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Efficacy of Oxaliplatin/5-Fluorouracil/Capecitabine-Cetuximab Combination Therapy and Its Effects on *K-Ras* Mutations in Advanced Colorectal Cancer

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to perform an accurate exploration on the efficacy of oxaliplatin/5-fluorouracil/capecitabine-cetuximab combination therapy and its effects on *K-Ras* mutations in advanced colorectal cancer.

Material/Methods: Among 96 patients who suffered metastatic colorectal cancer without mutated *K-Ras*, 41 patients who were receiving treatment with oxaliplatin/5-fluorouracil/capecitabine and administered cetuximab as the initial treatment comprised the observation group; the remaining 55 patients receiving cetuximab as an alternative treatment comprised the control group.

Results: The observation group experienced significantly higher objective response rates (ORRs), and disease control rates (DCRs), than the control group ($P<0.05$ for both). The median progression-free survival (PFS) rates of the observation group and the control groups were 11.2 months (95% confidence interval [CI]: 10.1–12.3 months) and 7.4 months (95% CI: 6.6–8.2 months). The median overall survival (OS) rates were 16.8 months (95% CI: 15.2–18.4 months) and 12.4 months (95% CI: 11.6–13.2 months), respectively. The observation group had significantly longer PFS and OS in comparison to the control group ($P<0.05$). The patients who underwent cetuximab treatment for ≥10 months had a slightly higher rate of *K-Ras* mutations than those treated with cetuximab for <10 months (9.1% versus 7.3%).

Conclusions: Oxaliplatin/5-fluorouracil/capecitabine plus cetuximab exhibited better efficacy as initial treatment than the alternative treatment; it was also highly safe. Unfortunately, some patients might develop *K-Ras* mutations after long duration of cetuximab treatment, suggesting that *K-Ras* mutations are correlated with tumor progression and depend on the duration or dose of cetuximab treatment.

MeSH Keywords: Colorectal Neoplasms • Drug Combinations • Treatment Outcome

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Background

The incidence of colorectal cancer, a common malignant tumor of the gastrointestinal system, has been increasing in recent years [1,2]. In 2012, the estimated incidence rates of colorectal cancer in China were 16.9/100 000 in men and 11.6/100 000 in women. In the 2014 report issued by the Shanghai Municipal Center for Disease Control and Prevention, Shanghai was reported to have a colorectal cancer ranking in the second place on the most common malignancy list, with 43.3 of 100 000 people suffering from it [3,4]. Due to the lack of characteristic symptoms in early disease stages, >20% of colorectal cancer patients have metastasis at the time of diagnosis, which make its treatment more difficult.

In a couple of large clinical studies, the initial treatment integrating the targeted therapy with 5-fluorouracil-based chemotherapy has been proven to significantly extend progression-free survival (PFS) and overall survival (OS) while improving the resectability of colorectal liver metastases [5]. Cetuximab is an immunoglobulin G1 monoclonal antibody that blocks epidermal growth factor receptor (EGFR) signaling, thereby effectively inhibiting proliferation of tumor cells expressing EGFR and improving the anticancer effect of chemotherapy [6,7]. Since cetuximab effectiveness is restricted to patients with colorectal cancer where wild-type *K-Ras* genes are found, the NCCN Guidelines provide clear indication that DNA-based tests are required for *K-Ras* mutations prior to treatment with cetuximab in colorectal cancer patients.

Importantly, less than 35 of 100 patients with colorectal cancer in Asia harbor *K-Ras* mutations [8], which allow constitutive activation of the K-Ras protein independently of the EGFR signaling. Therefore, patients carrying such *K-Ras* mutations are less responsive to cetuximab and chemotherapy and have worse prognosis [9,10]. Although several studies [11] recently found that some patients with colorectal cancer exhibited resistance to cetuximab after treated with cetuximab for certain time periods, the underlying mechanism remains unclear.

In this current study, we investigated the efficacy and safety of the initial treatment combined chemotherapy agents (oxaliplatin/5-fluorouracil/capecitabine) with cetuximab for patients suffering from metastatic colorectal cancer but not harboring the *K-Ras* mutations. In addition, we examined the *K-Ras* mutation status of the patients following treatment to elucidate the mechanism of acquired resistance to the treatment protocol.

Material and Methods

Eligibility criteria

Patients in whom metastatic colorectal cancer was progressing with wild-type *K-Ras* genes totaled 96 in the trials, including 65 males and 31 females, age average was 50.92±21.88 years old (ranging from 24 to 81 years old), who were treated at the Oncology Department of the study institution. The study cohort included 57 patients and 39 patients with rectal and colon cancer, respectively. The metastases were to the liver, pelvis, lungs, and lymph nodes in 39, 21, 12, and 9 patients, respectively; there were also 6 patients with local recurrence. Patients were recruited in accordance with the following criteria [12]: 1) histopathologic diagnosis of metastatic colorectal cancer regardless of previous treatment; the last treatment ended >4 weeks before enrollment for those who received treatment previously; 2) absence of *K-Ras* mutations by genetic analysis; 3) Eastern Cooperative Oncology Group (ECOG) score for performance status [13] ≤2; 4) no contraindications to chemotherapy based on blood tests, routine urinalysis, electrocardiography, and other routine tests, Karnofsky Performance Score ≥70, and an expected survival time of >3 months; and 5) having 1 or more lesions capable of being measured. The exclusion criteria were as follows: 1) history or diagnosis of neurological disorders; 2) severe heart, lung, liver, or kidney dysfunction; 3) concomitant malignant tumor(s); and 4) pregnancy or breastfeeding. The study was started with approval of the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University, and with documented informed consent signed by all patients and their families.

Treatments

The 96 patients were assigned in a 1: 1 random fashion into an observation group (n=48) and a control group (n=48) in line with a random number table. The observation group was treated with the oxaliplatin/5-fluorouracil/capecitabine chemotherapy protocol, which was administered in combination with cetuximab. Oxaliplatin (Sanofi Pharmaceutical Co., Ltd., Hangzhou, China) was administered at 130 mg/m^2 by continuous intravenous infusion for 3 hours on Day 1. In addition, 5-fluorouracil (Xudong Haipu Pharmaceutical Co., Ltd., Shanghai) was intravenously injected at 400 mg/m^2 as the initial dose, and then 600 mg/m^2 of 5-fluorouracil was administered using a continuous intravenous infusion for 2 hours on Day 1 and Day 2 or orally 1800 mg/m^2 of capecitabine (Shanghai Roche Pharmaceutical Co., Ltd., Shanghai) was given in 2 doses on Days 1–14 and 200 mg/m^2 of calcium leucovorin was administered by continuous intravenous infusion for 2 hours on Day 1 and Day 2. The chemotherapy was performed in 21-day cycles. Besides the aforementioned chemotherapy agents, cetuximab was also initiated by continuous intravenous infusion over

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1 hour, at an initial dose of 400 mg/m^2 followed by a weekly maintenance dose of 250 mg/m^2. In addition, 40 mg of diphenhydramine was administered by intramuscular injection 30 minutes before administration of cetuximab. Oxaliplatin/5-fluorouracil/capecitabine was the monotherapy administrated to the control group using the same doses and schedules adopted in the other group. During chemotherapy, the patients in both groups were also provided symptomatic treatment to prevent vomiting and nutritional support; changes in routine blood and urine parameters as well as liver and kidney functions were monitored between the chemotherapy cycles. Clinical efficacy was evaluated regularly. If the patient's condition was stable or if the patient achieved remission or partial remission, the original treatment plan was continued unless intolerable side effects occurred.

Clinical indicators

Following treatment, physical examination and relevant laboratory evaluations between treatment cycles were coupled with evaluation of changes in lesions through computed tomography (CT) and/or magnetic resonance imaging (MRI) performed every 6–8 weeks.

Efficacy evaluation

Efficacy was evaluated as per RECIST (Response Evaluation Criteria in Solid Tumors) [13]. Complete response (CR) refers to complete disappearance of the lesion for at least 4 weeks, partial response (PR) ≥30% reduction of tumor size for at least 4 weeks, and progressive disease (PD) ≥20% increase in tumor size or novel-lesion emergence; all other situations were considered to indicate stable disease (SD). The short-term efficacy indicators were objective response rate or ORR, which was defined as CR plus PR/case count in total, and disease control rate (DCR), for which the dividend was that of ORR plus SD while the divisor kept unchanged. PFS was among the long-term efficacy measures, which signified the length of time marked off by the start of any treatment and the progression of the disease involved or disease-related death, and OS.

Safety evaluation

Adverse reaction evaluation was in accordance with v.4.03NCI Common Terminology Criteria (also called common toxicity criteria or CTC) for Adverse Events (CTCAE) [14].

Genetic analysis for *K-Ras* mutations

At the end of the follow-up period, with consent from the patients and their families, fresh tissue from the tumor site was obtained by needle biopsy, colonoscopy, or other means for DNA extraction and genetic analysis to determine the presence of *K-Ras* codon 12 and 13 mutations, regardless of tumor recurrence.

Statistical analyzing

SPSS Statistics 19.0 was the software specified in the study for statistical analyses. Measurement data were represented as means±standard deviation. Comparisons between the treatment groups were performed using independent samples *t*-test. Comparisons before and after treatment within the same treatment group were performed using paired *t*-test. Quantitative data were represented by numbers and compared using the χ^2 test. The Kaplan-Meier method was used herein to get PFS and OS estimates, and medians with 95% CI were calculated. The results were considered to show statistically significant differences at $P<0.05$.

Results

Comparison of baseline characteristics of the treatment groups

As shown in Table 1, there were no significant differences in age, sex, ECOG PS score, primary tumor sites, number of metastases, differentiation, and pathological type between the 2 treatment groups ($P=0.715$, 0.563, 0.748, 0.688, 0.673, 0.675, and 1.000, respectively).

Comparison of short-term efficacy indicators

A significant increase in both ORR and DCR was observed in the observation group compared to the control group ($P=0.002$, $P=0.009$, respectively). Cetuximab was thus indicated to markedly elevate the short-term clinical efficacy that those suffering metastatic colorectal cancer without *K-Ras* mutations showed after exposed to oxaliplatin/5-fluorouracil/capecitabine (Table 2).

Comparison of long-term efficacy indicators

All the patients received follow-up survey lasting a median of 15.6 months (95% CI: 12.3–27.8 months) until the end of June 2018. The median PFS of the entire cohort, the observation group and the control group were 10.1 months (95% CI: 8.2–11.7 months), 11.2 months (95% CI: 10.1–12.3 months), and 7.4 months (95% CI: 6.6–8.2 months), respectively. The median OS of the entire cohort, the observation group, and the control group was 13.5 months (95% CI: 16.7–24.5 months), 16.8 months (95% CI: 15.2–18.4 months), and 12.4 months (95% CI: 11.6–13.2 months), respectively. Obviously, the observation group experienced much longer PFS and OS compared with the control group ($P=0.003$, $P=0.007$ for both indicators),

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Table 1. Baseline data.

Characteristics	Observation group (N=55)	Control group (N=55)	χ^2	*P*
Age, years	51.27±9.83	50.66±7.45	0.367	0.715
Male, n (%)	33 (60.0)	30 (54.55)	0.334	0.563
ECOG PS score*			0.103	0.748
0–1	34 (70.83)	40 (72.73)		
2	11 (20.0)	15 (27.27)		
Primary tumor sites			0.161	0.688
Colon	35 (63.64)	37 (67.27)		
Rectum	20 (36.36)	18 (32.73)		
No of metastases			–0.422	0.673
1	25 (45.45)	27 (49.09)		
2	22 (40.0)	21 (38.18)		
3	5 (9.09)	5 (9.09)		
>4	3 (5.45)	2 (3.64)		
Differentiation			0.176	0.675
Low grade	17 (30.91)	15 (27.27)		
High grade	38 (69.09)	40 (72.73)		
Pathological type	53 (96.36)	52 (94.55)	0.343	1.000
Adenocarcinoma	1 (1.82)	2 (3.64)		
Mucinous adenocarcinoma	1 (1.82)	1 (1.82)		

* When treated with cetuximab. ECOG PS – Eastern Cooperative Oncology Group performance score.

Table 2. Comparison of the short-term outcomes between the 2 treatment groups.

	n	CR	PR	SD	PD	ORR (%)	DCR (%)
Observation group	55	3	21	23	8	24 (43.64)*	47 (85.45)*
Control group	55	2	7	26	20	9 (16.36)	35 (63.64)
χ^2						9.740	6.899
P						0.002	0.009

* *P*<0.05 compared with control group. CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; ORR – objective response rate; DCR – disease control rate.

suggesting that cetuximab significantly enhanced the long-term efficacy that patients living with metastatic colorectal cancer and wild-type *K-Ras* showed clinically upon exposure to oxaliplatin/5-fluorouracil/capecitabine. This was indicated by the significantly longer survival (Figure 1).

Comparison of adverse reactions

As shown in Table 3, in both treatment groups, the adverse reactions included gastrointestinal adverse effects, neurotoxicity, myelosuppression, and abnormal liver function. The incidence of adverse reactions did not vary markedly between treatment groups (*P*=0.203, 0.787, 0.242, 0.125, 0.534, 0.736, 0.550, 0.574, respectively). The majorities of the adverse reactions were in cases of grade 1 or grade 2, and were improved after symptomatic treatment, suggesting that oxaliplatin/5-fluorouracil/capecitabine-cetuximab combination therapy had a level of safety in treating metastatic colorectal cancer bearing wild-type *K-Ras*.

Short-term efficacy of cetuximab as initial or alternative treatment

DCR was significantly higher when cetuximab was used as initial treatment instead of the alternative treatment (*P*=0.001);

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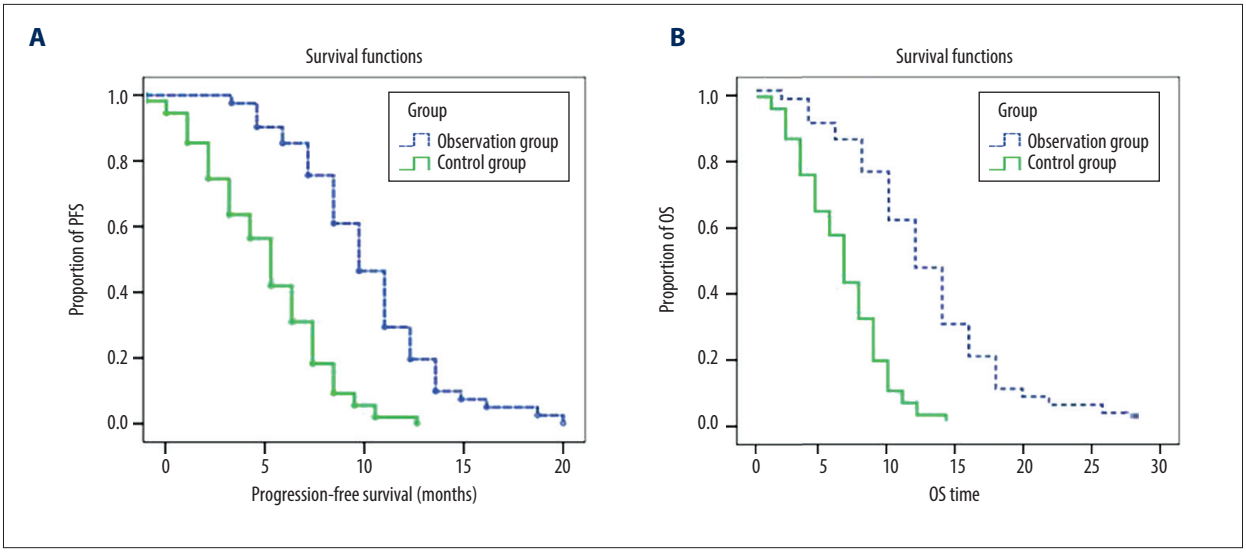

Figure 1. (**A, B**) Comparison of long-term survival.

Table 3. Comparison of the adverse reactions.

Adverse reactions	Observation group (n=41)			Control group (n=55)			χ^2	*P*
	1–2	3–4	n (%)	1–2	3–4	n (%)		
Leukopenia	16	5	21 (51.2)	19	2	21 (38.2)	1.622	0.203
Thrombocytopenia	6	0	6 (14.6)	7	0	7 (12.7)	0.073	0.787
Anemia	19	0	19 (46.3)	18	1	19 (34.5)	1.367	0.242
Gastrointestinal reaction	37	2	39 (95.1)	44	3	47 (85.5)	2.353	0.125
Nervous system toxicity	19	0	19 (46.3)	22	0	22 (40.0)	0.386	0.534
Altered liver function	7	0	7 (17.1)	8	0	8 (14.5)	0.114	0.736
Hand-foot syndrome	3	0	3 (7.3)	6	0	6 (10.9)	0.357	0.550
Rash	2	0	2 (4.9)	1	0	1 (1.8)	0.726	0.574

Table 4. Comparison of outcomes of Cetuximab as first-line and non first-line treatment.

	n	CR	PR	SD	PD	ORR (%)	DCR (%)
First-line treatment	26	3	13	8	2	16 (61.54)*	24 (92.31)*
Second-line treatment	29	0	5	16	8	5 (17.24)	21 (72.41)
χ^2						11.397	2.432
P						0.001	0.119

* *P*<0.05 in comparison to the control group. CR – complete response; DCR – disease control rate; ORR – objective response rate; PD – progressive disease; PR – partial response; SD – stable disease.

cetuximab was also associated with a slightly higher, albeit statistically non-significant (*P*=0.119), ORR when used as initial treatment (Table 4).

Long-term efficacy of cetuximab as initial or alternative treatment

The patients receiving cetuximab as initial treatment had a median PFS of 12.9 months (95% CI: 11.6–14.9 months) and a median OS of 19.4 months (95% CI: 18.1–24.5 months); furthermore,

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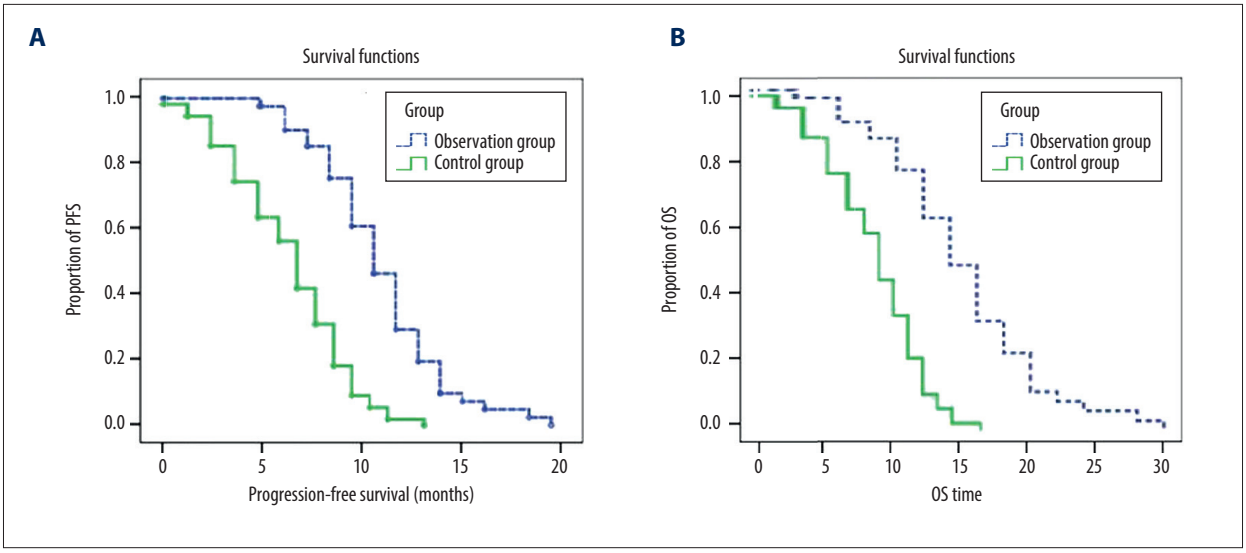

Figure 2. (**A, B**) Comparison of long-term efficacy between first-line and non first-line treatment with cetuximab.

Table 5. Rate of new *K-Ras* mutations detected in second testing after treatment.

	n	Wild type	Mutant	Mutation rate
First-line group	26	25	1	3.85%*
Second-line group	29	26	3	10.34%
χ^2				2.365
P				0.048

* *P*<0.05 versus second-line group.

Table 6. Efficacy of different cetuximab treatment cycles on *K-Ras* gene mutation.

	Wild type	Mutant	Total	Mutation rate
Cetuximab treatment <10 months	12	0	12	0*
Cetuximab treatment ≥10 months	28	15	43	34.9%
χ^2				4.131
P				0.042

* *P*<0.05 compared with cetuximab treatment for ≥10 months.

both PFS and OS were significantly longer in these patients than in those receiving cetuximab as alternative treatment: PFS was 10.5 months (95% CI: 10.1–12.4 months); OS was 15.9 months (95% CI: 15.2–18.2 months); *P*=0.016, *P*=0.027, respectively. This suggests that cetuximab had a higher efficacy when used as initial treatment than when used as alternative treatment in combination with oxaliplatin/5-fluorouracil/capecitabine (Figure 2).

The post-treatment rate of *K-Ras* mutations

A total of 55 patients, who were evaluated for *K-Ras* mutation status using the surgically resected lesions, underwent another genetic testing for *K-Ras* mutations. These patients received an average of 15.3 cycles of cetuximab (range, 4–35 cycles). All patients were subject to the second *K-Ras* testing in the last follow-up visit of the study. The samples were obtained by needle biopsy and colonoscopy in 17 and 38 patients, respectively. The analysis revealed that 5 of the 55 patients (7.27%) had *K-Ras* mutations in the second examination, and the rate of new *K-Ras* mutations was significantly greater in the patients receiving cetuximab as alternative treatment than in those receiving cetuximab as initial treatment. These results suggested that cetuximab was more inclined to association with *K-Ras* mutations in case of alternative treatment (Table 5).

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Effect of cetuximab treatment duration on *K-Ras* mutation rate

The 55 patients who were evaluated for post-treatment *K-Ras* mutation status were assigned to receive 2 therapeutic regimens based on the duration of cetuximab treatment: those treated with cetuximab for ≥10 months and <10 months. The second genetic evaluation which included the comparison of *K-Ras* mutation rates, found that patients who were treated with cetuximab for ≥10 months had significantly higher rates of *K-Ras* mutations than those who underwent cetuximab treatment for <10 months, suggesting that longer cetuximab administration was likely to cause an increase in rates of *K-Ras* mutations (P=0.042) (Table 6).

Discussion

Colorectal cancer morbidity and mortality rates have been steadily rising in recent years [15,16]. Cetuximab shines among EGFR-targeted medications that enable colorectal cancer to be treated in a novel approach due to its specific binding to the extracellular domain of EGFR, phosphorylation blocking capacity of its tyrosine kinase domain, and downstream signaling pathway activation suppression. It thereby inhibits malignant cell proliferation and the metastatic processes [17,18]. It has been found in some studies that cetuximab combined with chemotherapy for colorectal cancer patients showed a median PFS of 9.9 months, with ORR of about 57.3% [19]. Another study showed that ORR of bevacizumab combined with the first-line chemotherapy for advanced colorectal cancer reached 51.5%, and PFS was 12.6 months [20]. It has also been found that cetuximab prolongs PFS and OS in patients with left-sided colon cancer compared to optimal supportive therapy. All these studies have shown that cetuximab alone or in combination with chemotherapy can benefit colon cancer patients clinically. As shown in the results of the current study, the observation group had significantly higher or longer ORR, DCR, PFS, and OS than the controls, suggesting that the combination therapy that patients received for treating metastatic colorectal cancer with wild-type *K-Ras* resulted in significantly better short-term and long-term efficacy, mostly attributed to cetuximab. Our findings are consistent with those reported in the literature. However, the median PFS in this study was not as good as the clinical study afore mentioned but was similar to the reports of domestic Chinese scholars [21]. Considering the fact that this study was a single center study with small sample size, and some patients are treated with the second-line therapy, further studies are needed to expand the number of cases. In the BOND study of cetuximab as second-line therapy, the results showed that the combined treatment of cetuximab and irinotecan was significantly superior to the single-drug treatment in metastatic CRC patients with EGFR-positive expression and failure of basic chemotherapy [22]. Meanwhile, a FLIER study showed that cetuximab combined with FOLFIRI in second-line treatment of patients with advanced colorectal cancer had the median PFS of 7.4 months and ORR of 31.7% [23]. These studies showed that cetuximab combined with chemotherapy was significantly effective in second-line treatment of patients with advanced colorectal cancer. The study herein also covered examination of the combination therapy regarding its efficacy as either initial or alternative treatment. Upon our analyses, PFS and OS were valued at a median of 10.5 months (95% CI: 10.1–12.4 months) and 15.9 months (95% CI: 15.2–18.2 months), respectively, in patients receiving cetuximab as alternative treatment, suggesting that cetuximab remained beneficial even as an alternative treatment option, in agreement with previous reports [24]. Importantly, cetuximab led to significantly longer PFS and OS as initial treatment compared with the case in which the medication was dosed as alternative treatment. Conversely, ORR was slightly higher, albeit without significance, when cetuximab was taken as initial treatment other than as alternative treatment. This suggested that the earlier colorectal cancer patients of the specified genotype administrated cetuximab, the more benefits of the administration can be increased.

Most adverse reactions in the current study were in grade 1 or grade 2, none of which had an adverse effect on the continuation of the chemotherapy regimens, suggesting that cetuximab-chemotherapy combination therapy was a safe first-line treatment protocol adopted for treating advanced colorectal cancer with wild-type *K-Ras*.

Despite a good profile in advanced colorectal cancer treatment, cetuximab has its efficacy restricted to for those who harboring wild-type *K-Ras* [25,26], whereas its benefit in patients with mutated *K-Ras* is very limited [27]. Studies showed that colorectal cancer patients in the advanced stage of the disease had *K-Ras* mutations that were developed from wild-type *K-Ras* after treatment with EGFR-targeted therapies and that these mutations might have contributed to the resistance to drugs targeting EGFR [28]. In the current study, 4 of the 55 patients developed *K-Ras* mutations, with a mutation rate of 7.27%. Additionally, *K-Ras* mutations were at a much higher incidence rate when cetuximab was administrated to patients as an alternative treatment compared to given as initial treatment. The *K-Ras* mutations were also in significantly higher rates when cetuximab was given for ≥10 months compared to when cetuximab was administered for <10 months, revealing that long cetuximab use or cetuximab administration as alternative treatment might lead to higher rates of *K-Ras* mutation.

Conclusions

The current study demonstrated an association between secondary *K-Ras* mutations and tumor progression and the

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dependency of secondary *K-Ras* mutations on the length of cetuximab treatment and its use as an alternative option. However, due to the limited sample size, variations in sampling methods, and other potential human errors, the results are inevitably biased. Future studies including large cohorts with more effective control of non-tumor factors are necessary to provide confirmation of the findings in this study.

References:

1. Nakagawa H, Ito H, Hosono S et al: Changes in trends in colorectal cancer incidence rate by anatomic site between 1978 and 2004 in Japan. Eur J Cancer Prev, 2016; 26: 269–76
2. Ulanja MB, Beutler BD, Rishi M et al: Colorectal cancer presentation and survival in young individuals: A retrospective cohort study. Cancers (Basel), 2018; 10: pii: E472
3. Wang DX, Ji-Dong LI, Cong-Fei LI et al: [Incidence trend of colorectal cancer in Qiannan area of Guizhou Province, 1996–2015.] Modern Preventive Medicine, 2017 [in Chinese]
4. Han X, Huang C, Zhao J, Ding Y et al: [Incidence and survival of colorectal carcinoma among permanent residents in Yangpu district of Shanghai, from 2002 to 2012]. Zhonghua Liu Xing Bing Xue Za Zhi, 2014; 35: 289–94 [in Chinese]
5. Russo M, Siravegna G, Blaszkowsky LS et al: Tumor heterogeneity and lesion-specific response to targeted therapy in colorectal cancer. Cancer Discov, 2016; 6: 147–53
6. Arena S, Bellosillo B, Siravegna G et al: Emergence of multiple EGFR extracellular mutations during cetuximab treatment in colorectal cancer. Clin Cancer Res, 2015; 21: 2157–66
7. Arena S, Siravegna G, Mussolin B et al: Abstract B33: The oligoclonal antibody MM-151 overcomes acquired resistance to cetuximab and panitumumab in colorectal cancer cells harboring EGFR extracellular domain mutations. Cancer Res, 2016; 76: B33
8. Szpon L, Stal A, Zawadzki M, Lis-Nawara A et al: K-Ras gene mutation as an early prognostic marker of colon cancer. Pol Przegl Chir, 2016; 88: 15–19
9. Wang X, Wang J, Chen F et al: Detection of K-Ras gene mutations in feces by magnetic nanoprobe in patients with pancreatic cancer: A preliminary study. Exp Ther Med, 2018; 15: 527–31
10. Cárdenas-Ramos SG, Alcázar-González G, Reyes-Cortés LM et al: The frequency and type of K-Ras mutations in Mexican patients with colorectal cancer. Am J Clin Oncol, 2017; 40(3): 274–76
11. Lièvre A, Bachet JB, Boige V et al: K-Ras mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol, 2008; 26(3): 374–79
12. Qin S, Deng Y, Feng BI et al: Efficacy and safety of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of advanced metastatic colorectal cancer: A prospective, non-intervention and post-marketing multicenter clinical study (REACT). 2016.
13. Manig L, Käsmann L, Janssen S et al: Simplified Comorbidity Score and Eastern Cooperative Oncology Group Performance Score predicts survival in patients receiving organ-preserving treatment for bladder cancer. Anticancer Res, 2017; 37(5): 2693–96
14. Kosecoff J, Fink A, Cullen J et al: Guidelines for evaluating cancer control programs. Prev Med, 1982; 11(2): 187–98
15. Cheng X, Chen VW, Steele B et al: Greenlee R. Subsite-specific incidence rate and stage of disease in colorectal cancer by race, gender, and age group in the United States, 1992–1997. Cancer, 2001; 92(10): 2547–54
16. Safaee A, Fatemi SR, Ashtari S et al: Four years incidence rate of colorectal cancer in Iran: A survey of national cancer registry data – implications for screening. Asian Pac J Cancer Prev, 2012; 13(6): 2695–98
17. Rosenthal EL, Moore LS, Tipirneni K et al: Sensitivity and specificity of cetuximab-IRDye800CW to identify regional metastatic disease in head and neck cancer. Clin Cancer Res, 2017; 23: 4744–52
18. Bauml J, Seiwert TY, Pfister DG et al: Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: Results from a single-arm, phase II study. J Clin Oncol, 2017; 35: 1542–49
19. Van Cutsem E, Köhne C-H, Hitre E et al: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med, 2009; 360: 1408–17
20. Nishina T, Takano Y, Denda T et al: A phase II clinical study of mFOLFOX6 plus bevacizumab as first-line therapy for Japanese advanced/recurrent colorectal cancer patients. Jpn J Clin Oncol, 2013; 43: 1080–86
21. Xuewei L, Longwei C, Shumei C, Ze L: [Comparison of clinical efficacy between cetuximab and bevacizumab in patients with K-Ras gene wild-type metastatic colorectal cancer.] Chinese Journal of Gerontology, 2014; 6003–5 [in Chinese]
22. Cunningham D, Humblet Y, Siena S et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med, 2004; 351: 337–45
23. Iwamoto S, Hazama S, Kato T et al: Multicenter phase II study of second-line cetuximab plus folinic acid/5-fluorouracil/irinotecan (FOLFIRI) in K-Ras wild-type metastatic colorectal cancer: The FLIER study. Anticancer Res, 2014; 34: 1967–73
24. Taieb J, Zaanan A, Malicot KL et al: Prognostic effect of BRAF and K-Ras mutations in patients with stage III colon cancer treated with leucovorin, fluorouracil, and oxaliplatin with or without cetuximab: A post hoc analysis of the PETACC-8 trial. JAMA Oncol, 2016; 2(5): 643–53
25. Kim JS, Kim JE, Kim K et al: The impact of cetuximab plus AKT- or mTOR-inhibitor in a patient-derived colon cancer cell model with wild-type RAS and PIK3CA mutation. J Cancer, 2017; 8: 2713–19
26. Chan WL, Lee VH, Siu WK et al: Biweekly cetuximab and first-line chemotherapy in Chinese patients with K-Ras wild-type colorectal cancers. South Asian J Cancer, 2014; 3: 175–78
27. Ozaslan E, Topaloglu US, Inanc M et al: Efficacy and safety of cetuximab plus FOLFOX in second-line and third-line therapy in metastatic colorectal cancer. J BUON, 2017; 22: 863–68
28. Turhal NS, Savaş B, Çoşkun Ö et al: Prevalence of K-Ras mutations in hepatocellular carcinoma: A Turkish Oncology Group pilot study. Mol Clin Oncol, 2015; 3: 1275–79

Conflict of interest

None.

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