Original Study

Efficacy and Safety of Regorafenib With 2/1 Schedule for Patients ≥ 75 Years With Metastatic Colorectal Cancer (mCRC) After Failure of 2 Lines of Chemotherapy

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Abstract

Regorafenib was shown to improve survival of patients with metastatic colorectal cancer resistant or unfit for all available therapies. Data on the efficacy and safety of regorafenib in elderly patients are scarce. In this small analysis, regorafenib administered with a modified schedule (2 weeks-on/1 week-off) to patients who were aged ≥ 75 and non-frail with late-stage metastatic colorectal cancer appears to be tolerable and effective.

Background: In the CORRECT (patients with metastatic COloRectal Cancer treated with REgorafenib or plaCebo after failure of standard Therapy) trial, regorafenib was proven to extend survival of patients with metastatic colorectal cancer (mCRC) that progressed after all available therapies. Grade 3 to 4 toxicity occurred in 54% of patients, and data on the activity and tolerability of regorafenib in elderly patients were scarce. The aim of this study was to evaluate the efficacy and safety of an alternative schedule, 2-week-on treatment and 1 week-off (2/1 schedule), of regorafenib for elderly patients with mCRC. **Patients and Methods:** Patients ≥ 75 years with mCRC who progressed after oxaliplatin- and irinotecan-based chemotherapy received regorafenib on a 2/1 schedule. Potentially frail subjects were identified by G8 screening tool and excluded. The 2-month disease-control rate was the primary endpoint, and the secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and objective response rate. **Results:** Between February 2014 and May 2017, 23 patients with mCRC were recruited at our institution. No partial or complete responses were observed, and the stable disease and disease-control rate were 52.2%. The median PFS was 4.8 months (95% confidence interval, 3.8-6.3 months), and the median OS was 8.9 months (95% confidence interval, 6.9-10.6 months). Adverse events were uncommon, and the most frequent grade 3 toxicity adverse events were hand-foot skin reaction (9%) and fatigue (9%). Toxicity-related dose reductions and discontinuations occurred in 5 and 2 patients, respectively. **Conclusion:** Regorafenib administered with a modified 2/1 schedule to patients who were aged ≥ 75 years and non-frail with treatment-refractory mCRC seems to be tolerable and achieve encouraging results in terms of PFS and OS.

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Introduction

Colorectal cancer (CRC) is one of the most frequent malignancies worldwide. It is more common in the elderly (≥65 years), with approximately 60% of diagnoses in patients aged 65 years or over.[1] The average life expectancy in the developed world is rapidly increasing and so is the incidence of bowel cancer among elderly patients. However, this category is still underrepresented in clinical trials, and data supporting treatment for elderly patients with advanced CRC is scarce.[2,3]

The treatment of mCRC has drastically changed with the advent of targeted therapies. These molecules include regorafenib, an oral

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multikinase inhibitor that targets the multiple proangiogenic signaling pathways inhibiting vascular endothelial growth factor receptor (VEGF-R), fibroblast growth factor receptor (FGF-R), and platelet-derived growth factor receptor (PDGF-R) and targets other signaling oncogenic pathways such as KIT, RET, RAF-1, and BRAF, and immunoglobulin and EGF tyrosine kinase.[4,5] In the CORRECT (patients with metastatic COloRectal Cancer treated with REgorafenib or plaCebo after failure of standard Therapy) randomized trial, regorafenib was shown to improve overall survival (OS) of patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, or anti-VEGF or, in KRAS wild-type, anti-epidermal growth factor receptor (EGFR) targeted therapy compared with placebo (6.4 vs. 5.0 months; hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.64-0.94; $P = .0052$).[6] Although the subgroup analysis reported that patients $\geq$ 65 years achieved a survival benefit (HR, 0.86; 95% CI, 0.61-1.19), the information for patients $\geq$ 75 years is limited owing to their small number in this group (in the CORRECT trial, only 38 patients $\geq$ 74 years received regorafenib).

Additionally, toxicity was notably more severe with regorafenib than placebo, with grade 3 or 4 treatment-related adverse events occurring in 54% (N = 270) of the regorafenib-treated patients versus 14% (N = 35) of patients receiving placebo. Owing to the adverse events, dose reductions were observed in 38% (N = 188) of patients, and therapy was interrupted in 61% (N = 304) of patients. Additionally, it should be noted that the median age of the population was only 61 years, and adverse events data specific to the elderly population were not reported.[6] Therefore, evidence supporting use of regorafenib in elderly patients is currently weak. However, older adults with mCRC who failed the guidelines-recommended chemotherapy regimens and still have a good performance status (PS) and are considered fit on a comprehensive geriatric assessment (CGA) are not rare and might benefit from an active antitumoral treatment.[7,8] In this regard, regorafenib could be a viable option as last line of treatment if proven efficient and safe.

The standard dosing schedule for regorafenib is 160 mg once daily for 3 consecutive weeks followed by 1 week off (3/1 schedule), and most of the severe side effects occurred during early phases of exposure (after 1-2 cycles). To our knowledge, data in the literature concerning alternative schedules for this drug or the safety and efficacy of regorafenib in older adults are limited. With the aim to improve the toxicity profile of regorafenib, a modified schedule (2 weeks on treatment followed by 1 week off), entailing a shorter exposure to the drug, was tested on a small cohort of elderly patients at our institution. Based on the achieved promising preliminary findings (unpublished data), the current study was designed to evaluate the activity and safety of an alternative 2/1 schedule of regorafenib in patients who were age $\geq$ 75 years with mCRC who progressed after 2 or more previous chemotherapy lines.

Patients and Methods

Eligibility Criteria

Patients $\geq$ 75 years with documented mCRC who had progressed on previous oxaliplatin- and irinotecan-based chemotherapy were enrolled at our institution in this prospective observational study. The other eligibility criteria included age of 18 years or greater, Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2, bidimensionally measurable disease, a life expectancy of at least 3 months, adequate hematologic parameters (an absolute neutrophil count of $\geq 1.5 \times 10^9$/L and a platelet count of $\geq 100 \times 10^9$/L), creatinine serum levels less than 1.5 times the upper limit of the normal range, and total bilirubin levels less than 3-fold the upper normal limit; aspartate and alanine aminotransferase less than 3-fold the upper normal limit, and absence of a second primary tumor other than non-melanoma skin cancer or in situ cervical carcinoma, at baseline. Exclusion criteria were brain metastases or prior treatment for brain metastasis; uncontrolled pleural or pericardial effusion; clinically significant cardiovascular disease; and medically uncontrolled hypertension.

At baseline, the G8 screening tool was used to identify potentially frail subjects among the recruited patients[9]; subjects with $\leq$ 14 points were further evaluated by CGA.[8] Patients classified as frail were excluded from the study. The baseline geriatric assessment included the Charlson Comorbidity Index and was performed by 2 medical oncologists (R.P. and L.M.) and a geriatrist (I.M.).[10,11] Vulnerable patients were defined as subjects who resulted not independent in 1 or more activities according to the Instrumental Activities of Daily Living and had 1 or 2 comorbidities with intermediate comorbidity score.

All patients gave their written informed consent prior to starting treatment.

Patient Evaluation

A complete physical examination, monitoring of symptoms and toxic effects, assessment of renal function, and a complete blood count were performed on patients at day 1 of every cycle. In order to minimize the risk of administering a potentially toxic drug to very elderly patients without a clinical benefit, the disease was reassessed after completion of 3 2/1-cycles of regorafenib (approximately after 8 weeks), then every 2 months for 6 months, and thereafter at 3-month intervals until there was evidence of disease progression. Objective tumor response was evaluated radiologically according to Response Evaluation Criteria in Solid Tumors (RECIST criteria, version 1.1).

Treatment Delivery

Patients received regorafenib 160 mg once daily for 2 consecutive weeks of each 3-week cycle (2/1 schedule). The starting dose was reduced to 120 mg in patients considered vulnerable or with $>$ 1 comorbidity and 80 mg in patients $\geq$ 80 years old or with an ECOG PS of 2.

The dose was re-escalated to a maximum of 160 mg/day if no grade $\geq$ 2 toxicity occurred.

Toxicity

The common toxicity criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.02) were used to assess toxicity. Treatment was delayed if, on the planned treatment day, the neutrophil count was $<$ 1500/mm^3, the platelet count was $<$ 100,000/mm^3, or the patient had persistent diarrhea or stomatitis of grade 1 or higher. Any patient who required more than 3 weeks for recovery from adverse reactions was excluded from the study. In the event of grade 3 or greater

Table 1 Patient Characteristics

Characteristics	Patients, N = 23 (%)
Age, y	
Median	78
Range	75-87
≥80 y	8 (35)
Gender	
Male	16 (70)
Female	7 (30)
ECOG PS	
0	6 (26)
1	14 (61)
2	3 (13)
Comprehensive geriatric assessment	
Fit	18 (78)
Vulnerable	5 (22)
Charlson Comorbidity Index	
Median (range)	1 (0-2)
Primary tumor	
Colon	17 (74)
Rectum	6 (26)
Metastatic sites	
Liver	18 (78)
Lymph nodes	9 (39)
Peritoneum	6 (26)
Lung	8 (35)
Other	3 (23)
Metastatic sites >1	16 (70)
Previous anti-cancer treatments	
Oxaliplatin-based	23 (100)
Irinotecan-based	23 (100)
Anti-EGFR	8 (35)
Anti-VEGF	9 (39)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor.

hematologic or any other severe (≥grade 3) organ toxicity, treatment was delayed, and at recovery, regorafenib doses were reduced by 40 mg (to a minimum of 80 mg) daily for subsequent courses.

Statistical Considerations

The primary endpoint of the study was 2-month disease-control rate (DCR), defined as the percentage of patients who achieved stable disease (SD) or partial (PR) or complete response (CR) within 2 months after start of therapy.

Regorafenib was recently approved by the United States Food and Drug Administration and the European Medicine Agency as salvage treatment for patients with mCRC who progressed after, or are not considered fit for, available treatments including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, or anti-VEGF therapy or, if KRAS wild type, anti-EGFR targeted therapy. The CORRECT study showed a 2-month DCR of approximately 41% for patients treated with regorafenib. Given that specific data was not reported for elderly patients, and assuming a 0% to 5% 2-month DCR with best supportive care alone, the hypothesis for the current study was that using a modified schedule of regorafenib in patients ≥ 75 years, at least 25% of subjects would be progression-free after 2 months from the start of treatment. It was calculated that a total of 21 patients should be recruited to yield a 80% probability to correctly select the treatment when it is superior by absolute difference of 20% in 2-month DCR (Simon minimax design).[12]

Secondary endpoints included safety, progression-free survival (PFS), defined as time from treatment start to disease progression or death from any cause, OS, as time elapsed from treatment initiation to death from any cause, and objective response rate, as the proportion of patients who achieved PR or CR. The Kaplan-Meier method was used to determine PFS and OS. Statistical analyses were conducted by STATA software.

Results

Patient Characteristics

Between February 2014 and May 2017, 23 patients > 75 years of age with mCRC were enrolled in the study. The baseline characteristics of patients are summarized in Table 1. The median age was 78 years (range, 75-87 years), and 35% (N = 8) of patients were at least 80 years old. Most patients had an ECOG PS ≥ 1 (N = 17; 73.9%) and were considered fit by CGA (N = 18; 78%), whereas 5 (22%) were classified as vulnerable. The median G8 score of enrolled patients was 15 (range, 15-17) at baseline. The primary tumor was located in the colon in 17 (74%) and the rectum in 6 (26%) patients. Eighteen subjects (78%) had liver metastases, and 17 (74%) had at least 1 metastatic site. All patients had at least 1 comorbidity, and the majority (N = 17; 74%) had at least 2 (Table 2). The most frequent concomitant illnesses were cardiovascular diseases (48%).

Efficacy

All 23 patients received 1 or more cycles of regorafenib with schedule 2/1 (median, 5 cycles; range, 2-14 cycles) and were evaluable for response and toxicity. The starting dose is illustrated in Table 3. The mean duration of treatment was 4.1 months (range, 1.1-11.7 months). The mean daily dose was 132.4 mg ± 24.7 mg (median, 120 mg; range, 80-160 mg), and the planned dose rate was 82.6%.

Table 2 Patient Comorbidities

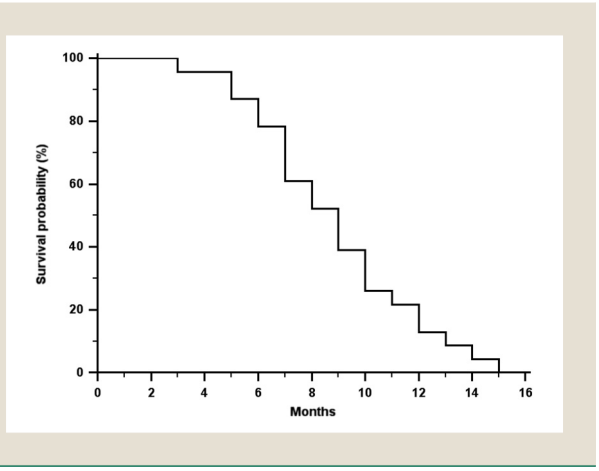
Comorbidities	N (%)
Cardiovascular	11 (48)
Hypertension	9 (39)
Coronary artery disease	6 (26)
Arrhythmia	5 (22)
Diabetes mellitus	5 (22)
Dyslipidemia	4 (17)
Respiratory	7 (30)
Genitourinary	3 (13)
>1 comorbidities	17 (74)

Table 3 Dose Modifications

	N (%)	Causes
Starting Dose		
160 mg	8 (35)	Fit, <80 y
120 mg	12 (52)	Vulnerable, or >1 comorbidity
80 mg	3 (13)	≥80 y or ECOG PS = 2
Escalated dose		
From 120 mg to 160 mg	4 (17)	After 1, 2, 2, 3 cycles, respectively
From 80 mg to 120 mg	3 (13)	After 2, 2, 3 cycles, respectively
Reduced dose		
From 160 mg to 120 mg	3 (13)	After 1, 2, 4 cycles, respectively
From 160 mg to 80 mg	1 (4)	After 1 cycle
From 120 mg to 80 mg	1 (4)	After 3 cycles

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.

Figure 1 Kaplan-Meier Estimates of Overall Survival



No patient achieved a CR or PR. Twelve patients (52.2%) achieved SD, which was the best response to therapy (Table 4). In this regard, computed tomography scans performed at 2 months highlighted relevant tumor necrosis in the liver and/or in the abdominal lymph nodes of 5 of the 12 patients with stable disease. The 2-month DCR was 52.2% (95% CI, 31.6%-72.6%) (Table 4). The median PFS was 4.8 months (95% CI, 3.8-6.3 months), and the median OS was 8.9 months (95% CI, 6.9-10.6 months) (Figure 1). At a median follow-up of 12.3 months (95% CI, 3.6-15.7 months), a total of 18 patients were deceased.

Regorafenib was discontinued owing to disease progression and treatment-related adverse events in 91% and 9% of cases, respectively. Four patients are still on treatment at data cut-off. Seven patients who progressed after regorafenib received the following anti-cancer treatments: oxaliplatin and capecitabine was administered to 3 patients, capecitabine and cetuximab to 3 patients, and capecitabine alone to 1 patient.

Treatment Toxicity

Adverse events rates are reported in Table 5. The most frequent grade 3 side effects were fatigue, which occurred in 2 (9%) patients, and hand-foot skin (HFS) reactions, which were reported in 2 (9%) patients. Among grade 2 or lower adverse events, stomatitis, HFS, and hypertransaminasemia were the most commonly observed. Five patients had grade 1 or 2 cardiac disorders, but no heart failure occurred. Hematologic toxicity was mild. No patient required hospitalization because of adverse events. Owing to toxicity, a dose reduction was required in 5 (22%) patients, 4 of whom had started with the conventional dose of 160 mg. Regorafenib was re-escalated to 160 mg daily in 4 patients who had started with 120 mg. Two (9%) patients interrupted the treatment: because of persistent HFS after 4 cycles in 1 case and because of continuous HFS and fatigue after 4 cycles in the other (Table 5).

Table 4 Results

Variables	N (%)
Objective response rate	
Complete response	0
Partial response	0
Stable disease	12 (52)
Progressive disease	11 (48)
Two-month disease control rate, % (95% CI, %)	52.2 (31.6-72.6)
Progression-free survival, mos (95% CI, mos)	4.8 (3.8-6.3)
Overall survival, mos (95% CI, mos)	8.9 (6.9-10.6)

Abbreviation: CI = Confidence interval.

Discussion

Despite the European Medicine Agency and United States Food and Drug Administration approval of regorafenib as salvage treatment for patients with mCRC who progressed after all available therapies, the not neglectable toxicity profile of the conventional 3/1 schedule as well as the lack of efficacy and safety data on the elderly population limit its use in clinical practice for the older adult.[6] To our knowledge, the present study is the first suggesting that an

Table 5 Adverse Events

Adverse Events	Grade ≤2, N (%)	Grade 3, N (%)	Grade 4, N (%)
Fatigue	3 (13)	2 (9)	0
Hand-foot skin reaction	4 (17)	2 (9)	0
Diarrhea	3 (13)	1 (4)	0
Hypertension	3 (13)	1 (4)	0
Rash or desquamation	3 (13)	0	0
Nausea	2 (9)	0	0
Vomiting	1 (4)	0	0
Stomatitis	4 (17)	0	0
Constipation	3 (13)	1 (4)	0
Anorexia	2 (9)	1 (4)	0
Cardiac disorders	3 (13)	0	0
Hypertransaminasemia	4 (17)	1 (4)	0
Hyperbilirubinemia	2 (9)	0	0
Neutropenia	2 (9)	0	0
Anemia	3 (13)	0	0
Trombocytopenia	2 (9)	0	0

alternative 2/1 schedule of regorafenib is tolerable and efficient for patients aged ≥ 75 years and screened as non-frail with late-stage mCRC. In fact, despite the limitations of a small observational study, regorafenib seems at least as active in our population as in that of the CORRECT trial. Similar to the latter, in our study there was no CR, and PR and disease stabilization was the best response to treatment, yet the 2-month DCR was 52.2%, the median PFS was 4.8 months (95% CI, 3.8-6.3 months), and the median OS was 8.9 months (95% CI, 6.9-10.6 months) versus 41% ($P < .0001$), 1.9 months (95% CI, 1.6-3.9 months), and 6.4 months (95% CI, 3.6-11.8 months), respectively, in the CORRECT study.[6] Furthermore, our findings compare well also with those described by the international phase III trial CONCUR (asian subjects with metastatic COlorectal caNCer treated with regorafenib or placebo after failURe of standard therapy), which compared regorafenib with best supportive care for Asian patients and reported a median OS of 8.8 months (95% CI, 7.3-9.8 months) in the regorafenib-treated group.[13] A recent large retrospective Japanese study assessed the efficacy of regorafenib versus the new agent trifluridine/tipiracil (TFTD) for patients with mCRC who were refractory to standard chemotherapy.[14] The subgroup analysis by age reported a median OS for the patients ≥ 65 years old treated with regorafenib of 6.2 months (95% CI, 4.9-7.4 months), which is comparable to that of the CORRECT trial and slightly shorter than that observed in our analysis. The incidence of discontinuation because of treatment-related toxicities was 24% in the regorafenib group versus 7% in the TFTD group, and the authors argued that regorafenib tolerance, unlike TFTD, decreased in elderly patients compared with younger patients. In a population aged 75 years or older (more than one-third were at least 80 years of age), with at least 1 co-morbidity (74% with 2), and who progressed after the standard chemotherapy lines for mCRC, further treatment could be questioned as the toxicity can easily outweigh the potential benefit. For this reason, this study used standard, validated tools of geriatric assessment to guarantee that regorafenib would be delivered with a personalized starting dose and only to non-frail patients. As a matter of fact, at baseline, 78% of patients were considered fit by CGA and, after a median follow-up of 12.3 months (95% CI, 3.6-15.7 months), 5 patients were still alive and 4 are still on treatment at data cut-off. The use of a 2/1 schedule of administration allowed for shortening the exposure to the drug, and this probably contributed to the good tolerability of treatment with no unexpected severe side effects. This is quite remarkable considering the advanced age of the population, the amount of chemotherapy previously received, and the presence of at least 1 concomitant disease. In particular, 48% of our population presented with cardiac illnesses at baseline, and recently, a large retrospective study comparing safety of targeted therapies for mCRC between older and younger adults reported more frequent cardiac disorders in the elderly patients treated with bevacizumab, cetuximab, and regorafenib.[15] In the current study, cardiac disorders were mild, with only 1 case of grade 3 hypertension, and no heart failure occurred. In general, the observed toxicity was milder than in the CORRECT trial. In this respect, except for a similar incidence of grade 3 fatigue (9%), the rates of nearly all grade 3 adverse events were lower than in the pivotal trial. Consequently, in the CORRECT study, the dose reductions and treatment interruptions rates were considerably higher (38% and 61%, respectively) than in our analysis (22% and 9%, respectively). Notably, 4 of the 5 patients who required a dose decrease in the present study had started regorafenib at the standard dose, whereas only 1 had a reduced starting dose of 120 mg. It should be noted that the starting dose was, in most cases, lower than the standard dose of 160 mg, and the 2/1 schedule allowed for a reduced treatment exposure over time. However, the mean daily dose was 132.4 mg, and the planned dose rate was 82.6%, which compare well with the mean daily dose of 147.1 mg and the dose intensity of 78.9% reported in the CORRECT trial.

Additionally, the reported safety profile was comparable to that of the REBECCA (REgorafeniB in mEtastatic Colorectal cancer: a french Compassionate progrAm) study, which analyzed in a real-life setting, the efficacy and toxicity of regorafenib given to patients with mCRC refractory to standard treatments.[16] Interestingly, almost one-half (47.6%) of the 1178 patients enrolled in this study were elderly. However, the side effects required treatment interruptions and dose reductions in 31% and 43% of patients, respectively, and thus were not as easily manageable as in our study.[16] This is probably the result of a combination of factors in our analysis, including the shorter exposure to regorafenib allowed by the modified 2/1 schedule, the accurate selection of non-frail subjects, and the starting dose reductions for the patients who were non-fit or aged ≥ 80 years. In this regard, as far as we are aware, no data surrounding the use of a modified schedule of regorafenib for mCRC have been previously reported. However, similar experiences have been documented with the multikinase inhibitor sunitinib for the treatment of metastatic renal cell cancer to improve its safety profile. A small study showed a better toxicity profile for sunitinib in a 2-weeks-on/1-week-off regimen compared with the conventional 4/2 schedule, while maintaining the standard dose intensity.[17] Moreover, a large retrospective analysis reported a better tolerability and no decrease in efficacy for the patients with metastatic renal cell cancer who switched from the standard 4/2 to the modified 2/1 schedule of sunitinib owing to adverse events.[18]

Despite the encouraging results of our analysis, the small size of the population is a limitation that prevents us from drawing general conclusions. Larger randomized trials of comparison between the conventional 3/1 and the alternative 2/1 schedule of administration should be performed in order to confirm our safety and efficacy results. However, these data showed that regorafenib given with a modified 2/1 schedule as last-line treatment for non-frail, 75 years or older patients with mCRC who are refractory to standard chemotherapy is well-tolerated and efficient. Finally, this altered schedule may also be relevant for patients younger than 75 years as the on-label dose and schedule of 160 mg for 3 weeks on, 1 week off is not well-tolerated. Further studies will be required to verify whether the modified 120 mg 2/1 dose and schedule might be a more tolerated and equally effective regimen for all patients, regardless of age.

Conclusion

Although careful monitoring of potential side effects is still recommended, this analysis suggests that regorafenib given with a modified 2/1 schedule may be safely proposed for selected elderly patients with mCRC who failed previous standard chemotherapy.

Clinical Practice Points

- In the CORRECT randomized trial, regorafenib was shown to prolong survival of patients with treatment-refractory mCRC. However, there is little data in the literature over the tolerability and efficacy of regorafenib in elderly patients or when administered with a different schedule. Additionally, regorafenib-related adverse events were not neglectable and mostly occurred during cycle 1 to 2.
- In this prospective study, 23 patients with mCRC who were ≥ 75 years old, had progressed after the standard lines of chemotherapy, and were screened as non-frail received regorafenib with a modified schedule consisting of 2 weeks on treatment and 1 week off. More than one-half (52.2%) of the patients obtained disease stabilization, and both median OS and PFS compared well with those observed in the CORRECT study. Adverse events, in particular grade 3, were uncommon and led to only 5 dose modifications and 2 treatment discontinuations.
- A modified 2/1 schedule of regorafenib combined with an initially personalized starting dose might be safely proposed for selected elderly patients ≥ 75 years with mCRC.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.02.005.

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