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ORIGINAL ARTICLE

Effect of cetuximab combined with chemotherapy in treating metastatic colorectal cancer and its prognostic analysis

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Summary

Purpose: *To explore the efficacy and safety of cetuximab plus chemotherapy in the treatment of metastatic colorectal cancer (mCRC), and to analyze the possible factors affecting the prognosis.*

Methods: *Clinical data were collected from 136 patients who were definitely diagnosed with mCRC in our hospital from January 2015 to December 2016, and whose genetic test showed wild-type (WT) Kirsten Ras (KRAS), and they were randomly divided into two groups and underwent cetuximab plus chemotherapy (n=68, Cetuximab group) or only chemotherapy (n=68, Chemotherapy group). The clinical short-term efficacy, incidence of adverse reactions and quality of life score of patients were compared between the two groups, and the survival and disease progression were recorded during follow-up.*

Results: *After treatment, statistically significant differences were observed between Cetuximab group and Chemotherapy group regarding objective response rate (ORR) and disease control rate (DCR) [69.1% (47/68) vs. 60.3% (41/68), 85.3% (58/68) vs. 79.4% (54/68)] (p=0.282, p=0.368). After treatment, Cetuximab group exhibited notably higher physical and emotional functioning scores on the function subscale [(92.53±12.11) points vs. (88.39±11.78) points, p=0.045, (94.63±12.72) points vs. (89.06±12.40) points, p=0.011] and rash score on the symptom subscale [(39.35±9.73) vs. (35.51±9.09) points, p=0.019)] than Chemotherapy group. According to the follow-up results, the median overall survival (mOS) and median progression-free survival (mPFS) were 25.1 and 9.5 months, respectively, in Cetuximab group, and 19.8 and 7.4 months, respectively, in Chemotherapy group. Log-rank test showed that the OS and PFS in Cetuximab group were dramatically longer than those in Chemotherapy group (p=0.038, p=0.013). Based on the results of multivariate analysis, poor tumor differentiation was an independent risk factor for the mPFS and mOS of patients [hazard ratio (HR) =0.894, 95% confidence interval (CI) (0.581-0.987), p=0.034, HR=0.907, 95%CI (0.603-0.960), p=0.041].*

Conclusion: *Cetuximab plus chemotherapy has significant efficacy in treating mCRC, which results in a higher long-term survival rate and a lower disease progression rate than chemotherapy alone, improves the quality of life of patients and produces tolerable adverse reactions. Besides, poor tumor differentiation is an independent risk factor for the mPFS and mOS of patients.*

Key words: *cetuximab, chemotherapy, colorectal cancer, efficacy, prognosis*

Introduction

Colorectal cancer (CRC), one of the most common malignancies worldwide, has metastasized in roughly 25% of the patients when diagnosed and will ultimately progress into metastatic CRC (mCRC) in about 50% of the patients [1]. At present, mCRC is prominently treated with chemotherapy, and conventional chemotherapy regimens, such as FOLFOX4, FOLFIRI and XELOX, can control tumor growth and extend the overall survival (OS) and disease-free survival (DFS) of patients, but they produce potent side effects [2,3]. With the significant advances in targeted therapy in recent years,

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chemotherapy combined with monoclonal antibodies as the targeted drugs can prolong the survival time of patients with advanced colon cancer by more than 24 months [4,5].

Cetuximab, as a molecular targeted drug, targets epidermal growth factor receptors (EGFRs) to effectively repress tumor cells with highly expressed EGFRs, thereby restraining tumor progression. According to the research results in recent years, cetuximab has significantly progressed in treating CRC [6,7]. Previous studies have found that Kirsten Ras (KRAS) gene mutation is a negative predictive factor for the efficacy of monoclonal antibodies against EGFRs. According to recent research, only all-RAS-wild-type (WT) patients can obtain benefits, but their response rate is only 60% or so after the first-line treatment combined with standard chemotherapy [8-10]. Since left-sided and right-sided colon cancer have different clinical and molecular features, anti-EGFR antibodies are more beneficial in RAS-WT left-sided colon cancer (including rectal cancer) than in right-sided colon cancer [11]. In the present study, a retrospective analysis was performed on the efficacy and safety of chemotherapy plus cetuximab and chemotherapy alone as the first-line therapy in mCRC, and the affecting factors for the efficacy and prognosis were analyzed.

Methods

General data

Clinical data were collected from 136 patients with mCRC admitted to our hospital from January 2015 to December 2016, and among them, 78 were male and 58 female, with an age range of 25-79 years and an average of 57.84±9.39 years. Inclusion criteria: (1) patients aged ≥18 years old, (2) those with inoperable mCRC, (3) those with tumor lesions in which the objective efficacy could be evaluated by computed tomography (CT), (4) those with WT-KRAS as shown by genetic test, (5) those with no contraindications to chemotherapy, and (6) those with an Eastern Cooperative Oncology Group (ECOG) score of 0-2 points. Exclusion criteria: (1) patients who were unable to tolerate chemotherapy for severe heart, lung, liver or kidney diseases, (2) those with metastasis in the central nervous system, (3) those with other malignant tumors, or (4) those with an expected survival time of <3 months. With the splenic flexure of the colon as a

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Cetuximab group (n=68)* n (%)	*Chemotherapy group (n=68)* n (%)	*p value*
Gender (Male/Female)	41/27	37/31	0.603
Age (years), mean±SD	58.86±9.52	57.06±8.84	0.255
BMI (kg/m^2), mean±SD	24.79±3.13	24.19±3.36	0.283
Tumor location			0.605
Left colon	61 (89.7)	58 (85.3)	
Right colon	7 (10.3)	10 (14.7)	
Differentiation grade			0.597
Poor	11 (16.2)	15 (22.1)	
Moderate	55 (80.9)	52 (76.5)	
High	2 (2.9)	1 (1.5)	
Metastasis			0.376
Single organ	23 (33.8)	28 (41.2)	
Multiple organs	45 (66.2)	40 (58.8)	
ECOG PS			0.385
0	21 (30.9)	17 (25.0)	
1	31 (45.6)	39 (57.4)	
2	16 (23.5)	12 (17.6)	
CEA level (ng/ml)			0.491
<10	39 (57.4)	35 (51.5)	
≥10	29 (42.6)	33 (48.5)	
Chemotherapy regimens			0.497
mFOLFOX6	27 (39.7)	29 (42.6)	
XELOX	19 (27.9)	23 (33.8)	
FOLFIRI	22 (32.4)	16 (23.5)	

BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; CEA: carcinoembryonic antigen

boundary, CRC was classified into left-sided colon cancer and right-sided colon cancer. Left-sided colon consists of the rectum, sigmoid colon, descending colon and splenic flexure, while right-sided colon is composed of the ascending colon, hepatic flexure and transverse colon. The baseline clinical data such as sex, age, tumor location, grade of differentiation and metastasis to organs showed no statistically significant differences between the two groups (p>0.05), and they were comparable (Table 1). All the enrollees were informed of this study and signed the informed consent in accordance with the *Declaration of Helsinki*. This study was approved by the Ethics Committee of Hubei Cancer Hospital.

Treatment methods

Cetuximab (Erbitux, Merck Serono Co., Ltd.) was first infused at 400 mg/m^2 for 120 min and then at 250 mg/m^2 per week or 500 mg/m^2 every two weeks for 60 min. Combined chemotherapy was conducted as follows: mFOLFOX6 regimen with oxaliplatin intravenously dripped at 85 mg/m^2, calcium folinate intravenously dripped at 400 mg/m^2 and fluorouracil intravenously injected at 400 mg/m^2 on d 1 and then fluorouracil persistently pumped at 2,400 mg/m^2 for 46 h (two weeks were taken as a course of treatment), XELOX regimen with oxaliplatin intravenously dripped at 130 mg/m^2 on d 1 and capecitabine tablets orally administered at 1,000 mg/m^2 twice daily during d 1-14 (a course of treatment lasted for three weeks), or FOLFIRI regimen with irinotecan intravenously dripped at 180 mg/m^2, calcium folinate intravenously dripped at 400 mg/m^2 and fluorouracil intravenously injected at 400 mg/m^2 on d 1 and then fluorouracil continuously pump-infused at 1,200 mg/m^2 for 22 h on d 1-2 (two weeks were set as a cycle of treatment). After 4-6 months of combined chemotherapy, maintenance therapy was administered with cetuximab and fluoropyimidine for patients with stable disease (SD) or response.

Observation indicators

At 8 weeks after treatment, all patients underwent CT for efficacy assessment based on the National Cancer Institute (NCI) Response Evaluation Criteria in Solid Tumors: complete response (CR): disappearance of all target lesions and no new lesions for at least 4 weeks, partial response (PR): a >30% decrease in the sum of the longest diameter of target lesions for at least 4 weeks, SD: neither sufficient shrinkage of lesions to qualify for PR nor sufficient increase in lesions to qualify for progressive disease (PD), and PD: a ≥20% increase in the sum of the longest diameter of target lesions or appearance of new lesions. The objective response rate (ORR) and disease control rate (DCR) were the proportions of cases of CR + PR and CR + PR + SD, respectively.

The incidence of adverse reactions of patients was recorded according to the NCI CTCAE 4.0, and the adverse reactions were classified as grade I-IV based on their severity. At 2 weeks after treatment, the quality of life of patients was assessed using the Quality of Life Questionnaire Core 30 (QLQ-C30) developed by the European Organization for Research and Treatment of Cancer (EORTC), and the results were converted to 0-100 points based on the EORTC scoring guideline. The higher scores on the function subscales and greater sum of scores for all subscales indicated better quality of life, while the quality of life was poorer in patients with higher scores on the symptom subscales.

All of the patients were followed up via outpatient clinic re-examination and telephone until December 2019, and patients' survival and disease progression were recorded. Overall survival (OS) was defined as the duration from the initiation of cetuximab therapy to the death of patients or the deadline of follow-up. Progression-free survival (PFS) was the duration from the initiation of cetuximab therapy to tumor progression or the death of patients for any reason.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were presented as mean ± standard deviation and intergroup comparisons were made using pairwise t-test. Enumeration data were expressed as ratio (%), and x^2 test was performed for intergroup comparisons. P<0.05 suggested that the differences were statistically significant. Survival curves were plotted using the Kaplan-Meier method, and log-rank test was used for survival comparisons between two groups. Multivariate survival analysis was conducted using Cox proportional hazards model to obtain independent factors affecting prognosis. P<0.05 was considered statistically significant.

Results

Clinical treatment outcomes

Cetuximab group and Chemotherapy group had 27 cases and 29 cases of mFOLFOX6 chemotherapy, respectively, 19 cases and 23 cases of XELOX chemotherapy, respectively, and 22 cases and 16 cases of FOLFIRI, respectively. Efficacy assessment was completed using CT for patients at 8 weeks after treatment. It was found that of the 68 patients in Cetuximab group, 8 achieved CR, 39 achieved PR, 11 had SD and 10 experienced

Table 2. Clinical effective rates of the two studied groups

	Cetuximab group (n=68) *n (%)*	*Chemotherapy group (n=68)* *n (%)*	*p value*
CR	8 (11.8)	5 (7.4)	
PR	39 (57.4)	36 (52.9)	
SD	11 (16.2)	13 (19.1)	
PD	10 (14.7)	14 (20.6)	
ORR	47 (69.1)	41 (60.3)	0.282
DCR	58 (85.3)	54 (79.4)	0.368

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; DCR: disease control rate

PD, with an ORR of 69.1% (47/68) and a DCR of 85.3% (58/68). Moreover, Chemotherapy group had 5 cases of CR, 36 cases of PR, 13 cases of SD and 14 cases of PD, and the ORR and DCR were 60.3% (41/68) and 79.4% (54/68), respectively. No statistically significant differences were observed between the two groups regarding ORR and DCR (p=0.282, p=0.368) (Table 2).

Quality of life scores

One month after treatment, the patients were followed up and their quality of life was recorded. According to the QLQ-C30 scale scoring, after treatment, Cetuximab group exhibited notably higher physical and emotional functioning scores on the function subscales [(92.53±12.11) points *vs.* (88.39±11.78) points, p=0.045, (94.63±12.72) points *vs.* (89.06±12.40) points, p=0.011] than Chemotherapy group. However, there were no statistically significant differences in the scores for role functioning, social functioning and cognitive functioning between the two groups (p>0.05). The scores for nausea and vomiting and fatigue on the symptom subscales after treatment were not statistically different between the two groups (p>0.05). Cetuximab group had a notably higher rash symptom score than Chemotherapy group [(39.35±9.73) points *vs.* (35.51±9.09) points, p=0.019) (Table 3).

Incidence of adverse reactions

No patients died of severe adverse reactions during treatment. All patients had different degrees of adverse reactions, mainly including bone marrow suppression, rash, gastrointestinal reactions, hepatic and renal function damage, neurotoxicity and hand-foot syndrome, and most of them were grade I-II and improved after symptomatic treatment. The following adverse reactions were of grade III and above: bone marrow suppression occurring in 2 (2.9%) cases and 3 (4.4%) cases, rash developing in 4 (5.9%) cases and 0 cases, gastrointestinal reactions found in 1 (1.5%) and 1 (1.5%) case, neurotoxicity appearing in 1 case (1.5%) and 2 cases (2.9%) and hand-foot syndrome affecting 1 case (1.5%) and 1 case (1.5%) in Cetuximab group and Chemotherapy group, respectively. It can be

Table 3. Comparison of posttreatment EORTC-QLQ-C30 scale scores of the studied patients in two groups

Complications	*Cetuximab group (n=68)*	*Chemotherapy group (n=68)*	*p value*
QLQ-C30			
Functioning scales			
Physical	92.53±12.11	88.39±11.78	0.045
Role	91.58±11.42	89.48±11.66	0.291
Emotional	94.63±12.72	89.06±12.40	0.011
Social	90.51±10.97	88.82±11.17	0.375
Cognitive	91.49±10.85	89.51±10.67	0.285
Symptom scales			
Fatigue	26.75±10.12	28.64±10.61	0.290
Nausea and vomiting	27.07±10.54	29.02±10.43	0.280
Rash	39.35±9.73	35.51±9.09	0.019

EORTC: European Organization for Research and Treatment of Cancer

Table 4. Comparison of complications of the studied patients in two groups

Parameters	*Cetuximab group (n=68)*		*Chemotherapy group (n=68)*		*p value*
	Grade I-II *n (%)*	*Grade III-IV* *n (%)*	*Grade I-II* *n (%)*	*Grade III-IV* *n (%)*	
Bone marrow suppression	36 (52.9)	2 (2.9)	39 (57.4)	3 (4.4)	0.486
Rash	41 (60.3)	4 (5.9)	15 (22.1)	0 (0)	0.001
Gastrointestinal reaction	37 (54.4)	1 (1.5)	34 (50.0)	1 (1.5)	0.606
Hepatic function damage	22 (32.4)	0 (0)	26 (38.2)	1 (1.5)	0.372
Renal function damage	7 (10.3)	0 (0)	10 (14.7)	0 (0)	0.437
Neurotoxicity	21 (30.9)	1 (1.5)	24 (35.3)	2 (2.9)	0.473
Hand-foot syndrome	23 (33.8)	1 (1.5)	5 (7.4)	1 (1.5)	0.001

seen that Cetuximab group had substantially higher incidence rates of rash and hand-foot syndrome than Chemotherapy group (p<0.001), while the incidence rates of bone marrow suppression, hepatic and renal function damage and neurotoxicity in Cetuximab group were lower than those in Chemotherapy group, with no statistically significant differences (p>0.05) (Table 4).

Postoperative follow-up results in the two groups

All patients were followed up for 6-36 months. According to the follow-up results, the median OS (mOS) and mPFS were 25.1 and 9.5 months, respectively, in Cetuximab group and 19.8 and 7.4 months, respectively, in Chemotherapy group. The 1-year OS rate was 77.9% (53/68) and 67.6% (46/68), 2-year OS rate was 54.4% (37/68) and 39.7% (27/68), and 3-year OS rate was 29.4% (20/68) 14.7% (10/68), respectively, in Cetuximab group and Chemotherapy group. Besides, the 1-year PFS rate was 41.2% (28/68) and 26.5% (18/68), and the 2-year PFS rate was 25.0% (17/68) and 11.8% (8/68), respectively, in Cetuximab group and Chemotherapy group. The OS and PFS curves were plotted using the Kaplan-Meier method in the two groups (Figure 1). The log-rank test showed that the OS and PFS in Cetuximab group were dramatically longer than those in Chemotherapy group (p=0.038, p=0.013).

Influencing factors for patient survival rate and tumor recurrence

The effects of the gender, age, tumor location, grade of tumor differentiation, number of organs affected by metastasis, level of serum carcinoembryonic antigen (CEA) before treatment, chemotherapy regimens and presence or absence of CR after treatment on the mPFS and mOS of patients were subjected to univariate analysis. According to the results, the mPFS of patients with mCRC was associated with the grade of tumor differentiation and presence or absence of CR after treatment (p=0.037, p=0.040), while their mOS was correlated

Table 5. Univariate analysis of predictors for mPFS and mOS in the studied patients.

Parameters	*Cases (n=136)*	*mPFS*		*mOS*	
	n (%)	*Months*	*p value*	*Months*	*p value*
Gender			0.284		0.570
Male	78 (57.4)	10.3		24.2	
Female	58 (42.6)	9.4		19.8	
Age (years)			0.197		0.728
<65	82 (60.3)	11.1		24.1	
≥65	54 (39.7)	9.5		22.6	
Tumor location			0.124		0.189
Left colon	119 (87.5)	10.6		24.8	
Right colon	17 (12.5)	8.9		17.9	
Differentiation grade			0.037		0.029
Poor	26 (19.1)	8.4		17.5	
Moderate	107 (78.7)	9.8		23.3	
High	3 (2.2)	11.7		25.4	
Metastasis			0.269		0.267
Single organ	51 (37.5)	10.9		24.6	
Multiple organ	85 (62.5)	9.1		20.9	
CEA level (ng/ml)			0.317		0.565
<10	74 (54.4)	10.8		24.4	
≥10	62 (45.6)	9.7		23.1	
Chemotherapy regimens			0.451		0.242
mFOLFOX6	56 (41.2)	10.9		24.3	
XELOX	42 (30.9)	10.6		23.7	
FOLFIRI	38 (27.9)	9.8		19.8	
CR after treatment			0.040		0.106
Yes	13 (9.6)	11.9		24.9	
No	123 (90.4)	8.8		19.7	

mPFS: mean progression free survival; mOS: mean overall survival; CEA: Carcinoembryonic antigen; CR: complete response

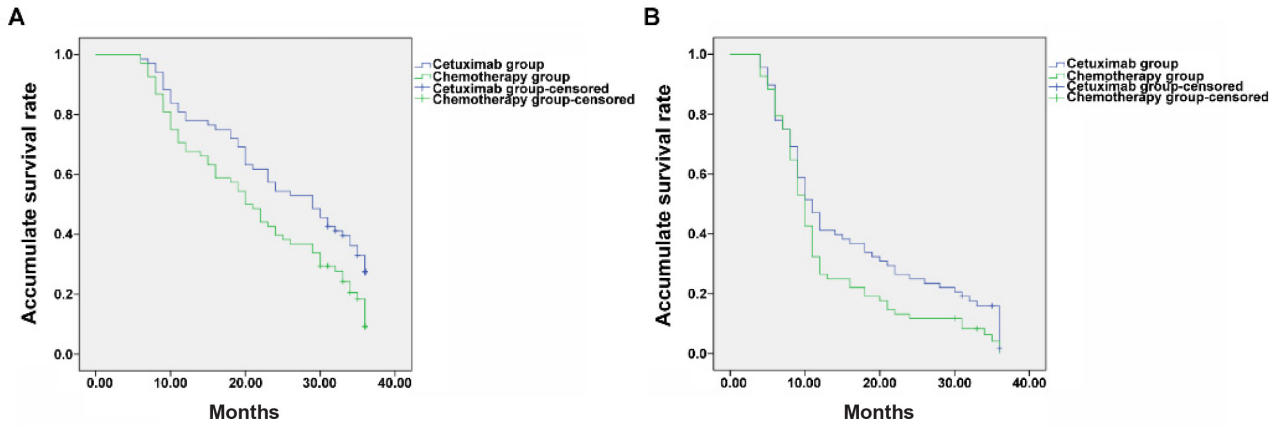

Figure 1. Kaplan-Meier survival curves of patients in Cetuximab group and Chemotherapy group. The overall survival rate **(A)** and progression free survival rate **(B)** of patients in Cetuximab group was significantly higher than that of Chemotherapy group (p=0.038, p=0.013).

with the grade of tumor differentiation (p=0.029) (Table 5). The above two factors were included into the Cox proportional hazards model for multivariate analysis, and the results revealed that poor tumor differentiation was an independent risk factor for the mPFS and mOS of patients [hazard ratio (HR) =0.894, 95% confidence interval (CI) (0.581-0.987), p=0.034, HR=0.907, 95%CI (0.603-0.960), p=0.041].

Discussion

Studies have demonstrated that EGFR is highly expressed in 72-82% patients with advanced mCRC and closely correlated with the malignant manifestations such as tumor cell invasion, metastasis and tumor angiogenesis [11]. According research findings in China and beyond, the high expression of EGFR indicates a poor prognosis [12]. The EGFR subfamily belongs to the tyrosine kinase receptor family, and the aberrant activation of EGFRs is closely associated with the growth, migration and angiogenesis of malignant tumors [13]. Cetuximab, a monoclonal antibody against EGFRs, can antagonize epidermal growth factor binding to EGFR site and restrain the activation of intracellular tyrosine kinases, thereby blocking the signaling in cell growth, which has become a hotspot in researching the treatment of EGFR KRAS-WT colon cancer in recent years [14].

A study showed that patients with KRAS-WT mCRC can obviously benefit from cetuximab combined with chemotherapy that prolongs their OS by more than 30 months [15]. In a meta-analysis of 2,188 patients with mCRC, it was found that the mutation rate of KRAS gene is 38% (829/2,188). Moreover, the response rate to cetuximab therapy was analyzed after grouping based on KRAS status, and the results revealed there is a statistically significant difference in the response rate between mutant group and WT group [14% (119/829) *vs.* 39% (529/1,359)] (p<0.01), and the former group exhibits significantly shorter mPFS and mOS than the latter group (p<0.05), indicating that neither tumor response nor no PFS and OS benefits are achieved in KRAS-mutant patients after treatment with chemotherapy plus cetuximab [16]. In the phase III CRYSTAL trial of Van Cutsem et al, the patients were assigned into C225 + FOLFIRI group and FOLFIRI group. It was discovered that the ORR, mPFS and mOS in the former group are considerably higher than those in the latter group (57.3% *vs.* 39.7%, 9.9 months *vs.* 8.4 months and 23.5 months *vs.* 20 months), and the differences are statistically significant (p<0.0001, p=0.0012 and p=0.0094) [17]. The OPUS study showed that the ORR, mPFS and mOS in C225 + FOLFOX group are notably higher than those in FOLFOX group (57.3% *vs.* 34%, p=0027, 8.3 months *vs.* 7.2 months, p=0.0064, and 22.8 months *vs.* 18.5 months, p=0.39) [18]. Additionally, the efficacy was compared among different targeted drugs combined with chemotherapy regimens in the CALGB 80405 trials, and the subgroup analysis showed that there are statistically significant differences between C225 + FOLFOX and C225 + FOLFIRI in terms of ORR, mPFS and mOS (67% *vs.* 62%, 11.3 months *vs.* 12.7 months, 32.5 months *vs.* 32 months) [19]. The above studies demonstrate that cetuximab combined with chemotherapy can notably benefit patients with advanced CRC, raise their ORR and extend their PFS and OS, but the benefits are not statistically correlated with the chemotherapy regimens.

In the present study it was found that there were statistically significant differences between Cetuximab group and Chemotherapy group with

regard to ORR and DCR [69.1% (47/68) *vs.* 60.3% (41/68), 85.3% (58/68) *vs.* 79.4% (54/68)] (p=0.282, p=0.368). According to the follow-up results, the mOS and mPFS were 25.1 months and 9.5 months, respectively, in Cetuximab group and 19.8 months and 7.4 months, respectively, in Chemotherapy group, and Cetuximab group had dramatically longer OS and PFS than Chemotherapy group (p=0.038, p=0.013), basically consistent with literature reports. Some authors have proposed that cetuximab may suppress tumors by enhancing the sensitivity of tumor cells to chemotherapy drugs in addition to a targeted effect. In the present study, no statistically significant difference was observed in ORR between Cetuximab group and Chemotherapy group probably because the overall sample size was slightly small and the combined chemotherapy regimens were not uniform. In terms of safety, adverse reactions were mostly of grade I-II, and they improved after symptomatic treatment. The incidence rates of rash and hand-foot syndrome in Cetuximab group were considerably higher than those in Chemotherapy group (p<0.001), with no statistically significant differences in the other adverse reactions.

Studies have suggested that the prognosis is poor in patients with mCRC involving multiple organs. The subgroup analysis of the NCIC CO.17 study has revealed better efficacy in single-organ metastasis. According to some literature reports, CEA ≥10 ng/mL indicates a poor prognosis in patients with stage I-III CRC. The results of this study suggested that poor tumor differentiation was an independent risk factor affecting the mPFS and mOS of patients. This result is different from that reported in the literature probably due to a small number of cases included and the difference in tumor stage in the present study [20,21].

This retrospective study was limited by its small sample size and less comprehensive follow-up contents. Therefore, the conclusion of the present study needs to be further corroborated by multicenter, large-sample prospective clinical studies combined with immunohistochemistry and test of tumor indicators and genes in the future.

Conclusions

Cetuximab plus chemotherapy has exact efficacy in treating mCRC. It increases the long-term survival rate and decreases the disease progression rate compared with chemotherapy alone, improves the quality of life of patients and produces tolerable adverse reactions. Besides, poor tumor differentiation is an independent risk factor for the mPFS and mOS of patients.

Conflict of interests

The authors declare no conflict of interests.

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