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Clinical therapeutic effects of hepatic arterial chemoembolization combined with cetuximab on patients with colorectal liver metastases.

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Abstract

Objective: To discuss clinical therapeutic effects of hepatic arterial chemoembolization combined with cetuximab on patients with colorectal liver metastases.

Methods: 50 patients with colorectal liver metastases admitted by our hospital from February 2010 to February 2012 were selected and divided into observation group and control group with 25 patients in each by random lottery. Hepatic arterial chemoembolization was given to patients in control group, and cetuximab was used based on it for patients in observation group. After treatment, clinical therapeutic effects, life quality and adverse effects of patients were compared between two groups. Three years of follow-up was conducted for patients in two groups, and survival rate was analyzed.

Results: After treatment, the effective rate of observation group was 88%, significantly higher than 64% for control group. Carcino-Embryonic Antigen (CEA) (18.53 ± 3.04) μg/L, CA242 (31.24 ± 2.85) IU/ml and CA19-1 (34.68 ± 3.06) KU/ml for patients in observation group were significantly lower than CEA (33.27 ± 4.23) μg/L, CA242 (53.13 ± 4.87) IU/ml and CA19-1 (62.35 ± 6.73) KU/ml in control group, while the life quality and survival rate of observation group were significantly higher than those of control group with statistical significance (P<0.05). The incidence rate of adverse effects, including acneiform rash of patients in observation was 80%, significantly higher than 4% in control group with statistical significance (P<0.05), while the incurrence rate of adverse effects, including nausea and vomiting and diarrhea had no statistical significance (P>0.05).

Conclusion: The therapeutic effects of hepatic arterial chemoembolization combined with cetuximab on patients with colorectal liver metastases were definite that it is worth to be promoted with effective improvement of life quality and survival rate.

Keywords: Hepatic arterial chemoembolization, Cetuximab, Liver metastases.

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Introduction

Rectal carcinoma is a common gastrointestinal cancer. A large amount of researches show that the morbidity rate of rectal carcinoma ranks the third, only following lung cancer and stomach cancer, and the morbidity rate of male is higher than that of female [1]. Liver is the most primary target organ for hematogenous metastasis of rectal carcinoma, while colorectal liver metastasis is the primary cause for the death of patients with rectal carcinoma. Relevant studies shows that about 20% patients with hepatic carcinoma also have liver metastases when obtaining definite diagnosis [2], while some patients are diagnosed with liver metastases in review after taking rectal carcinoma radical operation. The most patients with liver metastases cannot take radical lesionectomy. In clinical, chemotherapy is the major therapeutic method to treat colorectal liver metastases. Hepatic arterial chemoembolization is an important treatment means to treat liver tumor in clinical with significant therapeutic effect on primary hepatic carcinoma. Relevant reference shows that the therapeutic effect of hepatic arterial chemoembolization on liver metastases is worse than that on primary liver cancer [3], but it also has relatively better clinical therapeutic effect. Some scholars think that cetuximab combining with hepatic arterial chemoembolization has more significant clinical effects [4]. This work treated patients with colorectal liver metastases by hepatic arterial chemoembolization combined with cetuximab. The report is as follows.

Colorectal Liver Metastases (CLM) develop over half-developed metastases. Several CLMs are un-resectable due to the spread of intra-hepatic diseases as well as/or extra-hepatic diseases. For resections, as less as twenty percent of individuals with CLM as well as with modern oncosurgical methods, individuals with resected CLMs could have to around fifty to sixty percent five-year overall survival (OS). CLMs are typically asymptomatic as well as diagnosed with surveillance cross-sectional imaging, like Computed Tomography (CT). As eighty percent of metastases are found in the first three years, the primary diagnoses given below are for stage 3 as well as

higher-risk stage 2 individuals, annual CTs are recommended by the National Comprehensive Cancer Network for the first three to five years after primary resections. 5 imaging is augmented by interval colonoscopy as well as serum Carcinoem Bryonic Antigen (CEA) measurements. Sometimes, individuals suffer from pain, abdominal distention as well as liver insufficiency wherein the patients typically have severe CLMs with considerable hepatic tumour burden. The asymptomatic individuals have lesser likelihood of undergoing treatment because of cancer burdens as well as performance statuses. Percutaneous needle biopsies of doubted CLM are not necessary when imaging identifies novel lesions with unique imaging attributes for CLMs. When benign or non-CLM lesions are doubted, the needle biopsy is correct and could not be done non-invasively with MRIs and treatment plans might change on the basis of the outcomes [5].

Oncologically, individuals with restricted extra-hepatic diseases in controllable areas (for example, portal lymph nodes or tiny lung metastases) may find hepatic resections beneficial. Biologically, the individuals are at greater risk of recurrence and hence need perioperative chemotherapy. Although patients with restricted growth of already present CLMs when on pre-operative therapy, yet whose tumours are still anatomically resectable, ought to go through resection. However, individuals who have new CLM development or interval extra-hepatic disease when on therapy ought not to go through resections till their systemic diseases are controlled. Like other malignant issues, there are several individuals with CLMs who have other advanced diseases, which border on non-resectability. With CLMs, the problems which require addressal in the population are questionable Future Liver Remnants (FLR), perivascular location, as well as baseline liver parenchymal functions. The capacity for treating severe CLMs depends on institutional resource. Several individuals suffering from CLMs have treatment with chemotherapy before liver resections.

Table 1. *Comparison of general data between two groups.*

Group	Patients	Sex (n)		Age (years)	Differentiation degree (n)			Primary focus status (n)		Hepatic metastases (n)	
		Male	Female	High differentiation	Moderate differentiation	Low differentiation	Excised	Not excised	Single occurrence	Multiple occurrence	
Observation group	25	16 (64.0)	9 (36.0)	57.65 ± 4.75	5 (20.0)	15 (20.0)	5 (20.0)	7 (28.0)	18 (72.0)	5 (20.0)	20 (80.0)
Control group	25	18 (72.0)	7 (28.0)	57.17 ± 4.28	6 (24.0)	14 (56.0)	5 (20.0)	8 (32.0)	17 (68.0)	6 (24.0)	19 (76.0)
X^2/t value		X^2=0.3676		t=0.3754	X^2=0.1254			X^2=0.0952		X^2=0.1166	
P value		P=0.5443		P=0.7090	P=0.9392			P=0.7576		P=0.7328	

Materials and Methods

General data

A total of 50 patients with colorectal liver metastases admitted by our hospital from February 2010 to February 2012 were selected. Inclusion criteria: 1) Satisfying with diagnosis standard of malignant rectal tumor [6] and making definite diagnosis by relevant examination; 2) Being verified as colorectal liver metastases which cannot be excised by operation; 3) Focus of patient was measurable; 4) Patients did not have chemotherapy in one month after being admitted in hospital; exclusion criteria: 1) Patients had severe organ dysfunction; 2) The estimated survival period of patients was less than 3 months. All above patients were divided into observation group and control group randomly with 25 patients in each, including 16 male patients and 9 female patients in age of 44~70 years old. Among these patients, 5 were high differentiated, 15 moderate differentiated and 5 low differentiated. Moreover, 7 patients had primary focus excised, and 18 had no primary focus excised; 5 patients had 1 metastasis, and 20 had 2 or more. In control group, there were also 25 patients, including 18 male patients and 7 female patients in age of 45~70 years old. Among these patients, 6 patients were high differentiated, 14 moderate differentiated and 5 low differentiated. Moreover, 8 patients had primary focus excised, and 17 had no primary focus excised; 6 patients had 1 metastasis, and 19 had 2 or more. By comparing sex, age, differentiation degree, primary focus status, hepatic metastases and other general data between two groups, there was no significant difference (P>0.05) with comparability (P>0.05) (Table 1).

Methods

Before treatment, patients in two groups took routine examination. Patients in control group were given with hepatic arterial chemoembolization. Specifically, Seldinger method was conducted for femoral artery puncture, and conduit was placed in arteria coeliaca or arteria hepatica communis for radiography. Arteria hepatica propria or left hepatic arteries were selected for infusion chemotherapy and embolotherapy according to specific condition of patients. The main medicine for infusion was 5-Fluorouracil [Xi'an Haixin Pharmaceutical

Co., Ltd., 125 mg (5 ml), 20091024] (750-1000 mg) and oxaliplatin [Qilu Pharmaceutical (Hainan) Co., Ltd., 50 mg, 20090806] (100-200 mg), and embolic agent was 3-20 ml lipiodol emulsion and 10-20 mg mitomycin C suspension. Periodic treatment was conducted for patients with therapy interval of 1.5 months. Based on the treatment method for patients in control group, patients in observation group also used cetuximab (Boehringer Ingelheim Pharma GmbH Co KG, 100 mg/20 ml, 20090126). Specifically, the dose of the first irrigation was 400 mg/m^2 for 2 h intravenous drip. After then, the dose for each time was 250 mg/m^2 for 1 h intravenous drip once every week. Patients in both groups were treated for 4.5 months. After treatment, clinical efficiency, adverse effect and other conditions were observed in 3-year follow-up, and survival rate was analyzed in statistical.

Observation index

Before and after treatment, the level of tumor marker sin serum, carcino-embryonic antigen (CEA), mucus antigen related to tumor (CA242), carbohydrate antigen 19-9 (CA19-9) and living quality of patients in two groups were observed. Then, clinical curative effect, adverse reaction and survival rate after treatment were analyzed for comparison. The standard of life quality score was Karnofsky performance score with total score of 100 every 10 scores as one grade [7]. The higher the score is, the better the physical condition of patients will be. Evaluation criteria for clinical curative effect should follow relevant references [8]. Specifically, 1) Complete remission: all the target focuses disappear completely, and the level of tumor markers becomes normal; 2) Partial remission: the total sum of baseline focus length of patients shrinks by more than 30%; 3) Stabilization: the total sum of baseline focus length of patients shrinks by less than 30%, and the levels of tumor markers have no change; 4) The total sum of baseline focus length of patients shrinks by more than 30%, or new focus occurs.

Table 2. *Comparison of clinical efficiency between two groups [(n)%].*

Group	Patients	Complete remission	Partial remission	Stable	Progress	Effective rate
Observation group	25	2 (8.0)	15 (60.0)	5 (20.0)	3 (12.0)	22 (88.0)
Control group	25	1 (4.0)	8 (32.0)	7 (28.0)	9 (36.0)	16 (64.0)
χ^2/u value		u=2.3333				χ^2=3.9474
P value		P=0.0196				P=0.0469

Table 3. *Comparison of life quality score between two groups before and after treatment (score, x ± s).*

Group	Patients	Before treatment	After treatment	t value	P value
Observation group	25	69.86 ± 3.31	93.89 ± 4.23	22.3696	0
Control group	25	70.05 ± 3.62	85.74 ± 4.18	14.1872	0
t value		0.1937	6.8523		
P value		0.8472	0		

Table 4. *Comparison of tumor marker level between two groups before and after treatment (score, x ± s).*

Group	Patients	CEA (μg/L)		t value	P value	CA242 (IU/ml)		t value	P value	CA19-1 (KU/ml)		t value	P value
		Before treatment	After treatment	Before treatment		After treatment	Before treatment	After treatment					
Observation group	25	64.74 ± 5.05	18.53 ± 3.04	39.1981	0	89.67 ± 6.11	31.24 ± 2.85	43.3328	0	121.31 ± 11.14	34.68 ± 3.06	37.4936	0
Control group	25	63.93 ± 5.32	33.27 ± 4.23	22.555	0	88.75 ± 6.63	53.13 ± 4.87	21.6498	0	120.35 ± 10.93	62.35 ± 6.73	22.5931	0
t value		0.5521	14.1484			0.5102	19.3969			0.3076	18.7136		
P value		0.5834				0.6122	0			0.7597	0		

Statistical analysis

SPSS 18.0 was selected for data statistics. The measurement data in this work was represented with mean ± standard deviation ($\bar{x} \pm s$), and comparison was conducted with t test. Enumeration data was represented with [(n)%], and comparison was conducted with χ^2 test. The ranked data was compared with rank sum test. When P<0.05, difference has statistical significance.

Result

Analysis on clinical curative effect: After treatment, the effective rate of observation group was 88%, significantly higher than 64% of control group with statistical significance (P<0.05) (Table 2).

Analysis on life quality score: Before treatment, the life quality score of patients has no statistical significance between two groups (P>0.05). After treatment, the life quality score of patients in observation group was significantly higher than that in control group with statistical significance (p<0.05) (Table 3).

Analysis on tumor marker level: Before treatment, the level of CEA, CA242 and CA19-1 of patients had no statistical significance between two groups (P>0.05). After treatment, the level of CEA, CA242 and CA19-1 of patients in observation was significantly lower than that in control group with statistical significance (P<0.05) (Table 4).

Analysis on adverse reaction: During the treatment, patients in two groups all had adverse reactions, including nausea and vomiting, diarrhea, neurovirulence, myelosuppression, stomatitis, mucous membrane and acneiform rash. The difference of occurrence rate in acneiform rash between two groups had statistical significance (P<0.05), while the difference of occurrence rate in other adverse reactions had no statistical significance (P>0.05) (Table 5).

Table 5. Comparison of adverse reaction between two groups [(n)%].

Group	Patients	Nausea and vomiting	Diarrhea	Neurovirulence	Myelosuppression	Stomatitis and mucous membrane	Acneiform rash
Observation group	25	18 (72.0)	5 (20.0)	18 (72.0)	16 (64.0)	7 (28.0)	20 (80.0)
Control group	25	20 (80.0)	4 (16.0)	16 (64.0)	20 (80.0)	5 (20.0)	1 (4.0)
X^2value		0.4386	0.1355	0.3676	1.5873	0.4386	29.6388
P value		0.5078	0.7128	0.5443	0.2077	0.5078	0

Analysis on survival rate: The survival rate of patients in observation group was higher than that in control group after treatment with statistical significance (P<0.05) (Table 6).

Table 6. Comparison of survival rate after treatment between two groups (n (%)).

Group	Patients	One year	Three years
Observation group	25	20 (80.0)	6 (24.0)
Control group	25	13 (52.0)	1 (4.0)
χ^2 value		4.3672	4.1528
P value		0.0366	0.0416

Discussion

As one of digestive system cancers, rectal carcinoma has extremely high morbidity ranking the 4th among all cancers in China. With the increase of living standard at present, the morbidity of rectal carcinoma tends to rise gradually. Hepatic metastasis is the most common complication for rectal carcinoma and one of the important factors affecting prognosis [9]. Relevant references show that without treatment, patients with colorectal liver metastases can only survive for only about 7 months [10]. If patients with rectal carcinoma have hepatic metastases, it means that the disease has been in Stage Dukes D. Generally, however, liver is the only metastatic site, so positive and effective treatment has very important clinical significance to prognosis and can obviously improve the survival rate of patients. In clinical, after taking radical cure for primary tumor of rectal cancer, the curative target can be reached after excising liver metastasis by operation with good prognosis. However, this method is limited by the principle of radical treatment. Moreover, the excision must be feasible with visible focus and clean incisal edge without cancer. Meanwhile, liver with sufficient function has to be kept in excision. Therefore, only few patients can receive excision [11].

Patients with colorectal liver metastases who are not satisfied with excision will be treated by systemic chemotherapy, local therapy, etc. which can also improve the lifetime of patients. Moreover, some patients will obtain opportunity of operative treatment for stage II. Systemic chemotherapy becomes common operation method because of simple and feasible operation [12]. With the continuous development of medical technology in recent years, hepatic arterial chemoembolization also becomes common treatment method. For healthy people, common liver has dual blood supply with hepatic artery and portal vein, while the most supplied blood is from portal vein. For patients with colorectal liver metastases, when the volume of metastatic hepatic neoplasm increases in growth, new vessel will generate. When the tumor increases to 1.5~3 cm, the most blood is supplied by hepatic artery [13]. Hepatic arterial chemoembolization takes advantage of the difference between different blood supplies to significantly decrease the blood supplied to liver tumor and make the tumor avascular necrosis

after embolizing the hepatic artery. Therefore, the treatment of colorectal liver metastases with hepatic arterial chemoembolization can increase the local concentration of chemotherapeutics and make the drug release slowly and constantly act to tumor when inhibiting tumor.

Relevant scholars said that the proliferation of rectal carcinoma has very close relationship with epidermal growth factor receptor [14]. As the monoclonal antibody of IgG1, cetuximab can combine with the specificity of ectoenzyme kinase of epidermal growth factor receptor to competitively inhibit the combination between epidermal growth factor receptor and other ligands and interdict the signal conduction. Therefore, cetuximab can finally inhibit cell growth and control tumor [15]. Moreover, relevant references show that cetuximab has good clinical effects in treatment of colorectal liver metastases [16]. Therefore, the treatment with hepatic arterial chemoembolization combining with cetuximab can make curative effect more significant. The results of this work also show that the tumor marker level of patients receiving combined treatment had significant decrease, and their living quality also improved with effective rate of clinical curative effect up to 88%. In three-year follow-up, the survival rate of patients three years after treatment was up to 24%. During the treatment, patients had nausea, vomiting, diarrhea and other adverse reactions, but the conditions were not severe with obvious remission after expectant treatment. After combined treatment, the most patients had acneiform rash which changed one month after taking drugs.

In conclusion, the treatment of colorectal liver metastases combining hepatic arterial chemoembolization with cetuximab can significantly decrease tumor marker level, improve the living quality of patients, promote clinical effects, and increase the survival rate.

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