

Clinical efficacy of transcatheter arterial chemoembolization combined with DC-CIK in the treatment of colorectal cancer with liver metastasis and its effect on the survival of patients.

Ji-ming Du¹, Ai-ming Gong¹, Xiao-nan Dai², Fang-Wang³, Wen-cai Weng^{4*}

¹Department of Anus and Intestine Surgery, Xinhua Hospital Affiliated to Dalian University, PR China

²Oncology Department of Xinhua Hospital Affiliated to Dalian University, PR China

³Operating Room of Xinhua Hospital Affiliated to Dalian University, PR China

⁴Interventional Radiography of Xinhua Hospital Affiliated to Dalian University, PR China

Abstract

Objective: To investigate the clinical efficacy of interventional chemoembolization combined with dendritic cell, DC-cytokine-induced killer, CIK (DC-CIK) in the treatment of colorectal cancer with liver metastasis and the influence on the survival time of patients.

Methods: Eighty cases of colorectal cancer with liver metastasis in our hospital from January 2012 to January 2014 were randomly divided into study group and control group. The study group was treated by interventional chemoembolization combined with DC-CIK treatment, and the control group was treated with conventional intravenous chemotherapy combined with DC-CIK therapy. Tumor marker, clinical efficacy, survival rate and adverse reaction of two groups were compared.

Results: After treatment, the level of tumor markers in study group was significantly lower than that in control group ($P>0.05$); The treatment effect of study group was better than that of control group ($P>0.05$); The 1 y and 2 y survival rates of study group were 75% and 45%, respectively, which were significantly better than those of control group (50% and 25%) ($P>0.05$); 1~5 d after treatment, part of patients showed fever, nausea and vomiting and liver pain. These patients were recovered after symptomatic treatment within two weeks. Adverse reaction of two groups was not statistically difference ($P>0.05$).

Conclusion: Interventional chemoembolization combined with DC-CIK in the treatment of colorectal cancer patients with liver metastasis is better with prolonged survival period of patients and tolerable adverse reaction in clinical.

Keywords: Interventional chemoembolization, DC-CIK, Colorectal cancer with liver metastasis, Clinical effect, Survival period.

Accepted on June 2, 2017

Introduction

Colorectal cancer is the most common malignant tumor of digestive system. In recent years, the incidence of colorectal cancer is increasing in China with the improvement of living standard and the change of life mode [1]. Blood of colon vein flows into the portal vein mostly by the superior mesenteric vein and the transfer of blood has become an important way of tumor metastasis. Therefore, colorectal cancer can easily transfer to the liver [2]. Clinical study shows that in the newly diagnosed patients with colorectal cancer, about 20% have liver metastases and 30% to 50% of patients occur liver metastasis within 3 y after surgery [3]. Due to numerous and widely distributed lesions in liver metastases, liver resection of patients would greatly affect quality of life, while liver

metastases without treatment reduces median survival of only 6 to 9 months [4,5]. To find a positive and effective non-surgical treatment of colorectal cancer with liver metastasis is of great significance. Patients with colorectal cancer patients and liver metastases in our hospital from 2012 were treated with interventional chemoembolization combined with DC-CIK treatment, which has achieved remarkable results.

Materials and Methods

Clinical data

Eighty patients with colorectal cancer and liver metastasis selected from January 2012 to January 2014 were divided into study group and control group by random number table

method. Study group: 18 female patients and 22 male patients, 40 to 79 years, mean age (57 ± 2 y). Control group: 16 female patients and 24 male patients, 38 to 78 y, mean age (58 ± 3 y). Table 1 shows the general data of age, gender, primary lesion, primary foci size, comparison of single or multiple metastatic lesions of two groups.

Inclusion criteria and exclusion criteria

Patients selected to meet the following criteria: all colorectal cancer with liver metastasis was diagnosed by pathology and imaging; all patients with liver metastases had surgical contraindications or resection difficulties; expected survival >8 months. Patients with any of the following items were excluded from this study: severe heart and kidney and other systemic diseases; diabetes; gastrointestinal obstruction caused by foci; active bleeding or coagulation dysfunction; chemotherapy contraindications; contraindications of intervention chemoembolization treatment.

Methods

The patients in control group were given intravenous chemotherapy combined with DC-CIK treatment. The specific treatment regimen was as follows: intravenous chemotherapy: After mFOLFOX6 regimen for 4 courses, the curative effect was evaluated. Patients with significant effect continued the treatment while patients without effect applied mFOLFIRI regimen. The mFOLFOX6 regimen was as follows: oxaliplatin 100 mg/m^2 (intravenous infusion for 3 h), leucovorin 400 mg/m^2 (intravenous infusion for 2 h) and fluorouracil 2400 mg/m^2 (intravenous infusion for 46 h), two weeks as a course of treatment. The mFOLFIRI regimen was as follows: irinotecan 180 mg/m^2 (intravenous infusion for 1.5 h), calcium tetra hydro phosphate 400 mg/m^2 (intravenous infusion for 2 h), fluorouracil 2400 mg/m^2 (intravenous infusion for 46 h), and two weeks as a course of treatment. DC-CIK treatment: the peripheral blood mononuclear cells of patients were collected before intravenous infusion chemotherapy for DC-CIK cell cultivation. After two weeks, the endotoxin, bacteria and fungi contents of the cultured cells were detected. Qualified cells were dissolved in saline containing 2% albumin for 3 d continuous infusion, once a day for two courses.

The patients in study group were treated with interventional chemoembolization combined with DC-CIK. Interventional

chemoembolization: Seldinger method was used to place the catheter into the hepatic artery, followed by injection of fluorouracil 750 mg/m^2 , calcium folinate 200 mg/m^2 and oxaliplatin 120 mg/m^2 into the tumor blood supply artery. And then ultra-liquefied lipiodol and epirubicin 50 mg was fully mixed as emulsion into the arterial chemoembolization. The above operation repeated every 3 w for continuous 4 times. Postoperative patients were supplemented by hepatoprotective therapy. DC-CIK treatment was the same with control group.

Evaluation indicators

The tumor markers, clinical efficacy, survival rate and adverse reaction were compared between the two groups. Tumor markers mainly include Golgi protein 73 (GP73), Hypoxia-Inducible Factor (HIF-1 α) and High Mobility Group Protein B1 (HMGB1). The above-mentioned markers were detected by enzyme-linked immunosorbent assay.

According to the criteria of colorectal cancer with liver metastases, the therapeutic effect was divided into Complete Remission (CR), Partial Remission (PR), Stable Disease (SD) and Progressive Disease (PD), and overall response rate = CR + PR.

1 y and 2 y survival rate were determined.

Statistical methods

All the data of this study were analysed by SPSS19.0 software. The data were measured by t test. The chi-square χ^2 test was used for comparison between groups. $P > 0.05$ was defined as a significant difference.

Results

Comparison of serum tumor markers before and after treatment

The levels of serum tumor markers in groups were compared (Table 2).

Comparison of clinical efficacy of two groups

The clinical efficacy of study group and control group after treatment was compared (Table 3).

Table 1. General data of two groups.

Indexes		Study group (n=40)	Control group (n=40)	t value	P value
Gender (F/M)		22/18	24/16	1.104	0.062
Age (year)		40~79 (57 ± 2)	38~78 (58 ± 3)	0.932	0.067
Primary lesion (n)	Colon ascendens	4	5		
	Colon transversum	6	7		
	Colon sigmoideum	8	7	1.305	0.056

Clinical efficacy of transcatheter arterial chemoembolization combined with DC-CIK in the treatment of colorectal cancer with liver metastasis and its effect on the survival of patients

	Caecum	5	6		
	Rectum	17	15		
Metastatic lesions (n)	Single	14	12	0.953	0.085
	Multiple	26	28		

The contents of this study are informed and signed. The study was approved by the Ethics Committee.

Table 2. Comparison of serum tumor markers in both groups before and after treatment. (Note: #tumor markers serum level was not significantly different between groups before treatment, $P>0.05$; ##tumor markers serum levels were significantly different in control group before and after treatment, $P>0.05$; *tumor markers serum levels were significantly different in study group before and after treatment, $P>0.05$; **tumor markers serum level was significantly different between groups after treatment, $P>0.05$).

Time	Groups	GP73 (µg/L)	HIF-1α (ng/L)	HMGB1 (ng/L)
Before	Study	181.32 ± 20.62 [#]	587.75 ± 89.05 [#]	48.23 ± 5.71 [#]
	Control	179.53 ± 23.16 ^{##}	593.81 ± 86.63 ^{##}	48.29 ± 5.39 ^{##}
After	Study	48.38 ± 6.84 [*]	137.14 ± 17.52 [*]	15.23 ± 1.87 [*]
	Control	94.72 ± 10.35 ^{**}	217.34 ± 35.26 ^{**}	27.67 ± 3.63 ^{**}

Table 3. Comparison of clinical efficacy of two groups.

Groups	Cases (n)	CR (n (%))	PR (n (%))	SD (n (%))	PD (n (%))	ORR (%)
Study	40	21 (52.5)	13 (32.5)	4 (10.0)	2 (5.0)	85.0
Control	40	16 (40.0)	10 (25.0)	8 (20.0)	6 (15.0)	62.5
χ ² value						4.856
P value						0.023

As shown in the above table, the study group was superior to control group ($P>0.05$).

Comparison of survival rates in both groups

The 1 y and 2 y survival rates of study group and control group were shown in Table 4 below.

Table 4. Comparison of survival rates in both groups.

Groups	Cases (n)	1 y survival rate (n (%))	2 y survival rate (n (%))
Study	40	30 (75.0)	18 (45.0)
Control	40	20 (50.0)	10 (25.0)
χ ² value		5.408	4.984
P value		0.017	0.028

The above table showed that the long-term survival rate of study group was better than that of control group ($P>0.05$).

Comparison of adverse events in both groups

Some patients of the two groups showed fever, nausea, vomiting and liver pain 1 to 5 d's after treatment. After symptomatic treatment, patients were restored within two

weeks. The incidence of adverse reactions in two groups of patients had no significant differences ($P>0.05$).

Discussion

Colorectal cancer is a common malignant tumor of digestive tract, the incidence of which is only second to gastric cancer [6]. Near and distant metastases are likely to occur at late stage. There are three types of cancer metastasis, including lymph node metastasis, hematogenous metastasis and direct invasion. Hematogenous metastasis is a common way for colorectal cancer transferring to the liver. Except for transferring to lymph node, colorectal cancer is most liable to transfer to the liver. The natural course of liver metastases was more than 5 to 10 months if no active interventions were taken [7,8]. For patients with liver metastases of colorectal cancer, the most effective therapy was the liver radical resection. However, this therapy was only applicable to 1/5 of the patients because of the multiple metastatic foci [9].

Normal liver blood-supply comes from two parts, hepatic portal vein (about 70% of the liver blood supply) and proper hepatic artery (30% of the blood supply). For liver tumors (including primary tumors and metastatic tumors), the blood supply mostly came from hepatic artery and little from hepatic portal vein [10]. Transcatheter arterial chemoembolization was a new method for the treatment of liver tumors in recent years.

The advantages were as follows: drugs were directly directed to the tumor site, and drug concentration was significantly higher than that in intravenous chemotherapy; iodized oil emulsion could be used as a carrier of chemotherapy drugs, so that long-term retention of drugs in the foci site was ensured, thus achieving sustained-release drug activity and increased chemotherapy effect; slow injection of iodized oil mixed emulsion for embolization of tumor blood supply resulted in tumor tissue death [11].

Studies have confirmed that the immune function of colorectal cancer patients was in the suppression state. The lower the immune function, the more possibility to immunological drift, as well as the lower anti-cancer ability [12]. Biological immunotherapy was a new type of anti-tumor therapy. Through *in vitro* supplementation, induction and activation of the body's own biological immune system, the activated immune cell was infused back to the patient's body, thus playing its immune killing effect [13]. DC and CIK cell immunotherapy were common biological immunotherapies on clinic, which were characterized by rapid proliferation and strong killing effect. DC recognized the antigen and activated the immune system, while CIK played killing effect by cytotoxicity. Therefore, the combined application had a good prospect.

Hepatic artery embolization chemotherapy combined with DC-CIK treatment has been applied in our hospital since 2012 for colorectal cancer with liver metastases patients, and remarkable results were achieved. After review of the case study, we have found that the interventional embolization chemotherapy combined DC-CIK treatment could significantly reduce tumor markers for patients in the study group. Compared with intravenous chemotherapy combined DC-CIK treatment in the control group, the decline in study group was more significant ($P>0.05$); in the near period efficacy comparison, we also found that the decline in study group was better ($P>0.05$). The long-term efficacy showed the same result in study group ($P>0.05$), and there was no significant difference in the adverse reactions for the two groups.

In summary, interventional embolization chemotherapy combined DC-CIK therapy had good effect on colorectal cancer with liver metastases in patients. The therapy showed extended survival time and tolerated adverse reactions, which was worthy of clinical work reference.

References

1. Mainenti PP. Non-invasive diagnostic imaging of colorectal liver metastases. *World J Radiol* 2015; 7: 157-169.
2. Ramirez-Plaza CP, Moreno-Ruiz FJ, Perez-Daga JA. A multidisciplinary approach for peritoneal carcinomatosis and bilobar liver metastases from colorectal cancer: case report and review of the literature. *World J Surg Oncol* 2015; 13: 1-6.
3. Akhlaghpour S, Aziz-Ahari A, Amoui M, Tolooee S, Poorbeigi H. Short-term effectiveness of radiochemoembolization for selected hepatic metastases with a combination protocol. *World J Gastroenterol* 2012; 18: 5249-5259.
4. Chiara DD. Late complete response after long remission from treatment with FOLFIRI-aflibercept for metastatic colorectal cancer after progression to FOLFOX-bevacizumab. *Recent Prog Med* 2015; 106: 407-413.
5. Sperling J. Liver-directed chemotherapy of cetuximab and bevacizumab in combination with oxaliplatin is more effective to inhibit tumor growth of CC531 colorectal rat liver metastases than systemic chemotherapy. *Clini Exp Metastasis* 2013; 30: 447-455.
6. Imperatori A. Durable recurrence-free survival after pneumonectomy for late lung metastasis from rectal cancer: case report with genetic and epigenetic analyses. *BMC Cancer* 2015; 15: 567.
7. Ge SP, Liu Q. Interventional embolization chemotherapy combined with DC-CIK in the treatment of colorectal cancer with liver metastasis. *J Pract Oncol* 2016; 31: 1277-1279.
8. Brudvik KW. Aggressive treatment of patients with metastatic colorectal cancer increases survival: a Scandinavian single-center experience. *HPB Surg World J Hepatic Pancr Biliary Surg* 2013; 2013: 727095.
9. Youlong MA. Effect of docetaxel combined regimen transarterial interventional therapy on short and long-term survival rate of patients with liver metastasis of colorectal cancer. *China Medical Herald* 2015; 12: 78-89.
10. Chen-Jei T. Aqueous extract of *Solanum nigrum* leaves induces autophagy and enhances cytotoxicity of cisplatin, doxorubicin, docetaxel, and 5-fluorouracil in human colorectal carcinoma cells. *Evi Based Compl Altern Med* 2013; 2013: 514719.
11. Eichler K. First human study in treatment of unresectable liver metastases from colorectal cancer with irinotecan-loaded beads (DEBIRI). *Int J Oncol* 2012; 41: 1213.
12. Niu L. Study of outcomes and risk factors in patients undergoing simultaneous resection with colorectal liver metastases. *China J Mod Med* 2016.
13. Lahti SJ. KRAS status as an independent prognostic factor for survival after yttrium-90 radioembolization therapy for unresectable colorectal cancer liver metastases. *J Vasc Interv Radiol* 2015; 26: 1102-1111.

*Correspondence to

Wen-cai Weng

Interventional Radiography in Xinhua Hospital Affiliated to Dalian University

PR China