Original Article

Regorafenib Monotherapy for Patients with Metastatic Colorectal Cancer Who Progressed after Standard Chemo-target Therapy

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Key Words
Regorafenib;
Metastatic colorectal cancer;
Monotherapy

Purpose. Regorafenib, an oral multikinase inhibitor, shows promise in extending survival for patients with metastatic colorectal cancer (mCRC) who no longer respond to standard therapies. This study evaluates both regorafenib's effectiveness and safety in treating mCRC. Additionally, it aims to identify factors that can predict a favorable response to the drug.
Method. This retrospective, single-center study with 43 patients study explored the use of regorafenib in patients with advanced metastatic colorectal cancer (mCRC) who no longer responded to standard treatments. The starting dose was 120 mg daily for 8 weeks, continuing if scans showed no worsening or tumor shrinkage. Overall survival measured the time from starting regorafenib to death, while progression-free survival looked at the time to disease progression based on computed tomography scan (CT) scans.
Result. In total, 43 patients treated with regorafenib between 2016 and 2022 were included in this study. 9 patients (21%) responded well to the treatment, with tumor shrinkage or stabilization. These responders received an average of 4 treatment cycles (compared to 0.8 cycles for non-responders). The median overall survival was 9.2 months, with a significant difference between responders (28.2 months) and non-responders (7.9 months). The median progression-free survival (time to disease worsening) was also significantly higher in responders (8.6 months) compared to non-responders (2.1 months).
Conclusion. Patients with hand-foot skin reaction, lung metastasis cavitation, and possibly even grade II alopecia seemed to have potential positive response to regorafenib. Additionally, exploring earlier regorafenib initiation in the mCRC treatment sequence warrants further research to confirm potential benefits in overall survival and progression-free survival rates.

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The standard treatment for metastatic colorectal cancer (mCRC) consists of chemotherapy including regimen of fluoropyrimidine, irinotecan, oxaliplatin.[1] Monoclonal epidermal growth factor receptor (EGFR; cetuximab and panitumumab) antibodies are used in patients with RAS wild type tumor. Monoclonal antibody targeting vascular endothelial growth factor (VEGF; bevacizumab) was also used. Many pa-

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tients who still maintain good performance status after these standard therapy, and might be candidate for further therapy. Several signaling pathways have been found in progression of colorectal cancer, involving receptor tyrosine kinases (eg., EGFR, VEGF receptor, platelet-derived growth factor receptor [PDGFR], and fibroblast growth factor receptor [FGFR] and down stream signaling cascades (RAS-RAF-MEK-ERK and P13K-PTEN-AKT-mTOR).[2] Regorafenib is an oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumor angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2), oncogenesis (KIT, RET, RAF1, BRAF, and BRAF V600E), and the tumor microenvironment (PDGFR and FGFR).[3] Few study (CONSIGN,[4] CORRECT[5]) have showed the effect and safety of regorafenib treatment with metastatic colorectal cancer. This study aims to further evaluate the drug's effectiveness and identify potential factors that predict a favorable response to regorafenib therapy.

Material and Methods

This study is a retrospective, single center study, which enrolled 43 patients with metastatic colorectal cancer under standard treatment with chemotherapy (fluoropyrimidine, irinotecan, oxaliplatin) and monoclonal antibody (EGFR, VEGF).

Patients with metastatic colorectal cancer who progressed after standard chemotherapy and targeted therapy received regorafenib as a third-line treatment, following the guidelines set by the Taiwan Health Insurance Bureau. Nearly all patients (42 out of 43) underwent primary tumor resection. The initial dose of regorafenib was 120 mg daily, continued for 8 weeks as one treatment cycle. Six patients received a lower initial dose of 80 mg daily due to factors such as poor performance status (ECOG score > 2), low body weight (< 40 kg), advanced age (> 80 years old), or significant pre-existing medical conditions (high comorbidity). During treatment, treatment modification is defined as the change of the dose. Dose reduction to 80 mg daily was done due to undulate side effect including hand-foot skin reaction. Dose re-escalation to 120 mg daily if the side effect became tolerable or improved. To prevent hand-foot skin reaction, all patients received a urea topical cream (Sinpharderm Cream). If hand-foot skin reaction occurred, a combination cream of hydrocortisone and urea (Sinpharderm-HC Cream) was prescribed. Other common side effects, such as hypertension and diarrhea, were managed with oral medication. Regular blood tests (biochemistry and hematology) were performed at least every 2 months to monitor for potential complications. Patients were considered responders if they completed at least one treatment cycle (168 tablets) and imaging studies showed tumor regression or stable disease, allowing them to continue regorafenib treatment according to the Taiwan Health Insurance Bureau regulations.

Patients who experienced tumor progression within the first treatment cycle (168 tablets) were classified as non-responders.

Further image examination including abdominal and chest computed tomography scan is arranged for evaluation the treatment response. If image examination is regression or stationary of tumor, next 8 weeks of treatment will be applied until the disease progression or intolerable side effect.

All statistical analyses were performed using SPSS version 25 (IBM). Demographic characteristics of patients are summarized descriptively. Overall survival (OS) and progression free survival (PFS) were estimated using the Kaplan-Meier method. OS was defined as the time from the date of first administration of regorafenib to the date of death (regardless of the cause) or censored on the last date of survival. PFS was defined as the time from the date of first administration of regorafenib to the date or disease progression which by computed tomography scan.

Results

Patient characteristics

In total, 43 patients treated with regorafenib between 2016 and 2022 were included in this study. The majority were male (n = 26, 60.5%) and the median age at diagnosis was 61.2 years. The primary tumor

localization was the left colon including rectum in 37 patients (86%) and the right colon in 6 patients (14%). Most prevailing histology type was moderate differentiated adenocarcinoma (n = 41, 95%). Mutations of RAS gene was detected in 22 cases (51%). When initiating treatment with regorafenib, 29 patients (67%) had ECOG performance status 0, 14 (32%) patients had ECOG performance status 1-2. The mean time between diagnosis of metastatic disease and received regorafenib is 137.6 weeks. Basline characteristics related to regorafenib treatment are summarized in Table 1.

Table 1. Patient characteristics

	Overall (n = 43)	Response (n = 9)	Non-response (n = 34)	*p*
Initial age (years), Mean (SD)	61.2 (±11.0)	61.5 (±14.3)	61.1 (±10.2)	0.920
Male, n (%)	26 (60.5)	5 (55.6)	21 (61.8)	1.000
Performance (ECOG), n				0.745
0	29	7	22	
1	8	1	7	
2	6	1	5	
BMI, Mean (SD)	24.3 (±4.2)	23.1 (±3.9)	24.6 (±4.3)	0.351
Primary site of tumor, n				0.785
Ascending	5	1	4	
Transverse	1	0	1	
Descending	2	0	2	
Sigmoid	17	5	12	
Rectum	18	3	15	
Primary site of tumor, n				1.000
Right	6	1	5	
Left	37	8	29	
Histology type, n				1.000
Moderate	41	9	32	
Poor	2	0	2	
KRAS, n				0.872
WT	23	5	18	
Mutation	19	4	15	
Not test	1	0	1	
NRAS, n				0.760
WT	27	6	21	
Mutation	3	1	2	
Not test	13	2	11	
RAS, n				1.000
WT	21	4	17	
Mutation	22	5	17	
BRAF, n				0.572
WT	27	5	22	
Mutation	2	1	1	
Not test	14	3	11	
MMR, n				1.000
pMMR	23	5	18	
Not test	20	4	16	
EGFR, n				0.433
Over expression	36	7	29	
No over expression	2	0	2	
Not test	5	2	3	

During regorafenib treatment, 9 patients (21%) had treatment response including repression of tumor or stable disease and received 4 (±3.7) cycles of treatment. 34 patient (79%) had nonresponse, and only received 0.82 (±0.4) cycle of treatment. There are nine patients in the response group, and all of them received an initial daily dose of 120 mg. In the non-response group, there are 34 patients. Of these, 28 patients (82%) received an initial daily dose of 120 mg, while the remaining six patients (18%) received an initial daily dose of 80 mg (Table 2).

The mean follow-up overall survival is 11.6 months (±10.6), and the mean progression free survival is 43.1 months (±6.0). During the treatment, 8 patients (89%) had hand foot skin reaction in response group, whereas 16 patient (47%) in non-response group (p = 0.055). Alopecia was found in response group (n = 3, 33%), where no alopecia was found in non-response group. Lung cavitation was found in response group (n = 5, 56%), where no lung cavitation was found in non-response group (Table 3).

The median progression free survival is 2.4 months (95% CI: 1.8-2.9) in all patients. The PFS is 8.6 months (95% CI: 0.0-17.5) in response group and is 2.1 months (95% CI: 1.9-2.3) in the non-response group. The p value is 0.00 when comparing two groups (Fig. 1, Table 4).

The median overall survival is 9.2 months (95% CI: 4.8-13.5) in all patients. The OS is 28.2 months (95% CI: 20.8-35.6) in response group and is 7.9 months (95% CI: 5.3-10.4) in the non-response group. The p value is 0.005 when compared two groups (Fig. 2).

Table 3. Side effects

	Overall (n = 43)	Response (n = 9)	Non-response (n = 34)	*p*
HFSR, n				0.055
Yes	24	8	16	
No	19	1	18	
HFSR grade, n				0.153
1	4	3	1	
2	16	4	12	
3	4	1	3	
Lung cavitation, n				0.000
Yes	5	5	0	
No	38	4	34	
Alopecia, n				0.007
Yes	3	3	0	
No	40	6	34	

Table 2. Treatment results

	Overall (n = 43)	Response (n = 9)	Non-response (n = 34)	*p*
Time (weeks) from stage 4 diagnosis to start regorafenib, Mean (SD)	137.6 (±68.2)	132.3 (±54.1)	138.9 (±72.1)	0.799
Age (years) when start regorafenib, Mean (SD)	65.1 (±10.8)	66.8 (±12.7)	64.6 (±10.4)	0.594
Initial daily dose, n				0.315
80 mg	6	0	6	
120 mg	37	9	28	
Any treatment modification, n				0.057
Yes	25	8	17	
No	18	1	17	
Dose reduction, n				0.122
Yes	17	6	11	
No	26	3	23	
Dose re-escalation, n				0.095
Yes	6	3	3	
No	37	6	31	
Treatment interruption > 1 day, n				1.000
Yes	19	4	15	
No	24	5	19	
Total cycles, Mean (SD)	1.5 (±2.1)	4 (±3.7)	0.82 (±0.4)	0.032
Total treatment days, Mean (SD)	128.1 (±179.2)	352.2 (±305.7)	68.7 (±29.3)	0.024

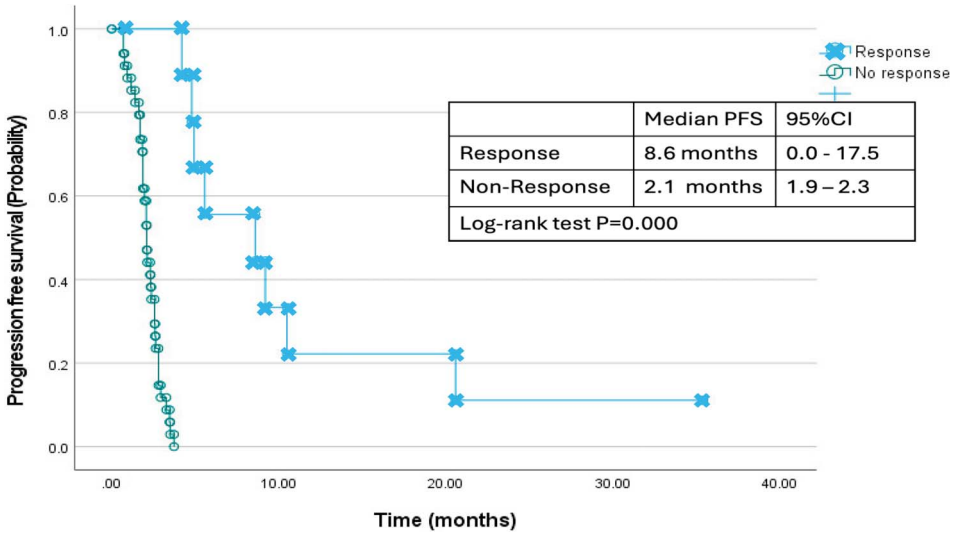

Fig. 1. Kaplan-Meier progression free survival (PFS) curves of response and non-response group.

Table 4. Oncological outcome

	Overall (n = 43)	Response (n = 9)	Non-response (n = 34)	*p*
Duration (days) from start therapy to disease progression, Mean (SD)	101.9 (±103.9) (n = 42)[a]	260.1 (±159.1) (n = 8)[a]	64.6 (±23.5) (n = 34)	0.010
PFS, months, Median	2.4	8.6	2.1	0.000
Duration (weeks) from start therapy to death, Mean (SD)	45.5 (±47.2) (n = 31)	100.0 (±74.4) (n = 5)	35.1 (±32.8) (n = 26)	0.123
OS, months, Median	9.2	28.2	7.9	0.005
Survival, n (%)	12 (27.9)	4 (44.4)	8 (23.5)	0.237

[a] One patient is undergoing treatment without disease progression.

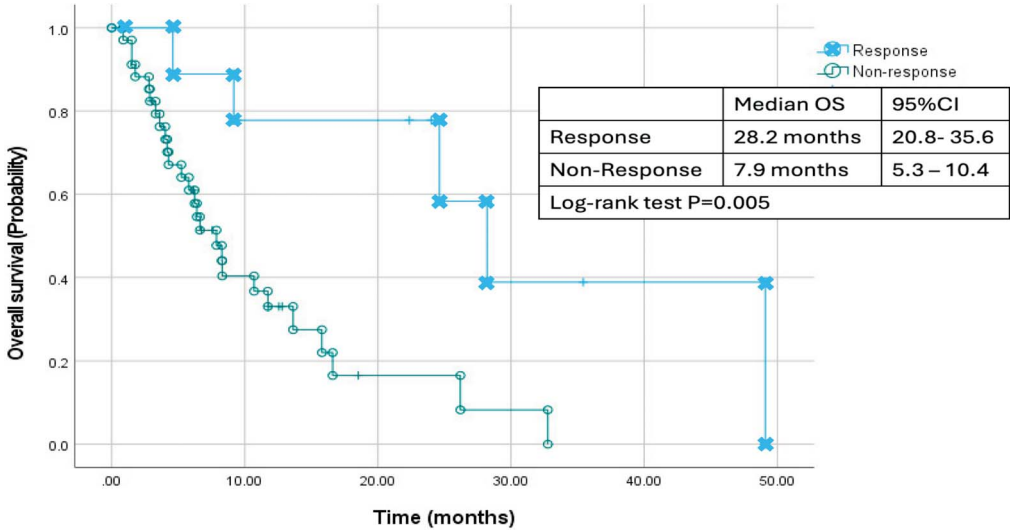

Fig. 2. Kaplan-Meier overall survival (OS) curves of response and non-response group.

Discussion

The RadioCORRECT study[6] showed that an early radiological evaluation of tumor response is helpful to predict clinical outcome to regorafenib in mCRC. Lung cavitation at week-8 treatment showed improved PFS

(HR 0.58, 95% CI: 0.36-0.93, $p = 0.03$). In our study, lung cavitation in week 8 was found in response group (n = 5, 56%), and no cavitation was found in non-response group.

The incidence of drug-related HFSR was numerically higher in the Taiwanese population than in the global population (all grade, 33.59% vs. 26%; grade ≥ 3, 10.16% vs. 7%).[7,8] In our study, the incidence of all grade HFSR is 56% (24/43), grade ≥ 3 is 9% (4/43), slightly higher than other study. In subgroup analysis, the treatment response group had significant higher HFSR than non-response group (all grade, 89% vs. 47%, $p = 0.055$).

The incidence of drug related alopecia is 7% in regorafenib treatment group comparing with placebo group (1%).[8] In our study, the incidence of alopecia is 7%, similar to the other study, and was all found in the response group. No alopecia was found in non-response group.

In our study, it seems that for patients who had HFSR, and cavitation in lung metastasis have better response to regorafenib. While patients who have rare clinical manifestation of adverse events with alopecia also seem to have good response to regorafenib.

The ReDOS[9] study evaluated two regorafenib dosing strategies: dose escalation (starting at 80 mg/day with weekly 40 mg increments to 160 mg/day) and a standard dose (160 mg/day) for 21 days of a 28-day cycle. And the dose-escalation strategy may be particularly attractive for patients likely to receive a third cycle (with lower incidence of adverse event), potentially leading to improved overall survival. For physicians managing refractory metastatic colorectal cancer, dose escalation offers a promising alternative for optimizing regorafenib treatment. In our study, a total of 40% (17 out of 43) patients required a dose reduction from the initial 120 mg/daily dose. Patients who responded to treatment (response group) had a higher dose reduction rate (67%, 6 out of 9 patients) compared to those who did not respond (non-response group) at 32% (11 out of 34 patients). There are a couple of possible explanations for this observation. Patients who respond to treatment might be more sensitive to the medication overall, leading to a higher rate of side effects that necessitate dose reduction. Alternatively, it's possible that patients who didn't respond had underlying health conditions that limited their ability to tolerate the initial dose.

For the response group, the average time between the diagnosis of mCRC and start treatment with regorafenib is 30.9 months, which is slightly shorter than the non-response group (32.4 months). Although there is no significant difference between two groups ($p = 0.8$), but there maybe something more. One patient who was diagnosis with metastasis rectal cancer, and received FOLFIRI and bevacizumab therapy. However, due to severe bleeding side effect, bevacizumab therapy was suspended. After m-FOLFOX-6 therapy, the toxicity of oxaliplatin cannot be tolerate. Therefore, regorafenib treatment was started, and the time between mCRC and regorafenib (19.4 months) is significantly shorter than other patients (32.1 months for all patients). The treatment effect is extremely good. After regorafenib therapy, the patient had received 35 months regorafenib therapy without any clinically progression or recurrence. In our observation, moving forward the regorafenib to treatment of mCRC may cause good treatment effect, but larger and more prospective studies are needed to confirm these associations.

Limitation

This study was retrospective and had a small sample size, limiting the generalizability of its findings. Larger, prospective studies are needed to confirm these associations and explore their clinical utility.

Conclusion

Our study suggests that patients who experienced hand-foot skin reaction and lung metastasis cavitation exhibited trends towards better response to regorafenib, while those with grade II alopecia might be associated with improved response. These findings require further investigation in larger, prospective studies. Additionally, exploring earlier regorafenib initiation in the mCRC treatment sequence warrants further research to confirm potential benefits in PFS and OS.

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原　著

癌瑞格單藥治療標準治療後惡化的轉移性結直腸癌患者

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目的　癌瑞格是一種口服的多激酶抑制劑，對於標準治療無效的轉移性大腸癌患者，似乎能延長存活期。本研究旨在評估癌瑞格治療轉移性大腸癌的有效性和安全性，並找出可能預測患者對藥物反應良好的因素。

方法　本研究為單中心回顧性研究，納入 43 位接受癌瑞格治療的晚期轉移性大腸癌患者，這些患者先前已對標準治療無反應。起始劑量為每日 120 mg，連續服用 8 周，如果掃描結果顯示腫瘤沒有惡化或縮小，則繼續服藥。研究評估了總生存期 (從接受癌瑞格治療開始到死亡的時間) 和無惡化生存期 (根據電腦斷層掃描評估疾病惡化前的時間)。

結果　研究納入 2016 年至 2022 年間接受癌瑞格治療的 43 位患者。其中 9 位患者 (21%) 對治療反應良好，腫瘤縮小或穩定。這些反應良好的患者平均接受了 4 個療程的治療 (而非反應者的平均療程為 0.8 個)。總體中位生存期為 9.2 個月，其中反應良好組 (28.2 個月) 和非反應良好組 (7.9 個月) 之間存在顯著差異。無惡化生存期中位數 (疾病惡化前的時間) 在反應良好組 (8.6 個月) 也顯著高於非反應良好組 (2.1 個月)。

結論　手足皮膚反應、肺轉移灶空洞化，甚至可能二級禿髮的患者似乎對癌瑞格的反應較好。此外，研究人員建議在轉移性大腸癌治療過程中更早使用癌瑞格，以期改善患者的生存期和無惡化生存期，但需要更多的研究來證實。

關鍵詞　癌瑞格、轉移性大腸癌、單藥治療。