의학석사 학위논문

Efficacy of regorafenib monotherapy in metastatic colorectal cancer patients refractory to standard chemotherapy

치료 저항성 대장암 환자에서 레고라페닙 단독 치료의 효과 분석

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임유주

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Efficacy of regorafenib monotherapy in metastatic colorectal cancer patients refractory to standard chemotherapy

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Professor	Chairman
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Professor	

ABSTRACT

Efficacy of regorafenib monotherapy in metastatic colorectal cancer patients refractory to standard chemotherapy

Background: Only limited treatment options are available for patients with metastatic colorectal cancer that progresses after standard chemotherapy. Regorafenib is an oral multikinase inhibitor that has been recently shown to be effective in metastatic colorectal cancer after failure to standard therapy.

Methods: Patients with metastatic colorectal cancer in Seoul National University Hospital who have failed to standard therapy were treated with regorafenib, 160mg p.o daily, for the first 3 weeks of each 4 week cycle. For practical reasons, failure to standard therapy was defined as failure to all of fluoropyrimidine, oxliplatin and irinotecan, but did not mandate failure to bevacizumab or cetuximab. The primary end point was progression-free

survival.

Results: Between December 1, 2013 and February 1, 2014, 40 patients initiated treatment with regorafenib. Median progression-free survival of all patients was 4.3 months. Disease control rate was 70%. Patients who have not previously received bevacizumab showed significantly longer progression-free survival compared to those who have already failed to bevacizumab (2 vs. 4 months, *P*=0.003). Treatment-related adverse events occurred in 32 (80%) patients, but most were grade 1 or 2 and were generally manageable. The most common adverse event was hand-foot syndrome, occurring in 24 (60%) patients.

Conclusion: Regorafenib is an acceptible treatment option in patients with metastatic colorectal cancer refractory to standard chemotherapeutic agents, with a manageable toxicity profile. Further study of identifying a subset of patients who would benefit more from the drug is warranted.

Keywords: metastatic colorectal cancer, regorafenib, efficacy

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Introduction

Colorectal cancer is a major cause of morbidity and mortality globally. In Korea, the incidence of colorectal cancer is on the rise, with 25,782 new cases registered in 2010, and is currently the 3rd most common cancer in Korea.[1] Even with the increase in curative surgery following increase of early detection rate, it is still the 4th common cause of cancer mortality. Approximately 25% present with metastatic disease at initial diagnosis and 50-60% of patients are expected to eventually develop metastatic disease.[2] And although recent advances in systemic chemotherapies did improve survival in recurrent or metastatic colorectal cancer, still there are limitations to the options and many patients with recurrent or metastatic disease do not survive over 2 years.

Standard treatment of recurrent or metastatic colorectal cancer is based on chemotherapy with fluoropyrimidines, oxaliplatin and irinotecan (used in combination and sequentially). Recently, monoclonal antibodies targeting vascular endothelial growth factor (VEGF; bevacizumab) and epidermal growth factor receptor (EGFR; cetuximab) in KRAS wild type patients have also been incorporated into practice.[3,4] There is no standard therapy after failure of all these therapies. However, as a significant proportion of patients

still remain in good performance status after failing all these options, the unmet medical need in these patients have become an important issue.

Regorafenib (BAY 73-4506; Stivarga; Bayer HealthCare Pharmaceuticals, Inc.) is an oral multikinase inhibitor with activity against multiple target kinases including KIT, platelet-derived endothelial growth factor receptor (PDGFR)1, 2, 3, RET, fibroblast growth factor receptor (FGFR)1, rAF and p38 mitogen-actived protein kinase (MAPK)[5]. In preclinical models, regorafenib has been shown to have antitumor activity against multiple tumors including colorectal cancer models.[5] Recently, the efficacy of regorafenib monotherapy for previously treated metastatic colorectal cancer has been proven in international, multicenter phase 3 trial.[6] Regorafenib improved OS and PFS in patients who had failed fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy regimens plus bevacizumab or cetuximab in KRAS wild type patients, with manageable side effect profiles.

This study was planned to assess efficacy and safety of regorafenib monotherapy in Korean patients with metastatic colorectal cancer. As only a small proportion of Korean patients with metastatic colorectal cancer were able to afford bevacizumab or cetuximab due to economic reasons,

regorafenib effects in patients with metastatic colorectal cancer refractory to all cytotoxic chemotherapeutic options regardless of previous bevacizumab or cetuximab use was analyzed in this study.

Methods

Patients

This study was an open-label, non-randomized, single-group study done in Seoul National University Hospital. Adult patients of age 20 years or older with pathologically proven metastatic adenocarcinoma of colon or rectum who have already failed to standard chemotherapies including all of fluoropyrimidine, oxaliplatin and irinotecan were included. Failure was defined as progression during or within 3 months following the last administration of therapy. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent before progression of disease have also be allowed into the study. Patients treated in an adjuvant setting who have progressed during or within 6 months of

completion of adjuvant therapy are regarded as failure of those agents used in the adjuvant therapy. Patients were eligible regardless of previous bevacizumab or cetuximab use. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, life expectancy of at least 3 months, and adequate bone-marrow, liver and renal function at the start of the trial. Patients who had previously received regorafenib or had uncontrolled other medical disorders were excluded.

All patients provided written informed consent before any-study specific procedures. The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University Hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

Study design and Treatment

Patients received 160mg of regorafenib orally once daily, on days 1 to 21 of a planned 28-day cycle (21 days on, 7 days off per cycle). Dose reduction and delay were allowed to manage adverse events. Treatment was continued until occurrence of progressive disease, intolerable toxicity, withdrawal of consent or investigator’s decision that stopping treatment would be in the

patient's best interest.

The primary end point was progression free survival (PFS). Secondary endpoints were disease control rate, overall survival (OS) and toxicity. PFS was calculated as the time from first dose of regorafenib to first documented radiological or clinical disease progression or death from any cause. Disease control rate was defined as the proportion of patients with a confirmed best response of complete response (CR), partial response (PR) or stable disease (SD). OS was calculated as the time from first dose of regorafenib to death from any cause.

Response Assessment and Toxicity

We used CT or MRI to measure tumor size at baseline and after completion of every 2 cycles until PD. Additional images were also obtained when there was any clinical suspicion of PD, or when the treatment was permanently discontinued any other reasons. Tumor response and progression were assessed with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Patients who unexpectedly discontinued treatment without adequate assessment were deemed non-responder in this study.

Safety assessments included assessing all adverse events, laboratory changes, vital signs and physical exam results. All adverse events and biochemical toxic effects were classified by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Sample size calculation and statistical Analysis

The study was designed to have a 95% power to detect a 20% increase in proportion of patients staying progression-free at the end of 3 months after starting the treatment, assuming progression-free rate of 10% without the treatment. Assuming a one-sided overall α of 0.05 and a power of 90% for a single stage, single group study design, 39 patients were calculated to be needed.

Survival and safety analyses were done in all patients who received at least one dose of regorafenib, and disease control rate was calculated with data from patients assessable for response. Results of efficacy and safety analyses are presented with descriptive statistics. PFS and OS data were calculated using the Kaplan-Meier method and compared between subgroups with log-rank test. All statistical analyses were performed with

IBM SPSS version 20.0 (IBM Corp., Armonk, NY).

Results

Patient Characteristics

A total of 40 patients were treated with the study drug from December 2013 to March 2014. The median age of patients was 56 years (range, 41-74 years), and 24 (62.5%) patients were male. Twenty-six (65%) of the 40 patients had metastatic disease at the time of initial diagnosis, and the median time from the documentation of metastatic disease to study enroll was 24.5 months (range, 6-68 months). Patient characteristics are summarized in Table 1.

Treatment Duration and Efficacy

During median follow-up period of 3.9 months, a median number of 3 cycles (range: 1-5 cycles) of treatment was given. At the time of data cut-off, 23 (57.5%) patients were being continued on receiving regorafenib and 17

were off therapy. The reasons for discontinuation in the 17 patients were as follows; progressive disease in 14, death in 2 and patient refusal due to unacceptable toxicity in 1. Cause of death for the 2 deceased patients was pneumonia in both cases.

The median PFS was 4.3 months. Progression-free rate at 2 months was 67.5% and was 64.6% for 3 months and after. Figure 1A shows Kaplan-Meier curves for PFS. Patients who have not previously received bevacizumab showed significantly better PFS after regorafenib treatment compared to those who have already failed to bevacizumab (log rank P=0.003) (Figure 1B). No difference of PFS was observed between subgroups regarding previous cetuximab use (Figure 1C). Patients with 1 year or less time from metastatic disease to the study enroll showed tendency toward shorter PFS, but statistical significance was not found (log rank P=0.261) (Figure 1D). No differences in PFS were observed between colon and rectal cancer (Figure 1E), as well as KRAS mutant and wild type (Figure 1F). Median OS could not be assessed at the time of analysis because of censored data. A total of 5 deaths were observed during the follow-up period; 2 due to pneumonia and 3 due to disease progression after discontinuing study medication.

The best change in target lesion from base line in 39 evaluable patients were; SD in 28 (70.0%) patients and PD in 11 (27.5%), exhibiting disease control rate of 70%. Response could not be assessed in 1 patient who died of pneumonia during the first cycle of study treatment. No CR or PR was observed. The waterfall plot showing the percent changes in target lesion size from baseline is given in Figure 2. Subgroup of patients who experienced hand-foot syndrome of any grade tended to show better response to regorafenib (P=0.068).

Safety and Tolerability

Thirty-two (80.0%) of all 40 patients experienced at least one drug-related adverse events. The most commonly observed adverse event of any grade was hand-foot syndrome, occurring in 60% of patients. Overall, 3 cases of grade 3 or higher adverse events were observed. (2 hepatitis, 1 hand-foot-syndrome) Most adverse events occurred early in the course of treatment, and were manageable by adequate supportive care and dose modification if required. One patient with grade 2 hand-foot syndrome refused further therapy after 1 cycle and was withdrawn from study. Table 2 summarizes the incidence of drug-related adverse events.

Dose reduction was required in 16 (40.0%) of patients, and cycle delay was required in 12 (30.0%). Both dose reduction and delay was required in 8 (20.0%) patients. Dose reduction levels were 1 in 12 (30.0%) and 2 in 4 (10.0%) patients. Most common reason for reduced dose intensity was hand-foot syndrome.

Discussion

In this study of efficacy and safety of regorafenib monotherapy in patients with colorectal cancer refractory to fluoropyrimidine, oxaliplatin and irinotecan, median progression free survival of 4.3months was observed, with 70% disease control rate. Patients without previous bevacizumab use seemed to have longer PFS compared to those who have already failed to bevacizumab. Although toxicity of any grade was observed in majority of treated patients, they were usually manageable with supportive cares, dose reductions or treatment interruption, and permanent discontinuation of the drug because of toxicities was rare.

With recent study data, regorafenib has been highlighted as a feasible option in chemo-refractory metastatic colorectal cancer patients and has been approved by FDA in 2012 for patients in this setting. After preclinical data and phase I dose-escalation study results in solid cancer showing preliminary activity of regorafenib in cancer patients at a dose of 160mg daily, with a treatment schedule of 21 days on and 7 days off in a 28-day cycle, with acceptable safety profile, phase Ib extension cohort study was conducted in metastatic colorectal cancer patients.[7] In the phase Ib study, a disease control rate of 74% (PR in 4%, SD in 70%) was reported in 27 evaluable patients with acceptable toxicity profile. Based on this result and the high unmet need in the population of metastatic colorectal cancer patients, a phase III trial was directly followed without a phase II trial. The international phase III CORRECT trial evaluated the effect of regorafenib monotherapy in colorectal cancer patients who have progressed after all standard therapies including bevacizumab and cetuximab. In CORRECT trial, 505 patients treated with regorafenib showed significantly improved OS of 6.4 months versus 5.0 months in 255 patients with placebo (P=0.0052), again with acceptable toxicity profile. PR was achievecd in 1.0% and SD in 41% in regorafenib group.

The main effect of regorafenib on metastatic colorectal cancer seems to be disease stabilization, rather than tumor shrinkage. This data of Korean patients showing prolonged PFS but no objective tumor response and 70% with best response of SD is in consistence with the best response results phase Ib study and CORRECT trial. Also, the toxicity profile shown in this study was similar to that in CORRECT trial.

However, there was an important difference of this study from CORRECT study, that this study did not obligate prior use of bevacizumab or cetuximab to be eligible for study enrollment. And as the patient in this study was accrued at Seoul National University Hospital, all of the included patients were Korean. As a consequence, there were a few differences in patient characteristics between the CORRECT study and this study. First and the most important difference is that all of the patients in the CORRECT study has already used bevacizumab, compared to only 12.5% of patients in this study. Also, more patients with wild type KRAS were included in this study, as well as more rectal cancer than colon cancer. The difference in patient characteristics between CORRECT study and this study is summarized in Table 3. In this study, the observed PFS was longer than CORRECT study

(4.3 months versus 1.9 months), despite shorter follow-up period. In our study, the results showed significantly better PFS in bevacizumab-naïve patients than bevacizumab-refractory patients. Deducing from the results, the conclusion can be drawn that higher PFS in this study seems to have been attributed by the bevacizumab-naïve patients. The better efficacy in these bevacizumab-naïve patients implicates the importance of VEGF pathway in the mechanism of regorafenib effect on colorectal cancer. In the CORRECT study, regorafenib seemed to have benefited colon cancer patients slightly more than rectal cancer patients, although the difference was not proven in our study. And no significant difference in treatment results were found according to KRAS status in either of the studies.

However, the curve pattern of PFS in this study resembled that of CORRECT study, showing abrupt drop in progression-free rate around 2 months after treatment initiation. This implies that besides resistance to angiogenesis inhibition, there may be more yet unknown biomarker that would separate the subset of patients who would benefit more from the drug from others. Further studies in understanding complex mechanism of regorafenib action in refractory colorectal cancer and finding efficacy biomarker are warranted.

The fact that the efficacy and safety results of this study were comparable with that of the international phase III trial provides grounds that further study results conducted in Korea will have a globally meaningful value.

There are limitations in this study. First, the results of this study were not derived after a sufficient follow-up duration. However, the target patients of the intended treatment were heavily treated metastatic cancer patients with generally expected survival of less than 6 months. And given the data of this study and that of the phase 3 study that definite non-responders usually progress rapidly within 2 months after start of regorafenib, data after longer follow-up is not expected to be very much different from the results presented. Second, there is debate on whether RECIST version 1.1 is an adequate evaluation tool to estimate the effect of regorafenib. As already mentioned, the main effect of regorafenib seems not to be shrinking tumor size, and thus reponse evaluated per RECIST version 1.1 may not be able to sensitively represent the true response. However, there are as yet no data regarding adequate evaluation tool of regorafenib in case of colorectal cancer. RECIST version 1.1 was used in this study, but caution need to be taken in interpreting the data assessed.

The results of present study confirm that regorafenib is an acceptible treatment option in patients with metastatic colorectal cancer refractory to standard chemotherapeutic agents, with a manageable toxicity profile. Further study of defining biomarker identifying a subset of patients who would benefit more from the drug is warranted.

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Table 1. Patient Characteristics

	Patients (N=40)
Median age at initial diagnosis, years (range)	54.5 (37-68)
Median age at enroll, years (range)	56.0 (41-74)
Sex	
M	25 (62.5%)
F	15 (37.5%)
ECOG	
0	18 (45.0%)
1	22 (55.0%)
Primary site of disease	
A-T Colon	7 (17.5%)
D-S Colon	15 (42.5%)
Rectum	16 (40.0%)
KRAS mutation	
no mutation	22 (55.0%)
mutant	13 (32.5%)
not tested	5 (12.5%)
Histology	
Adenoca. W/D	2 (5.0%)
Adenoca. M/D	35 (87.5%)
Adenoca. P/D	1 (2.5%)
Mucinous	2 (5.0%)
Number of metastatic sites at enrollment	
1	7 (17.5%)
2	19 (47.5%)
≥ 3	14 (25.0%)
Number of prev. anticancer therapies for metastatic disease	14 (35.0%)
1-2	17 (42.5%)

3 ≥ 4	9 (22.5%)
Time from initial diagnosis to metastatic disease (months) median (range)	0 (0-63.0)
Time from metastatic disease to study enroll (months) median (range)	24.5 (6-68.0)
Previous chemo-agent use	
Fluoropyrimidine	40 (100%)
Oxaliplatin	40 (100%)
Irinotecan	40 (100%)
Bevacizumab	5 (12.5%)
Cetuximab (in 21 KRAS wild type patients)	4 (19.0%)

Table 2. Incidence of drug-related adverse events

	Any grade, n (%)	Grade ≥3, n (%)
Any adverse event	32 (80.0%)†	3 (7.5%)
Hand-foot syndrome	24 (60.0%)	1 (2.5%)
Fatigue	5 (12.5%)	0
Hepatitis	5 (12.5%)	2 (5.0%)
Fever	4 (10.0%)	0
Hypertension	2 (5.0%)	0
Stomatitis	2 (5.0%)	0
diarrhea	2 (5.0%)	0
Hypothyroidism	1 (2.5%)	0
Myalgia	1 (2.5%)	0
Vomiting	1 (2.5%)	0
Skin Rash	2 (5.0%)	0
Hematuria	1 (2.5%)	0

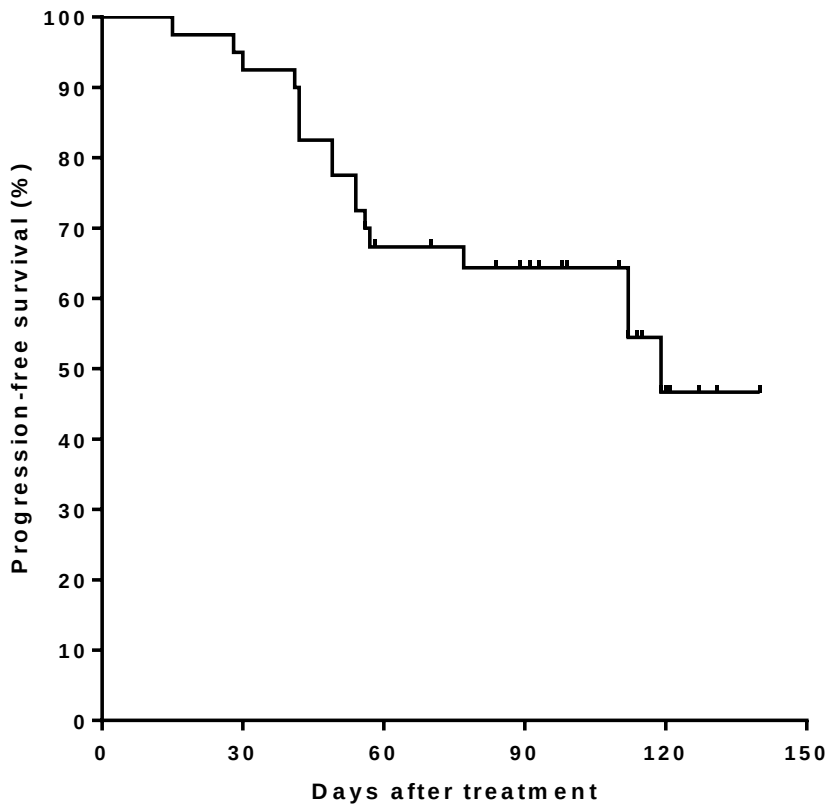
†Total 50 adverse events in 32 patients

Table 3. Summary of differences in enrolled patient characteristics between this study (SNUH) and the CORRECT study

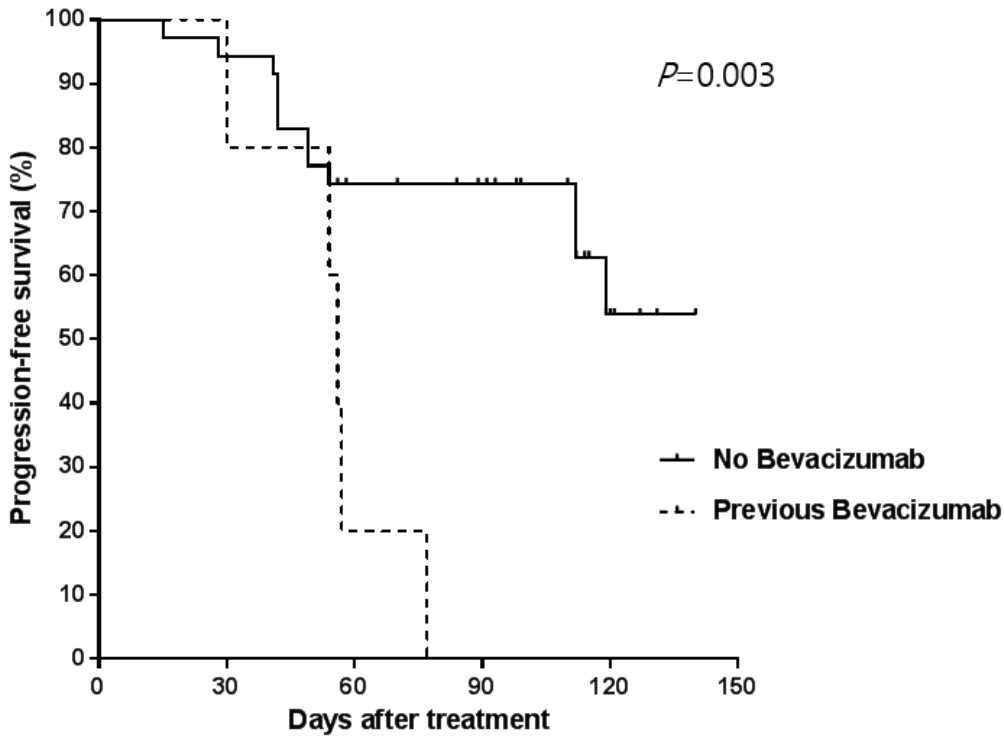
	SNUH	CORRECT
Race		
White	0	78%
Black	0	1%
Asian	100%	15%
Other/not specified	0	6%
Primary Site of Disease		
Colon	60%	64%
Rectum	40%	30%
Colon and rectum	-	6%
KRAS status		
Wild type	53%	41%
Mutant	35%	54%
Not tested	13%	5%
Previous anti-VEGF treatment		
Bevacizumab	12.5%	100%

Figure 1. Progression-free survival (A) in all-patients; (B) according to previous bevacizumab use; (C) according to previous cetuximab use (in 22 KRAS wild type patients); (D) in patients who was diagnosed with metastatic disease less than 1 year before the study enrollment, compared to those who survived longer than 1 year after confirmation of metastases to study enrollment; (E) according to KRAS status (in 35 patients whose test results were available); and (F) according to sites of primary cancer.

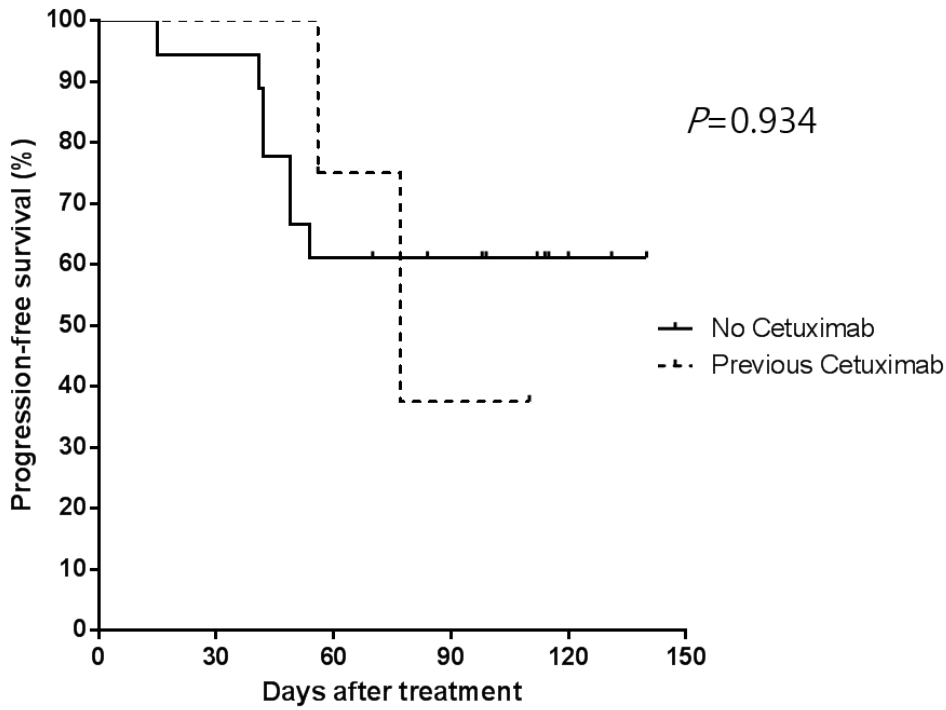
(A)


Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
Days after treatment

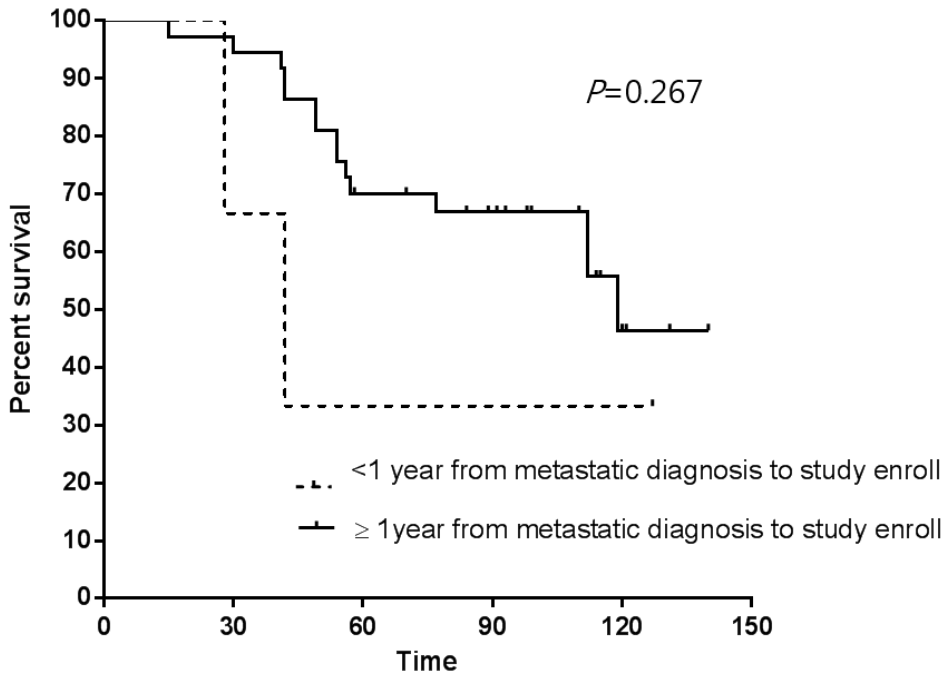
(B)


P=0.003
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
Days after treatment
No Bevacizumab
Previous Bevacizumab

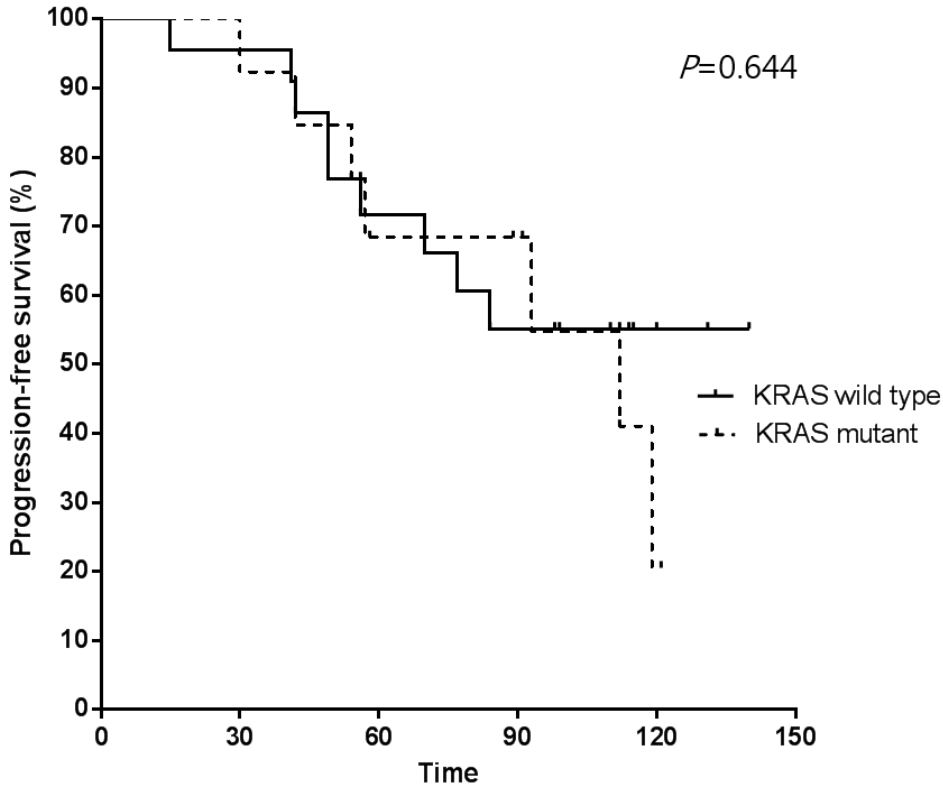
(C)


100
90
80
70
60
50
40
30
20
10
0
Progression-free survival (%)
0
30
60
90
120
150
Days after treatment
P=0.934
No Cetuximab
Previous Cetuximab

(D)


100
90
80
70
60
50
40
30
20
10
0
Percent survival
0
30
60
90
120
150
Time
P=0.267
<1 year from metastatic diagnosis to study enroll
≥ 1year from metastatic diagnosis to study enroll

(E)


100
90
80
70
60
50
40
30
20
10
0
Progression-free survival (%)
0
30
60
90
120
150
Time
P=0.644
KRAS wild type
KRAS mutant

(F)

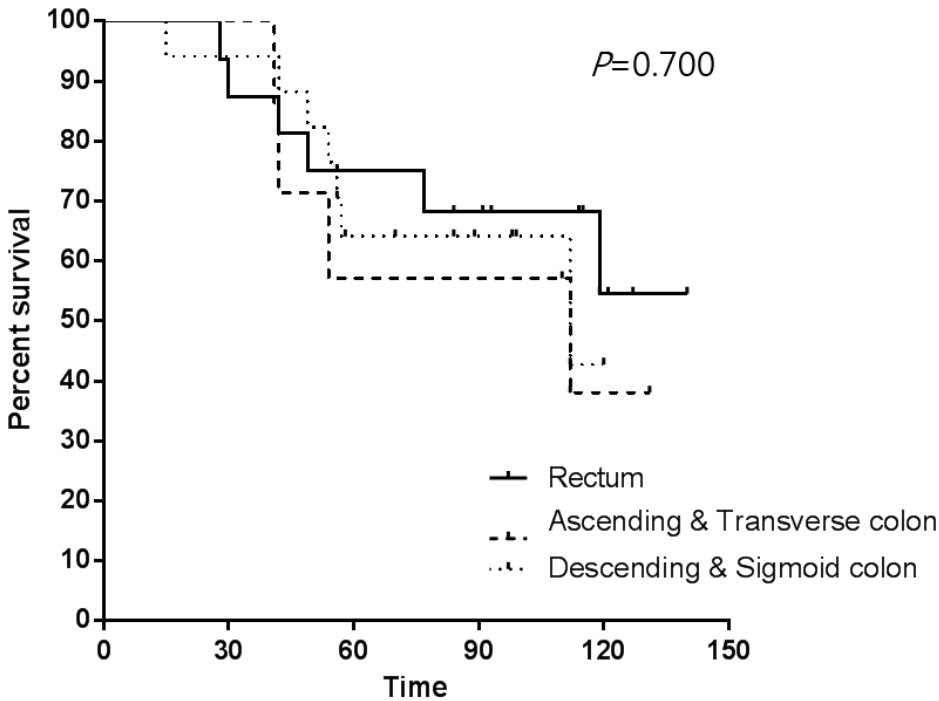
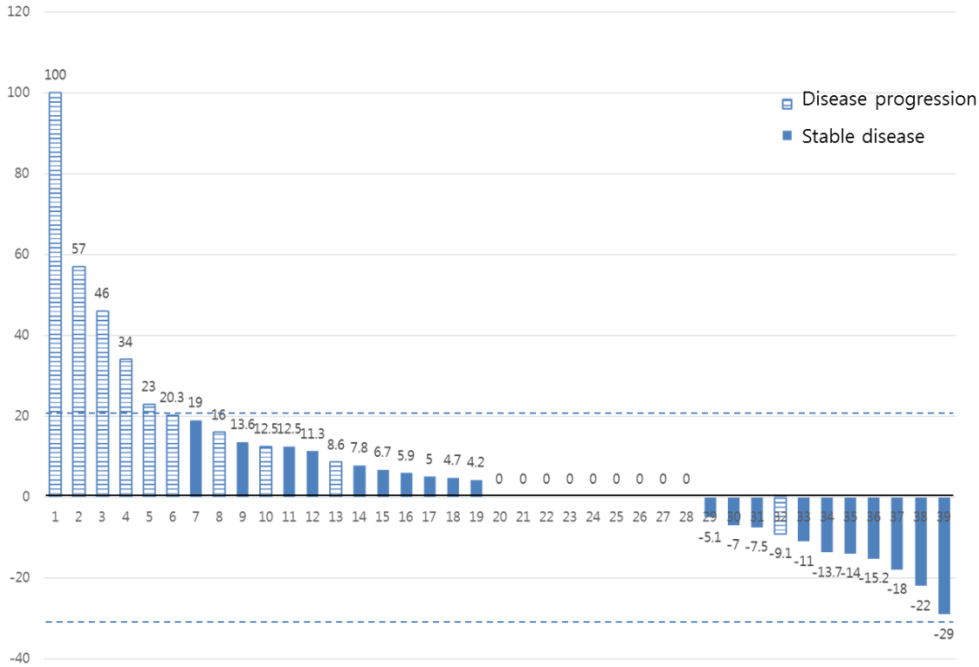

100
90
80
70
60
50
40
30
20
10
0
Percent survival
0
30
60
90
120
150
Time
P=0.700
Rectum
Ascending & Transverse colon
Descending & Sigmoid colon

Figure 2. Best response in 39 evaluable patients



국문초록

제목: 치료 저항성 대장암 환자에서 레고라페닙 단독 치료의 효과 분석

배경: Fluoropyrimidine, Oxaliplatin 및 Irinotecan을 위주로 하는 현재의 표준 치료에 이미 저항성을 보이는 전이성 대장암 환자의 치료 방법은 현재로서는 매우 제한적이다. 레고라페닙은 최근에 개발 된 경구 약제로 여러 키나아제를 억제하며 이와 같은 치료 저항성, 전이성 대장암 환자에서 효과가 있는 것으로 생각 되고 있으나, 우리나라 환자에서도 현실적으로 효과가 있는지에 대해서는 밝혀진 바가 없다.

연구 방법: 이 연구는 우리나라의 치료 저항성 대장암 환자에서 레고라페닙 단독치료의 효과를 분석하기 위하여 계획 되었다. 연구 방법은 서울대학교병원에서 표준 치료에 저항성을 보이는 전이성 대장암 환자를 대상으로 하여 레고라페닙을 4주 주기로 하루 160mg씩 3주간 경구 투약 하고 1주 휴약 하는 일정으로 치료 한 후, 그 효과를 분석하였다. 한국 현실을 고려하여 표준 치료에 대한 저항성은 floropyrimidine, oxaliplatin 및 irinotecan에 대한 실패로 정의하였으며, bevacizumab이나 cetuximab은 포함시키지 않았다.

연구 결과: 2013년 12월부터 2014년 2월까지의 기간 동안 40명의 전이성 대장암 환자가 레고라페닙으로 치료를 받았다. 추적 기간 동안 중앙 무진행 생존기간은 4.3개월이었으며, 질병제어율은 70%였다. 이전에 bevacizumab에 노출 되지 않았던 환자들이 (4개월) bevacizumab에 이미 저항성을 보이는 환자들 (2개월) 에 비하여 유의하게 긴 무진행 생존기간을 보였다 (P=0.003). 치료관련

독성은 32 (80%)명의 환자에서 관찰 되었으나, 대부분 1-2등급의 독성으로, 치료 가능하였다. 가장 흔히 관찰 되었던 독성은 수족증후군으로, 24명 (60%)의 환자에서 관찰 되었다.

고찰: 레고라페닙은 우리나라 치료 저항성 대장암 환자에서 치료 가능한 수준의 독성을 보이면서 무진행 생존 기간을 연장 시킨 다는 면에서 현실적으로 사용 가능한 대안이 될 수 있다.

중심단어: 치료 저항성 대장암, 레고라페닙, 효과

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