

For the patients received one time of TACE before disease

Table 3 Multivariate prognostic analysis for progression-free survival of HCC patients after TACE

Variate	B	SE	Wald	Sig.	Exp(B)	95.0% CI for Exp(B)
Times of TACE	−0.340	0.131	6.748	0.009	0.712	0.551–0.920
ECOG score	0.649	0.193	11.304	0.001	1.914	1.311–2.795
CIK cell therapy	−0.572	0.228	6.264	0.012	0.564	0.361–0.883
Child-Pugh	0.185	0.321	0.332	0.564	1.203	0.642–2.255
Portal vein thrombosis	0.442	0.247	3.212	0.073	1.556	0.959–2.524

progression, there was no significant PFS difference between the two groups (P = 0.133); for those received 2–4 times of TACE, the PFS was significantly better in combination group than in TACE group (P < 0.001). For the patients with ECOG performance status of 0–1, the PFS was significantly better in combination group than in TACE group (P < 0.001); for those with ECOG performance status of 2–3, the difference was not significant between the two groups (P = 0.450).

Overall survival

The estimated 6-month, 1-year, and 2-year OS rates were 90.3%, 71.9%, 62.4% in combination group, and 74.6%, 42.8%, 18.8% in TACE group. The median OS was 31 months (95% CI, 26.7–35.3 months) for combination group and 10 months (95% CI, 7.3–12.7 months) for TACE group (Figure 2), with significant difference (P < 0.001).

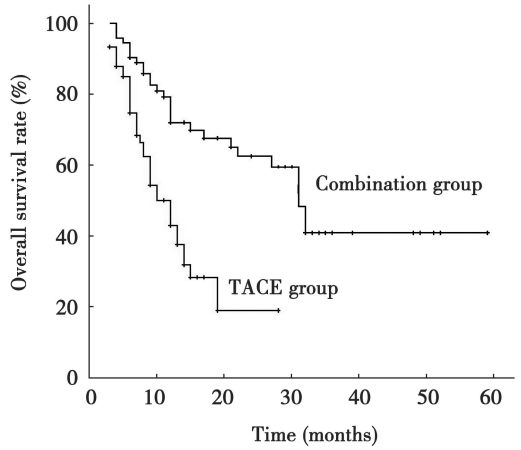

Figure 2 Overall survival curves of HCC patients in combination group and TACE group (log-rank test, P < 0.001)

Table 4 Comparison of progression-free survival between the two groups stratified by the independent prognostic variables

Variate	Progression-free survival (months)		P
	Combination group	TACE group	
Times of TACE		4.0 ± 0.7	0.133
1	5.0 ± 1.3	5.4 ± 0.6	< 0.001
⩾ 2	12.0 ± 2.8		
ECOG performance status		5.7 ± 0.4	< 0.001
0–1	12.0 ± 1.8	3.0 ± 0.8	0.450
2–3	3.0 ± 2.2		

All values are presented as mean ± standard errors.

Univariate analysis showed that portal vein thrombosis, Child-Pugh classification, ECOG performance status, BCLC stage, arteriovenous fistula, CIK cell therapy, and times of TACE were associated with OS. With multivariate analysis, the times of TACE, ECOG performance status, and CIK cell therapy were independent prognostic factors of all patients (Table 5).

Discussion

Our study has shown that adjuvant immunotherapy with CIK cells may greatly prolong PFS and OS of HCC patients after TACE.

HCC is a common malignant tumor in Asia. Hepatic resection offers a chance of cure for a minor proportion of patients with early stage tumor 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 HCC are treated by various palliative therapies. TACE is the most widely used treatment for unresectable HCC with proven improvement on survival in selected patients with well preserved liver function[11,12]. 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. But the shortcoming of TACE which could not be overcomed by itself is unable to completely kill tumor cells, even if patients were treated with superselective TACE[13]. The liver tumor has two blood

Table 5 Multivariate prognostic analysis for overall survival of all HCC patients

Variate	B	SE	Wald	Sig.	Exp(B)	95% CI for Exp(B)
Times of TACE	−0.499	0.168	8.845	0.003	0.607	0.437–0.844
ECOG score	0.709	0.269	6.931	0.008	2.031	1.199–3.443
CIK cell therapy	−0.803	0.310	6.723	0.010	0.448	0.244–0.822

supplies unlike healthy liver tissue, the hepatic artery provides almost all tumor blood supply and the portal vein provides remains. The portal blood supply feeding mainly in the tumor periphery, and the blood may flow into tumor via the portal vein in the tumor periphery in a retrograde manner by following a pressure gradient in tumor sinusoids after TACE. Accordingly, tumor periphery could continue to grow with portal vein branch feeding, thus result in disease progression after TACE[14,15].

HCC patients are often found to have functional deficiency in host adaptive immunity response and innate immunity response[16]. Antitumor immunity mainly depends on cellular immune response. Therefore, cellular immunity dysfunction is one of the reasons why tumors are incurable, and easy to relapse or metastasize. Many studies reported that CIK cells could suppress the growth of HCC cells, boost the cellular immunity in HCC patients[17,18]. Many case analyses showed that CIK cell therapy could enhance the efficacy of interventional treatment. For advanced HCC patients or those who were unfit for surgery or chemotherapy, CIK cell therapy could ameliorate symptoms, improve quality of life and prolong survival of patients[19-21]. Many studies have illuminated that CIK cells possessed strong cytotoxicity, could kill drug-resistant HCC cells by inducing apoptosis, and could produce IL-2, IL-6, IFN-γ and other anti-tumor cytokines[22,23]. The cellular immunity of HCC patients is significantly impaired by anticancer drugs for TACE[24], TACE combined with CIK cell infusion hereby become an important treatment for HCC patients.

Because of high cost of CIK cells, it is difficult to conduct randomized controlled clinical trials to evaluate the efficacy of CIK cells in the adjuvant treatment of HCC after TACE. Thus, we conducted this non-randomized concurrent control trial to evaluate the efficacy of CIK cells on HCC after TACE. In the present study, the median PFS and OS were significantly increased for the patients received TACE combined with CIK cell therapy. The median PFS increased by 6 months, the median OS increased by 21 months. The times of TACE, ECOG performance status, and CIK cell therapy were independent prognostic factors of all patients. For patients adopted more than one time of TACE before disease progression, there would be low residual tumor burden which plays an important role in prolonging PFS of HCC patients after TACE. For the patients with ECOG performance status of 2–3, usually associated with impaired immune function[25], CIK cell therapy did not contribute to the survival benefit.

To sum up, adjuvant immunotherapy with CIK cells may greatly improve efficacy of TACE on HCC, and plays an important role in prolonging the PFS of HCC patients after TACE.

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