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ORIGINAL RESEARCH

The use of regorafenib for patients with refractory metastatic colorectal cancer in clinical practice

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Aim: Patients in clinical practice are relatively vulnerable compared to those enrolled in clinical trials. We focused on analyzing the pattern of regorafenib use in routine clinical practice, which included initial starting dose and follow-up schedule. We also evaluated the efficacy and safety according to clinical regimen.

Methods: We retrospectively reviewed the medical records of 134 Korean heavily pretreated metastatic colorectal cancer (mCRC) patients who had received regorafenib monotherapy as salvage treatment in routine clinical practice between January 2014 and January 2018.

Results: Among the 134 mCRC patients, the median age was 55 years (range, 22–80 years), and 51% had previously received four or more chemotherapy treatments. Thirty-eight (28.3%) patients had more than three metastatic lesions. As an initial starting dose, 120 mg regorafenib was mostly frequently used (n=65, 48.5%), followed by 80 mg (32.8%) and 160 mg (18.7%). The first follow-up after regorafenib initiation was most frequently at 28 days (45.5%), followed by 14 days (29.9%), 7 days (13.4%), and 21 days (11.2%). There was no significant difference in response rate according to initial dose of regorafenib (80 mg vs 120 mg vs 160 mg, 4.5% vs 1.5% vs 4.0%, P=0.596) or disease control rate (80 mg vs 120 mg vs 160 mg, 38.6% vs 29.2% vs 31.6%, P=0.299). Progression-free survival did not differ according to initial dose (80 mg vs 120 mg vs 160 mg, 2.8 months [95% CI 2.1–3.5] vs 2.2 months [95% CI 1.7–2.8] vs 1.9 months [95% CI 1.3–2.4], P=0.076). Grade 3/4 adverse events occurred in 17 (12.7%) patients and were not related to initial dose of regorafenib (P=0.126).

Conclusion: Here, we present efficacy and safety data according to different initial doses of regorafenib in clinical practice. These data may provide useful information when using regorafenib for refractory mCRC in clinical practice.

Keywords: regorafenib, colorectal cancer, initial dose

Introduction

Regorafenib (Stivarga, BAY 73–4506; Bayer Pharma AG, Berlin, Germany) is a novel oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumor angiogenesis (VEGFR1 [also known as FLT1], VEGFR2 [KDR], VEGFR3 [FLT4], TIE2 [TEK]), oncogenesis (KIT, RET, RAF1, *BRAF*, and BRAFV600E), and the tumor microenvironment (PDGFR and FGFR).[1,2] In two recent Phase III trials, CORRECT and CONCUR, regorafenib had shown a survival benefit in patients with metastatic colorectal cancer (mCRC) who had progressed on standard treatments.[3] Currently, regorafenib is regarded as one of the standard therapies for refractory mCRC patients.

The purpose of chemotherapy in refractory cancer patients is palliation.[4] Thus, when considering chemotherapy in refractory cancer patients, clinicians must consider treatment efficacy as well as treatment safety.[5–7] In two large Phase III clinical trials,

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regorafenib has been shown to be efficacious and safe. However, the criteria for enrollment in clinical trials were strict and selective; thus, findings from clinical trials may differ from results in clinical practice. In particular, although strict criteria were applied, grade 3 or 4 treatment-related adverse events were reported in ~54% of patients on regorafenib in the CORRECT and CONCUR trials,[3,8] and the dose was reduced in 38% of patients. It is important to assess the clinical benefit of regorafenib while also considering the clinical impact of its toxicities. Due to toxicities associated with the standard recommended dose of 160 mg regorafenib, investigators have studied a reduced dose in mCRC patients. Osawa et al had reported that an initial dose of 120 mg regorafenib was also effective and tolerable in eight Japanese refractory mCRC patients.[9] Also, some investigators have recommended a starting dose of 80 mg.[10] However, there have been little data describing the efficacy and safety of different initial doses of regorafenib, in particular 80, 120, and 160 mg.

Patients in clinical practice are relatively friable compared to those in clinical trials. In clinical practice, patients may be managed differently than the protocol applied in clinical trials. Here, we analyzed the pattern of regorafenib use in routine practice, which included initial starting dose and follow-up schedule. We also evaluated the efficacy and safety according to clinical practice regimen.

Materials and methods

Patients

mCRC patients who received regorafenib monotherapy at Samsung Medical Center between January 2014 and January 2018 were included in this analysis. All patients had previously received fluorouracil (FU), irinotecan, and oxaliplatin with or without biologic agents such as cetuximab or bevacizumab.

Each patient's medical records, which included age, sex, primary site, histologic type, *KRAS*/*BRAF* mutation results, extent of metastasis, treatment details, and treatment outcomes, were analyzed. We also evaluated patient data on dose, safety, and efficacy of regorafenib.

This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2018-08-013) and the requirement for informed consent was waived. This retrospective study was a level of research that does not exceed the minimum risk to the subject and is expected to have social benefits in treatment of similar patients. We used data from which personally identifiable information had been removed, so did not require a separate privacy plan for subject. To protect the personal information of the subject and confidentiality of the data, all data were anonymous. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Korea Good Clinical Practice guidelines.

Regorafenib

In routine clinical practice, patients received oral regorafenib once daily for the first 3 weeks of each 4-week cycle until disease progression, death, or unacceptable toxic effects. The initial dose of regorafenib and the first follow-up visit were determined by the physician. Dose reductions and delays in the following cycle were also by physician's choice. If the patient required an additional dose reduction at 80 mg or a delay of more than 28 days between cycles, discontinuation of regorafenib treatment was recommended.

Assessment

Tumor response to regorafenib was assessed with computed tomography (CT) scan after every two cycles. The response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease based on the RECIST criteria (version 1.1).[11] The adverse effects of regorafenib treatment were calculated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[12,13]

Statistical methods

We analyzed the clinical practice patterns including initial starting dose, first follow-up visit, treatment outcomes, and toxicities of regorafenib in refractory mCRC patients. Descriptive statistics were calculated as proportions and medians. Treatment outcomes were estimated as response rate (RR), progression-free survival (PFS), and toxicity. Treatment outcomes were compared by the Fisher's exact test or chi-squared test according to initial dose of regorafenib. PFS was defined as the time from the first study treatment to the date of disease progression. Survival data were assessed using the Kaplan–Meier method. We also calculated the 95% CI for the median time to event.

Results

Patients

A total of 134 patients with mCRC receiving regorafenib as salvage therapy were included in this study. Patient baseline characteristics are given in Table 1. The median age was 55 years (range, 22–80 years) with the majority of patients younger than 65 years (n=111, 82.8%).

Table 1 Baseline patient characteristics (N=134)

Characteristics	N (%)
Median age (years [IQR])	55 (22–80)
Age (years)	
<65	111 (82.8)
≥65	23 (17.2)
Sex	
Male	72 (53.7)
Female	62 (46.3)
ECOG	
0–1	129 (96.3)
2	5 (3.7)
Primary site of disease	
Ascending colon	89 (66.4)
Descending colon	38 (28.4)
Rectosigmoid	7 (5.2)
Disease status	
Metastatic	90 (67.2)
Recurrence	44 (32.8)
KRAS mutation	
Wild	66 (49.3)
Mutant	53 (39.6)
Unknown	15 (11.2)
BRAF V600E	
Wild	72 (53.7)
Mutant	4 (3.0)
Unknown	58 (43.3)
No of previous systemic anticancer therapies	
≤3	66 (49.2)
≥4	68 (50.7)
Metastatic site	
<3	96 (71.6)
≥3	38 (28.3)
Previous anti-VEGF treatment (bevacizumab)	116 (86.6)
Previous anti-EGFR treatment (cetuximab)	55 (41.0)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

The numbers of males and females were 72 (53.7%) and 62 (46.3%), respectively, and 51% of patients had previously received four or more chemotherapy treatments. Thirty-eight (28.3%) patients had more than three metastatic lesions. Fifty-three (39.6%) patients had a *KRAS* mutation, and four had the *BRAF* V600E mutation (3.0%). In total, 116 (86.6%) patients had received prior bevacizumab-containing therapy, and 55 (41.0%) patients with the wild-type RAS were previously treated with cetuximab-containing therapies.

Regorafenib

The median Eastern Cooperative Oncology Group performance status of patients receiving regorafenib was 1 (0–2). The initial starting doses of regorafenib and the first follow-up visit are listed in Table 2. A starting dose of 120 mg regorafenib was most frequently used (n=65, 48.5%), followed by 80 mg (32.8%) and 160 mg (18.7%). The first follow-up after starting regorafenib treatment was most commonly 28 days (45.5%), followed by 14 days (29.9%), 7 days (13.4%), and 21 days (11.2%). Sixty-one patients (45.5%) visited the hospital 28 days after initiating regorafenib according to the standard follow-up schedule.

Among the 134 patients analyzed in this study, 130 were available for response evaluation (Table 3). None of the patients showed a CR, and a PR was reported in only four patients (3.0%). Thirty-seven patients showed SD. The response rate was 3.0%, and disease control rate was 30.4%. There was no significant difference in response rate according to initial dose of regorafenib (80 mg vs 120 mg vs 160 mg, 4.5% vs 1.5% vs 4.0%, P=0.596) or disease control rate (80 mg vs 120 mg vs 160 mg, 38.6% vs 29.2% vs 31.6%, P=0.299). Additionally, there was no difference in response rate according to *KRAS*/*BRAF* mutation results (Table S1).

The median PFS was 2.4 months (95% CI, 2.0–2.8 months) (Figure 1). PFS also did not differ according to initial dose (80 mg vs 120 mg vs 160 mg, 2.8 months [2.1–3.5] vs 2.2 months [1.7–2.8] vs 1.9 months [1.3–2.4], P=0.076).

Grade 3/4 adverse events occurred in 17 (12.7%) patients (Table 4). The most frequent grade 3/4 toxicities were hand-foot skin reaction (n=9, 6.7%), followed by bowel perforation (n=3, 2.2%) and mucositis (n=1, hepatitis, diarrhea, and fatigue). Grade 3/4 adverse events were not related to initial regorafenib dose (P=0.126). Dose modification occurred in 49 patients (36.5%), which included dose reductions in 42 (31.3%)

Table 2 The initial starting dose of regorafenib and the first follow-up after initiating regorafenib treatment

	N (%) (total=134)	80 mg (n=44)	120 mg (n=65)	160 mg (n=25)
Regorafenib first dose				
80 mg	44 (32.8)	44 (32.8%)		
120 mg	65 (48.5)		65 (48.5%)	
160 mg	25 (18.7)			25 (18.7%)
First follow-up date				
7 days	18 (13.4)	2 (4.5%)	12 (18.5%)	4 (16.0%)
14 days	40 (29.9)	7 (15.9%)	25 (43.1%)	5 (20.0%)
21 days	15 (11.2)	2 (4.5%)	9 (13.8%)	4 (16.0%)
28 days	61 (45.5)	33 (75.0%)	16 (24.6%)	12 (48.0%)

Table 3 Treatment efficacy according to initial regorafenib starting dose

Treatment outcomes	Total	80 mg (n=44)	120 mg (n=65)	160 mg (n=25)	*P*-value
PR	4 (3.0%)	2 (4.5%)	1 (1.5%)	1 (4.0%)	
SD	37 (27.4%)	15 (34.1%)	18 (27.7%)	4 (16.0%)	
PD	89 (66.4%)	26 (59.1%)	44 (67.7%)	19 (76.0%)	
NE	4 (3.0%)	1 (2.3%)	2 (3.1%)	1 (4.0%)	
Response rate	3.00%	4.50%	1.50%	4.00%	0.596
Disease control rate	30.40%	38.60%	29.20%	31.60%	0.299

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.

and dose increases in seven (5.2%). Dose reductions were observed in 44.0% of patients receiving 160 mg regorafenib as the initial dose and 38.5% of patients receiving 120 mg initially.

Discussion

The CORRECT and CONCUR studies demonstrated that regorafenib significantly prolongs survival in heavily pretreated mCRC patients as compared to best supportive care.[3,8] These results led to US Food and Drug Administration approval of regorafenib 160 mg orally once daily on days 1–21 of each 28 days cycle. However, grade 3 or 4 treatment-related adverse events were reported in 54% of patients assigned to regorafenib in these trials. Therefore, physicians have been cautious when using regorafenib in refractory mCRC patients. The present study showed that an initial dose of 80 mg or 120 mg regorafenib had similar efficacy as compared to a standard 160 mg dose of regorafenib. Furthermore, grade 3 or 4 adverse effects were observed at a lower frequency for 80 mg and 120 mg regorafenib doses than for the 160 mg dose.

In the present study, there were only 25 (18.7%) patients who received the standard 160 mg dose of regorafenib. This observation suggests that physicians were concerned about the adverse effects. The patient characteristics of heavily pretreated mCRC patients in clinical practice differ from patients enrolled in clinical trials. The concern of using an initial dose of 160 mg regorafenib has been addressed in previous studies.[10]

In CONSIGN study, survival data were similar to those reported by previous clinical trials; however, treatment-related adverse events led to dose reduction in 46% of patients and severe adverse effects occurred in 44% of patients.

Here, we report that the preferred initial dose in clinical practice was 120 mg (n=65, 48.5%) or 80 mg (n=44, 32.8%). Grade 3/4 side effects (80 mg vs 120 mg vs 160 mg, 6.8% vs 12.3% vs 24.0%) were more frequent as the initial starting dose increased. Interestingly, there were no significant differences in RR, disease control rate, and PFS associated with initial regorafenib dose. Recently, the ReDOS study also showed that a strategy with weekly dose escalation of regorafenib from 80 mg to 160 mg/day was found not to be inferior to a starting dose of 160 mg/day for survival outcomes.[10]

The tolerability was better in a strategy including weekly dose escalation as compared to the standard dose.

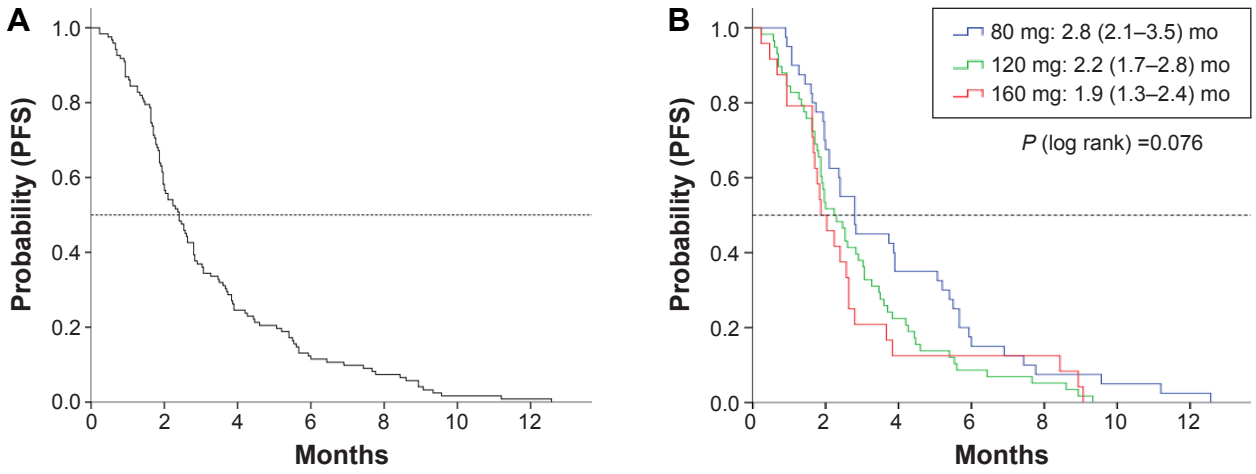

Figure 1 (**A**) Kaplan–Meier estimate of progression-free survival (PFS). (**B**) Kaplan–Meier estimate of PFS according to initial starting dose of regorafenib.

Table 4 Grade 3 or 4 adverse events

	N (%)	80 mg (n=44)	120 mg (n=65)	160 mg (n=25)	*P*-value
Dose modification					0.02
Reduction	42 (31.3)	6 (13.6%)	25 (38.5%)	11 (44.0%)	
Increase	7 (5.2)	4 (9.1%)	3 (4.6%)	0 (0.0%)	
No modification	85 (63.4)	34 (77.3%)	37 (56.9%)	14 (56.0%)	
Grade 3/4 AE					0.126
No	117 (87.3)	41 (93.2%)	57 (87.7%)	19 (76.0%)	
Yes	17 (12.7)	3 (6.8%)	8 (12.3%)	6 (24.0%)	
Type of grade 3/4 AE					
HFSR	9 (6.7)	1 (2.3%)	5 (7.6%)	3 (12.0%)	
Mucositis	2 (1.4)	0 (0.0%)	2 (3.1%)	0 (0.0%)	
Bowel perforation	3 (2.2)	1 (2.3%)	1 (1.5%)	1 (4.0%)	
Hepatitis	1 (0.7)	1 (2.3%)	0 (0.0%)	0 (0.0%)	
Diarrhea	1 (0.7)	0 (0.0%)	0 (0.0%)	1 (4.0%)	
Fatigue	1 (0.7)	0 (0.0%)	0 (0.0%)	1 (4.0%)	

Abbreviations: AE, adverse event; HFSE, hand-foot skin reaction.

These findings may be helpful in routine clinical practice in regard to the use of regorafenib in heavily pretreated refractory mCRC patients.

Most treatment-related adverse events occur early within the first 3 weeks of starting regorafenib, particularly in patients who receive a 160 mg dose.[12] In the REBACCA study which administered 160 mg regorafenib, the median time to first treatment modification was also 0.7 months, due mainly to toxicity.[14]

Thus, monitoring patients in the first treatment cycle of regorafenib is important for managing and preventing treatment-related adverse effects. In this study, we also analyzed the first follow-up visit after initiating regorafenib treatment. More than half of patients (n=73, 54.5%) regularly visited the hospital within 21 days after starting regorafenib. Early monitoring may detect treatment-related adverse effects before they become more severe. In this study, grade 3 or 4 treatment-related adverse events accounted for only 12.7% of all events. This was fewer than reported in previous Phase III trials (54%).[3] This discrepancy may be due to the heterogeneous patient population, different initial regorafenib doses, and/or different follow-up schedules.

In a previous Phase I study of regorafenib, grade 3 or higher adverse effects were fewer with 120 mg than with 160 mg. Both pharmacokinetic and pharmacodynamic analyses revealed that regorafenib had similar effects at doses 120 mg to 220 mg.[15] Pharmacodynamic assessments showed pharmacologic activity for dose levels of 120 mg and above, but without significant difference across the dose levels between 120 mg and 220 mg.

Previous clinical studies have also reported that an initial regorafenib dose of 80 mg or 120 mg had good tolerability and modest antitumor activity as salvage therapy for mCRC.[9] However, these studies had small sample sizes ranging from 20 to 48 patients. This study has some limitations, such as the retrospective nature, small sample size, and lack of consistency in patients' follow-up and overall survival. Nevertheless, the efficacy and safety according to initial dose of regorafenib in clinical practice were shown. These data may be useful for physicians considering regorafenib for refractory mCRC in the clinic.

Conclusion

The present study showed that an initial dose of 80 mg or 120 mg regorafenib had similar efficacy as compared to a standard 160 mg dose of regorafenib. Furthermore, grade 3 or 4 adverse effects were observed at a lower frequency for 80 mg and 120 mg regorafenib doses than for the 160 mg dose. These data may provide useful information when using regorafenib for refractory mCRC in clinical practice.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 The response rate according to *KRAS* and *BRAF* mutation status.

	N (%)	Na (N)	PR	SD	PD	*P*-value
KRAS						
Wild	66 (49.3)	2	1 (1.5%)	24 (36.4%)	39 (59.1%)	0.245
Mutant	53 (39.6)	2	2 (3.8%)	11 (20.8%)	38 (71.7%)	
NA	15 (11.2)					
BRAF						
Wild	72 (53.7)	3	3 (4.2%)	18 (25.0%)	48 (66.7%)	1.000
Mutant	4 (3.0)	0	0	1 (25.0%)	3 (75.0%)	
NA	58 (43.3%)					

Abbreviations: NA, non assessable; PR, partial response; SD, stable disease; PD, progressive disease; Na, not available.