Original Article

Impact of KRAS Mutation on Second-line Oxaliplatin-based (FOLFOX-6) Chemotherapy for Metastatic Colorectal Cancer

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Key Words
Kirsten-ras;
Metastases;
Colorectal cancer;
Chemotherapy;
Oxaliplatin

Purpose. The aim of the present study was to evaluate the correlation between progression-free survival and different Kirsten–ras statuses in second-line oxaliplatin-based treatment.
Patients and Methods. From January 2010 to May 2014, 144 patients who had disease progression after treatment with irinotecan and bevacizumab for unresectable metastases or relapses from non-stage IV colorectal cancer were enrolled in this study. All patients received second-line oxaliplatin-based chemotherapy alone and were followed until December 2014. Their progression-free survival rates were compared among Kirsten-ras categories.
Results. Of the patients, 59 (41%) had Kirsten-ras mutation of exon 2. We identified several similarities between the wild-type and mutation groups in the distribution of primary cancer resection (p = 0.402), first-line irinotecan-based chemotherapy with bevacizumab (p = 0.273), median age (60 vs. 61), sex (p = 0.609), and numbers of metastatic sites (p = 0.518). The progression-free survival was longer for patients in the mutation group than for those in the wild-type group when they received second-line oxaliplatin (4.8 mo; 95% CI, 3.1 to 6.5 mo vs. 3.4 mo; 95% CI, 3.0 to 3.8 mo; p = 0.0048). In multivariate analysis, Kirsten-ras mutation of exon 2 showed prognostic value regarding progression-free survival during second-line oxaliplatin therapy (hazard ratio, 0.585; 95% CI, 0.399-0.858; p = 0.006). Second-line oxaliplatin-based chemotherapy might cause metastatic colorectal cancer patients with the KRAS mutation of exon 2 to have longer progression-free survival than that of patients with the wild-type Kirsten-ras gene.
Conclusions. Second-line oxaliplatin-based chemotherapy prolonged progression-free survival for patients with metastatic colorectal cancer in the Kirsten-rasmutation group compared with those in the wild-type group.
Mini Abstract. The study demonstrated differences in the impact of second-line oxaliplatin-based chemotherapy on progression-free survival in patients with different KRAS statuses. In multivariate analysis, KRAS mutation showed independent prognostic value.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2017;28:34-42*]

Received: August 31, 2016. Accepted: November 21, 2016.
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Authors' contributions: Kuo YH and Chin CC contributed equally to this work; Dr. Kuo and Chin designed the report, analyzed the raw data and provided the discussion and review of literature.

Colorectal cancers were the third most common cause of cancer mortality in Taiwan in 2012. Approximately 15-20% of rectal and colon cancer patients were diagnosed with synchronous metastasis (http://www.hpa.gov.tw). Generally, chemotherapy can provide substantial improvements in these patients' survival, but curing metastatic colorectal cancer with chemotherapy alone is rare. The median overall survival (OS) has been improved from 1 year with fluorouracil monotherapy to more than 2 years with oxaliplatin-based or irinotecan-based chemotherapy following the addition of current biological agents.[1] In the last decade, a detrimental effect has been reported in patients with Kirsten-ras (KRAS) mutation who received cytotoxic chemotherapy combined with anti-epidermal growth factor receptor (EGFR) agents.[2-5] Cetuximab is now considered efficacious only in patients with the wild–type KRAS gene, and current guidelines on cetuximab treatment recommend testing for KRAS mutationas a routine procedure.

In efficacy studies of anti-EGFR agents combined with oxaliplatin, OPUS study revealed that KRAS mutation maybe related to the efficacy of oxaliplatin-only therapy in the first-line setting. A trend toward improved progression-free survival (PFS) was noted, but this trend lacked statistical significance in patients carrying KRAS mutation compared with patients carrying the wild-type KRAS gene.[5] Unlike anti-EGFR therapy, there is still no effective biomarker for predicting the efficacy of oxaliplatin-based therapy. Two cohort studies revealed that activating KRAS mutation might predict the response to oxaliplatin-based therapy for advanced colorectal cancer patients.[6,7] Most descriptions of the issue were focused on first-line oxaliplatin-based treatment, possibly because no other effective therapeutic options were available for patients with KRAS mutation if their chemotherapy failed in the second-line setting. Two phase III trials (CONCUR and CORRECT) have shown a survival benefit of regorafenib in patients receiving treatment for refractory metastatic colorectal cancer.[8,9] As the introduction of new drugs for treating metastatic colorectal cancer after multiple-line therapies, the clinical value of KRAS mutation as a prognostic factor in second-line oxaliplatin-based therapy might provide new option.

We hypothesized that in metastatic colorectal cancer patients receiving oxaliplatin-based chemotherapy alone, PFS might vary depending on whether the patient has KRAS mutation or the wild-typegene; our hypothesis was primarily based on 2 prospective clinical trials, PRIME and OPUS.[2,5] In addition, patients with KRAS mutation may have a more positive response than that of patients with the wild-type KRAS gene when they receive oxaliplatin-based treatment (FOLFOX-6) as a second-line therapy for their metastatic colorectal cancer.

Materials and Methods

Patient population

From January 2010 to May 2014, a total of 352 patients with metastatic colorectal cancer were enrolled at Chang Gung Memorial Hospital, Chiayi and Linkou Branches. They had received first-line irinotecan-based chemotherapy (FOLFIRI) with or without bevacizumab for synchronous metastases or metachronous cancer relapses from non-stage IV colorectal cancer. The role of KRAS mutation of exon 2 as a positive predictor for second-line oxaliplatin-based chemotherapy (FOLFOX-6) was analyzed. Patients were excluded if they had (1) no KRAS mutation analysis, (2) metastasectomy for resectable metastases after the first-line chemotherapy, (3) discontinuous chemotherapy due to severe sepsis or adverse effects, (4) double cancer diagnoses, (5) initial cancer surgery and treatment at other institutions, or (6) cancer relapse within 1 year after adjuvant chemotherapy with oxaliplatin for stage III colorectal cancer. This study was approved by an institutional review board in Chang Gung Memorial Hospital.

The primary endpoint, PFS, and the secondary endpoint, the disease control rate (DCR), in the second-line treatment for metastatic colorectal cancer were analyzed in the patients' series. PFS was defined as duration from first-line failure until progression after second-line treatment according to computed tomography (CT) of the chest, abdomen, and pelvis. The DCR concerned patients with complete response

(CR), partial response (PR) and stable disease (SD) after second-line therapy according to CT images. All assessments of tumor response to chemotherapy were based on CT of the chest, abdomen, and pelvis, either after the patients had received oxaliplatin-based chemotherapy every 3 months or when there was rising carcinoembryonic Antigen (CEA) with possible cancer progression. The response was evaluated and classified according to the Response Evaluation Criteria in Solid Tumors (RECIST, ver. 1.0). Each patient's performance was classified according to the Eastern Cooperative Oncology Group (ECOG) score. To prevent the inaccuracy of PFS calculation resulting from delay in discontinuation of the second-line oxaliplatin therapy due to the limitation of available drugs in third-line chemotherapy, we did not record the interval of FOLFOX-6 treatment; we defined an event occurring during the second-line FOLFOX-6 treatment if any findings about PD were noted following CT examination.

Our study excluded 1 patient who had a rapid cancer relapse during adjuvant therapy with oxaliplatin (5.1 months after adjuvant therapy), 6 patients who received treatment at other institutions, 12 patients who had resectable metastases before or after first-line chemotherapy, 85 patients without KRAS analysis, 80 patients without second-line FOLFOX-6 chemotherapy, and 24 patients who received second-line FOLFOX-6 less than two times because of poor performance, severe side effects, or sepsis. All of the 144 patients who were included had ECOG 0-2; they were treated and followed until December 2014.

Chemotherapy regimens

A first-line regimen for patients with metastatic colorectal cancer is FOLFIRI with bevacizumab; this regimen is based on recommendations from the National Health Insurance (NHI) Administration in Taiwan. An oxaliplatin-based regimen, FOLFOX-6, is the common second-line treatment for patients for whom the first-line regimen has failed. The FOLFOX-6 regimen comprises oxaliplatin (85 mg/m^2) administered as a 2-hour infusion on day 1; leucovorin (400 mg/m^2) administered as a 2-hour infusion on day 1, a loading dose of a 5-FU (400 mg/m^2) IV bolus administered on day 1, and then 5-FU (3000 mg/m^2) administered using an ambulatory pump for 46 hours every 2 weeks.

KRAS analysis

KRAS mutation was analyzed in our study by extracting genomic DNA from formalin-fixed, paraffin-embedded tissue in the Department of Pathology of Chang Gung Memorial Hospital. The tumors were identified in hematoxylin- and eosin-stained sections. DNA was extracted from 5-μm sections of paraffin-embedded tissue. Mutation of exon 2 of the KRAS gene, including codons 12 and 13, was determined through polymerase chain reaction.

Statistical analysis

In the present study, the chi-square and Fisher's tests were used to compare patients' categorical variables between the KRAS wild-type and mutation groups. PFS and the survival difference were estimated using the Kaplan-Meier method with the log-rank test. A Cox proportional hazards regression model was used in univariate and multivariate analyses to identify the independent prognostic factors for PFS. Variables with significance ($p < 0.05$) in univariate analysis for PFS were evaluated in multivariate analysis. All statistical analyses were performed using SPSS version 17.

Results

Patient's characteristics

All enrolled patients' ECOG score were between 0 and 2 when they received the second-line chemotherapy. The characteristics of the patients in the study were summarized in Table 1. We included 144 patients who had received FOLFIRI with or without bevacizumab as the first-line treatment for metastatic colorectal cancer (8 patients received FOLFIRI only) and oxaliplatin-based chemotherapy (FOLFOX-6)

Table 1. Patients' characteristics, n = 144

Categorical variables	KRAS* wild-type, n = 85		KRAS mutation, n = 59	
	Number/total	Percentage, %	Number/total	Percentage, %
Gender				
Male	54/85	63.5%	35/59	59.3%
Female	31/85	36.5%	24/59	40.7%
Age, median	60 (27-79)		60 (32-82)	
CRC* stage				
Stage IV CRC	70/85	82.4%	44/59	74.6%
Relapse in stage I-III	15/85	17.6%	15/59	25.4%
Primary tumor locations				
Ascending colon	12/85	14.1%	15/59	25.4%
Transverse colon	3/85	3.5%	0/59	0
Descending/sigmoid colon	33/85	38.8%	13/59	22.0%
Rectum	37/85	43.5%	31/59	52.5%
Synchronous metastases				
Liver	48/70	68.6%	34/44	77.3%
Lung	27/70	38.6%	24/44	54.5%
Distant lymph nodes	22/70	31.4%	6/44	13.6%
Peritoneum	14/70	20.0%	8/44	18.2%
Others*	6/70	8.6%	2/44	4.5%
Relapse in stage I-III				
Liver	5/15	33.3%	2/15	13.3%
Lung	9/15	60.0%	8/15	53.3%
Distant lymph nodes	8/15	53.3%	3/15	20.0%
Local recurrence	1/15	6.7%	3/15	20.0%
Peritoneum	1/15	6.7%	2/15	13.3%
Others*	2/15	13.3%	0/15	0
Number of metastatic sites				
1	41	48.2%	34	57.6%
2	32	37.6%	19	32.2%
≥ 3	12	14.1%	6	10.2%
Primary cancer resection	61/85	71.8%	46/59	78.0%
1st line IRI*-based therapy				
With Bevacizumab				
Without Bevacizumab				
Cycles of Bevacizumab				
Complete 12 cycles	63/82	76.8%	47/54	87.0%
Not complete	19/82	23.2%	7/54	13.0%
Status in the last follow-up				
Survive with cancer	46/85	54.1%	33/59	55.9%
Death due to cancer	38/85	44.7%	26/59	44.1%
Death due to other etiology	1/85	1.2%	0	0

KRAS: Kirsten-ras; CRC: colorectal cancer; Other: metastatic locations except lung/liver, distal lymph nodes, and peritoneum; IRI: irinotecan.

without targeted agents as the second-line therapy for their disease progression. The enrolled 144 patients were stratified by the KRAS status (wild-type or mutation on exon 2, including codons 12 and 13). Eighty-five (59%) and 59 (41%) patients had the wild-type KRAS gene and KRAS mutation, respectively. Sixty-one (71.8%) patients with the wild-type KRAS gene and 46 (78%) patients with KRAS mutation underwent surgical resection for their primary cancer (p = 0.402). Thirty of the 144 patients had received curative surgery for their stage I-III colorectal cancer (3 patients with stage I disease, 2 patients with stage II disease, and 25 patients with stage III disease). Twenty-four of 25 patients received adjuvant chemotherapy for their stage III disease (9 patients received oxaliplatin therapy, 9 patients received 5-FU infusion, and

6 received oral tegafur-uracil), and their median cancer relapse time was 19.3 months (from 6.1 to 62.5 mo). The cancer relapses were 7 liver metastases, 17 lung metastases, 11 distant lymph node metastases, 4 local recurrences, 2 bone metastases, and 3 carcinomatoses. Similarities in the median age (60 y), sex distribution (p = 0.609), distribution of first-line FOLFIRI chemotherapy with bevacizumab (p = 0.273), and distribution of the metastatic number (p = 0.518) were also identified.

Outcome for second-line oxaliplatin chemotherapy

One hundred and thirty-six patients received first-line irinotecan with bevacizumab and 8 patients received irinotecan without bevacizumab. All patients received the second-line oxaliplatin treatment (FOLFOX-6) without anti-EGFR or anti-vascular endothelial growth factor (VEGF) agents after disease progression (PD). The DCR was evaluated for patients with different KRAS statuses when they received the second-line therapy. The overall median follow-ups were 26.6 and 33 months respectively in the wild-type and mutation groups. In the KRAS wild-type group, we observed 13 patients with PR, 25 patients with SD, and 47 patients with PD. In the KRAS mutation group, 13 patients had PR, 18 patients had SD, and 28 patients had PD in their first CT image follow-up. Among 57 patients with at least SD after the first CT follow-up, 21 and 17 had PD in the KRAS wild-type and mutation groups, respectively. The DCR and PFS during the second-line oxaliplatin treatment were superior in the KRAS mutation group (Table 2). Median PFS for the patients receiving second-line oxaliplatin chemotherapy showed a significant difference between the wild-type KRAS and mutation groups (3.4 mo; 95% CI, 3.0 to 3.8 mo vs. 4.8 mo; 95% CI, 3.1 to 6.5 mo; p = 0.0048) (Fig. 1). The results of prognostic analysis were shown in Table 3. In the univariate analysis, the predictive factors related to the PFS for second-line oxaliplatin therapy for our metastatic colorectal cancer patients were pathologic differentiation and the KRAS mutation status. In the multivariate analysis, we found that KRAS mutation was an independent predictor for PFS during second-line oxaliplatin-based chemotherapy (hazard ratio [HR], 0.585; 95% confidence interval [CI], 0.399-0.858; p = 0.006).

Discussion

In many cohort studies, increased risks of cancer relapse and cancer-specific death have been linked to KRAS mutation.[10,11] However, different results concerning the prognostic value of KRAS mutation were noted in metastatic or advanced colorectal cancer. Al-

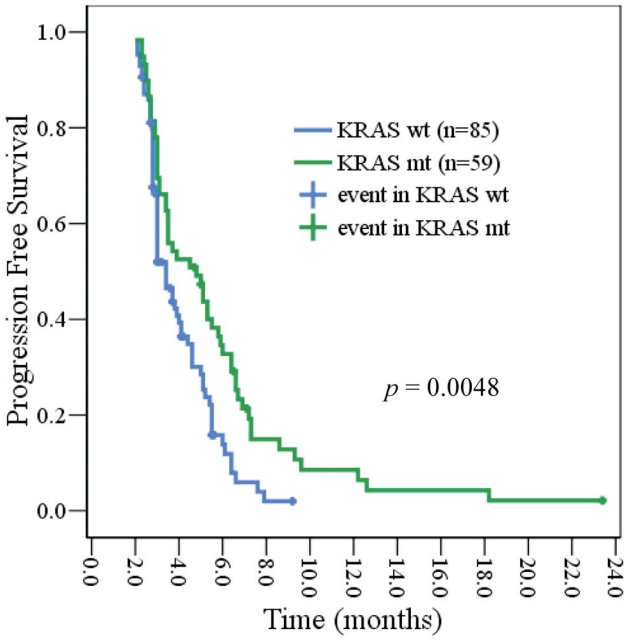

Fig. 1. Kaplan-Meier progression-free survival curves of metastatic colorectal cancer patients stratified by KRAS mutation (mt) and wild-type (wt).

Table 2. Disease control rate (DCR) in the 1st and the 2nd image evaluation for the 2nd-line oxaliplatin-based chemotherapy

KRAS status, (number)	DCR in the 1st image number (%)	p value	KRAS status, (number)	DCR in the 2nd image number (%)	p value
KRAS wild-type (85)	38 (44.7%)	0.355	KRAS wild-type (26)	5 (19.2%)	0.039
KRAS mutation (59)	31 (52.5%)		KRAS mutation (31)	14 (45.2%)	

Table 3. Uni- and multivariable survival analysis (PFS) with proportional hazard regression in patients with metastatic CRC who received the 2nd-line oxaliplatin-based chemotherapy

Categorical variables	Univariable analysis			Multivariable analysis (Wald test)		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age						
≥ 65 vs. < 65	1.196	0.830-1.722	0.336			0.810
Gender						
Male vs. female	1.020	0.707-1.471	0.916			0.921
Pathologic grade*						
WD vs. PD	0.413	0.181-0.942	0.036			0.405
MD vs. PD	0.531	0.280-1.009	0.053			0.729
Number of Mets*						
2 vs. 1	1.118	0.755-1.656	0.578			0.893
≥ 3 vs. 1	1.276	0.730-2.229	0.392			0.624
KRAS						
Mutant vs. wild type	0.592	0.406-0.864	0.006	0.585	0.399-0.858	0.006
Primary tumor resection						
Yes vs. No	0.806	0.545-1.194	0.283			0.433

Number of Mets: metastatic organ in cancer relapse from stage I-III colorectal cancer or synchronous stage IV colorectal cancer.
Pathologic grade: WD, well differentiated; MD, moderate differentiated; PD, poorly differentiated.

though poor prognoses were noted in the KRAS mutation group, KRAS mutation did not seem to be a predictive biomarker for backbone chemotherapy with irinotecan or oxaliplatin. There was no evidence proving that colorectal cancer patients with KRAS mutation had less benefit from these standard chemotherapy agents.[12] There was also no significant difference in PFS and OS when patients carrying either KRAS mutation or the wild-type KRAS gene received first-line oxaliplatin- or second-line irinotecan-based chemotherapy.[13] The correlation between a commonly used biomarker, KRAS, and the traditional cytotoxic agents seems controversial to date.

Richman et al. indicated that KRAS mutation was not a predictive marker for the PFS or OS achieved using oxaliplatin or irinotecan.[12] However, patients in their post hoc study received many cytotoxic agents and post study treatments that might have influenced their survival. Therefore, the OS, as a primary endpoint, seemed inappropriate for efficacy analysis of oxaliplatin-based treatment for patients with different KRAS statuses. The PFS in our present study was an acceptable endpoint for evaluating the impact of FOLFOX-6 on patients with different KRAS statuses.

Several studies were published for researching the mechanism of platinum resistance. The repair of DNA damage played a critical role in resistance to platinum drugs. The over expression of excision repair cross-complementation group 1 (ERCC1) was a mechanism association between resistance and platinum-based chemotherapy for other malignancies.[14,15] In other in vitro study, Lin et al. suggested that KRAS mutation was a predictor of oxaliplatin sensitivity, and ERCC 1 down-regulation in colon cancer cells with KRAS over expression following mutant vector transfection was the mechanism underlying this relationship.[16]

A meta-analysis of anti-EGFR in metastatic colorectal cancer revealed that patients with wild-type KRAS metastatic colorectal cancer seemed to gain-limited benefit from oxaliplatin-based chemotherapy.[17] Our study demonstrated that unresectable metastatic colorectal cancer patients with KRAS mutation had significantly longer PFS and greater disease control than those of patients with the wild-type KRAS gene during second-line chemotherapy with FOLFOX-6. Notably, our result was similar to those of other cohort studies that evaluated differences in the response to oxaliplatinin first-line therapy between KRAS mutation and wild-type groups. Basso et al. suggested that the benefit was more significant in patients receiving FOLFOX-6 as first-line chemotherapy than in patients who received it as second-line therapy. PFS was lon-

ger in patients with KRAS mutation than in patients with the wild-type gene during FOLFOX-6 treatment (10 vs. 8 mo, respectively; $p = 0.0069$).[6] Lin et al. also reported that the median PFS was 8.5 months in patients with KRAS mutation versus 5.8 months in those with the wild-type gene for first-line oxaliplatin-based therapy ($p = 0.008$).[7] In the first- and second-line setting, Basso's study was the first to analyze the activity of FOLFOX-6 in relation to the KRAS status. Their study indicated less benefit on disease control when second-line FOLFOX was used for patients with KRAS mutation. To observe the statistically significant difference in PFS between the patients in the mutation and wild-type groups during second-line FOLFOX-6 therapy, we analyzed a larger series of patients than that in Basso's study. To the best of our knowledge, our present study was the second to evaluate the response of second-line FOLFOX-6 in relation to KRAS mutation or the wild-type gene. The benefit of oxaliplatin-based treatment was statistically significant in univariate and multivariate analyses.

In clinical practice, the choices of second- and first-line regimens may be correlated. Guglielmi and Sobrero ever reviewed the available evidence from randomized control trials regarding the correlation between first- and second-line chemotherapy regimens.[18] They concluded that (1) active regimens included irinotecan, oxaliplatin, and IROX (irinotecan with oxaliplatin) following 5-FU failure; (2) oxaliplatin was in general the most favorable choice, but the combination of oxaliplatin and bevacizumab could be used after irinotecan-based first-line failure; and (3) irinotecan-based chemotherapy was currently the most appropriate regimen following first-line oxaliplatin-based therapy. During our cohort study, between 2010 and 2014, the NHI system in Taiwan has provided the anti-VEGF agent, bevacizumab, for metastatic colorectal cancer patients with FOLFIRI as a first-line therapy. The FOLFOX-6 regimen alone has also commonly been applied in the second-line setting after failure of first-line palliative therapy in Taiwan. Data from the cohort of the present study could be used to evaluate the impact of the KRAS status on second-line oxaliplatin treatment without targeted agents.

For most cases with unresectable metastatic colon cancer, PFS during second-line palliative chemotherapy is usually shorter than it during first-line therapy. In previous first-line and our second-line therapy, the PFS for oxaliplatin therapy was 8.5-10 months in first-line treatment and shortened to 4.8 months in second-line setting. The benefit and response of FOLFOX-6 for patients with KRAS mutation would decrease in later lines. This finding demonstrates that determining the mutation status of KRAS is not only useful for selecting patients who are suitable for treatment using anti-EGFR agents but also for personalizing chemotherapy for metastatic colorectal cancer. When patients have metastatic colorectal cancer with KRAS mutation, first-line oxaliplatin is more efficient than it is second-line.

Our study had some limitations. First, our series was analyzed retrospectively. Although the sample size was larger than those of previous studies on the correlation of KRAS mutation with the efficacy of oxaliplatin therapy, a prospective study with alarger sample size maybe required to confirm the positive impact of second-line oxaliplatin treatment on patients with KRAS mutation. Second, selection bias was difficult to avoid in a retrospective study, because PFS could not be evaluated independently by researchers blind to the KRAS status. Third, we had no data about all RAS mutations in this retrospective study. Different KRAS mutation subtypes and other RAS mutations may have different presentations and outcomes.[19,20]

In conclusion, our retrospective data suggested that second-line oxaliplatin regimen might cause metastatic colorectal cancer patients with the KRAS mutation of exon 2 to have longer PFS than that of patients with the wild-type KRAS gene. According to the literature review, the benefit of first-line oxaliplatinis more significant. These findings might facilitate selecting patients for optimized personal chemotherapy.

Acknowledgment

Contribution from Chao-Fen Lee and Shu-Mei Liang for collecting the patients' raw data is gratefully acknowledged.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

References

1. Heinemann V, von-Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15(10):1065-75.
2. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28(31):4697-705.
3. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360(14):1408-17.
4. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; 359(17):1757-65.
5. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; 27(5):663-71.
6. Basso M, Strippoli A, Orlandi A, Martini M, Calegari MA, Schinzari G, et al. KRAS mutational status affects oxaliplatin-based chemotherapy independently from basal mRNA ERCC-1 expression in metastatic colorectal cancer patients. *Br J Cancer* 2013;108(1):115-20.
7. Lin YL, Liau JY, Yu SC, Tseng LH, Lin LI, Liang JT, et al. Oxaliplatin-based chemotherapy might provide longer progression-free survival in KRAS mutant metastatic colorectal cancer. *Transl Oncol* 2013;6(3):363-9.
8. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381(9863):303-12.
9. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015;16(6): 619-29.
10. Andreyev HJ, Norman AR, Cunningham D, Oates JR, Clarke PA. Kirsten ras mutations in patients with colorectal cancer: the multicenter "RASCAL" study. *J Natl Cancer Inst* 1998; 90(9):675-84.
11. Andreyev HJ, Norman AR, Cunningham D, Oates J, Dix BR, Iacopetta BJ, et al. Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. *Br J Cancer* 2001; 85(5):692-6.
12. Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, et al. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. *J Clin Oncol* 2009;27(35): 5931-7.
13. Kim ST, Park KH, Kim JS, Shin SW, Kim YH. Impact of KRAS mutation status on outcomes in metastatic colon cancer patients without anti-epidermal growth factor receptor therapy. *Cancer Res Treat* 2013;45(1):55-62.
14. Breen D, Barlési F. The place of excision repair cross complementation 1 (ERCC1) in surgically treated non-small cell lung cancer. *Eur J Cardiothorac Surg* 2008;33(5):805-11.
15. Cobo M, Isla D, Massuti B, Montes A, Sanchez JM, Provencio M, et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. *J Clin Oncol* 2007;25(19): 2747-54.
16. Lin YL, Liau JY, Yu SC, Ou DL, Lin LI, Tseng LH, et al. KRAS mutation is a predictor of oxaliplatin sensitivity in colon cancer cells. *PLoS One* 2012;7(11):e50701.
17. Song QB, Wang Q, Hu WG. Anti-epidermal growth factor receptor monoclonal antibodies in metastatic colorectal cancer: a meta-analysis. *World J Gastroenterol* 2015;21(14):4365-72.
18. Guglielmi AP, Sobrero AF. Second-line therapy for advanced colorectal cancer. *Gastrointest Cancer Res* 2007;1(2):57-63.
19. De Roock W, Jonker DJ, Di Nicolantonio F, Sartore-Bianchi A, Tu D, Siena S, et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA* 2010;304(16):1812-20.
20. Cannon TL, Kokon MA, Shafqat S, Deeken JF. RAS mutations beyond KRAS exon 2: a review and discussion of clinical trial data. *Curr Treat Options Oncol* 2015;16(7):33.

原　著

在發生遠端轉移的結直腸癌患者，存有 KRAS 突變對第二線 Oxaliplatin (FOLFOX–6) 的治療影響

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目的　探討不同的 KRAS 基因表現對第四期結直腸癌病患接受第二線 Oxaliplatin 治療的反應與疾病無惡化存活期的差異。

方法　於 2010 年 1 月至 2014 年 5 月間，共 144 位無法進行手術治療的第四期結直腸癌病患於第一線化療後 (FOLFIRI+/-Bevacizumab)，因疾病進展接受第二線 Oxaliplatin (FOLFOX6) 治療。參與研究的病患追蹤至 2014 年 12 月，期間分析病患 KRAS 突變與野生型在第二線 Oxaliplatin 治療下的疾病無惡化存活期。

結果　144 位病患中共有 59 位病患 (41%) 存在有 KRAS (exon 2) 突變；在突變與野生型兩個分群中，原發結直腸惡性腫瘤接受手術切除率 (p = 0.402)、第一線化療，FOLFIRI，併用 Bevacizumab 比例 (p = 0.273)、年齡中位數 (60 vs. 61) 及性別 (p = 0.609)、與遠端轉移器官數目 (p = 0.518) 均不存在統計意義的差異。在接受第二線 Oxaliplatin 治療下，KRAS 突變分群病患比起野生型分群有較佳的疾病無惡化存活期 (4.8 mo; 95% CI, 3.1 to 6.5 mo vs. 3.4 mo; 95% CI, 3.0 to 3.8 mo; p = 0.0048)。在對疾病無惡化存活期進行多變數分析後也顯示出，KRAS 突變對使用 oxaliplatin 作為第二線化療，具有較佳反應的預後 (hazard ratio, 0.585; 95% CI, 0.399-0.858; p = 0.006)。

結論　在這一個觀察研究中發現，無法手術切除的第四期結直腸癌病患接受第二線 FOLFOX6 治療時，KRAS 突變的病患可能比野生型病患擁有較長的疾病無惡化存活期。

關鍵詞　Kirsten-ras、轉移、結直腸癌、化學治療、Oxaliplatin。