Original Research Article

Title:

Comparison of initiating regorafenib dose for colorectal cancer: A retrospective cohort study

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A running heading: Comparison of initiating regorafenib dose for colorectal cancer

Abstract

Background

The benefit of regorafenib for colorectal cancer has already been shown by previous randomized studies. However, these studies showed a high rate of treatment-related adverse events. In particular, adverse events were more common in Japanese patients. Some studies showed fewer adverse events and longer survival time with a reduced initial dose. However, the benefits of a reduced initial dose of regorafenib have been evaluated only with limited data based on small samples.

Objective

Our objective was to analyze the efficacy of initial regorafenib dose reduction compared with a standard dose for colorectal cancer patients.

Patients and Methods

We used a hospital-based nationwide claims database. Patients who received regorafenib for metastatic colorectal cancer between June 2013 and June 2016 were included in this study. We divided the patients into a standard initial dose group (standard group) and a reduced initial dose group (reduced group). Overall survival (OS) and adverse events were compared between the 2 groups. We performed propensity score matching for sensitivity analysis.

Results

We included 2376 patients (1208 in the standard group and 1168 in the reduced group). The median OS

were 12.3 months (95% confidence interval (CI), 11.0–13.3) in the standard group and 12.6 months (95% CI, 11.7–13.6) in the reduced group. A log-rank test showed no significant difference between the 2 groups (p=0.41). Most adverse events occurred less frequently in the reduced group. In the sensitivity analysis, the results showed no significant difference in OS.

Conclusions

No significant difference in OS was observed between the standard group and reduced group; however, there were fewer adverse events in the reduced group. The optimal initial dose of regorafenib should be identified in further studies.

Key Points

Although there is no initial dose reduction recommendation for regorafenib, half of the patients started at a reduced dose in Japan.

There were no differences in OS between patients receiving the standard initial dose and the reduced initial dose.

Fewer drug-related adverse events were observed in the reduced initial dose group.

1 Introduction

Colorectal cancer (CRC) is the third most common cancer and represents about 8–10% of all incident cancer worldwide [1, 2]. Around 25% of patients have metastases at initial diagnosis, and almost 50% of patients will develop metastases [3]. Standard therapy for metastatic CRC (mCRC) is combination chemotherapy [3-5]. Fluoropyrimidine-based treatments combined with oxaliplatin or irinotecan, and targeted therapy, such as anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) antibodies, are used as standard therapies [4, 5]. After these therapies fail, regorafenib is one of the available therapies [6, 7].

Regorafenib is an oral multi-kinase inhibitor. Two previous international randomized trials (CORRECT and CONCUR) showed the efficacy and safety of regorafenib compared with best supportive care in patients with progressive mCRC after standard therapies (median OS: 6.4 months vs. 5.0 months in CORRECT and 8.8 months vs. 6.3 months in CONCUR) [6, 7]. However, these studies also showed high rates of treatment-related toxic effects and dose modification. Furthermore, post hoc subpopulation analyses for Japanese and non-Japanese patients from CORRECT reported that the incidences of treatment-related toxic effects and dose modification were higher in Japanese patients [8]. Although CORRECT noted no clear relationship between adverse events and body mass index (BMI) or body surface area in Japanese and non-Japanese subpopulations, the median bodyweight was about 10 kg lower in Japanese patients. In CONCUR, Asian patients had frequencies of adverse events similar to those of the non-Japanese patients in CORRECT [7,

8]. However, the rate of patients receiving previous targeted treatments in CONCUR was lower than that among Japanese patients in CORRECT (60% vs. 100%).

In previous studies, the majority of adverse events occurred in the first month of treatment [6, 9]. Therefore, reconsideration of initial therapy may be necessary. Regardless of body weight and age, the recommended dose of regorafenib is 160 mg/daily for 3 weeks, followed by 1 week with no treatment. Several previous studies suggested the importance of initial dose modification [10-14]. However, there is no published randomized controlled study about initial dose, and, therefore, the appropriate initial dose is still controversial.

The present study aimed to identify current clinical practice patterns of regorafenib treatment and examine the efficacy of a reduced initial regorafenib dose compared with the standard initiating dose using a nationwide database in Japan.

2 Methods

This retrospective observational study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [15]. The study was approved by the ethics committee of the Kyoto University Graduate School and Faculty of Medicine (approval number: R1275, October 8, 2016), which waived the requirement for informed consent due to the anonymous nature of the data.

2.1 Data sources

This study was a retrospective cohort study of mCRC and was conducted using the Japanese database provided by Medical Data Vision Co, Ltd., (MDV; Tokyo, Japan), which is an electronic, record-based healthcare database. This database contains patient-level information on demographic characteristics; diagnoses coded according to the International Classification of Diseases, 10th revision (ICD-10); clinical data; and prescription information, such as dose, quantity, and number of days of supply. The database also contains data on inpatient and outpatient medical care from a panel of 242 hospitals in different regions throughout Japan and includes 13,930,000 patients covering approximately 10% of the Japanese population as of March 2016. Age and sex distributions of the source population were similar to those of the national census in Japan, and several epidemiologic studies using the database have been published [16, 17].

2.2 Study cohort

Within the database, we identified CRC patients aged over 20 years diagnosed from June 2013 through July 2017 by ICD-10 codes (Supplemental Table A). We then identified patients who received regorafenib by receipt code. The follow-up period was until September 2018. We excluded 1) patients who received regorafenib for conditions other than CRC, such as gastrointestinal stromal tumor and small intestine cancer, 2) patients who received other chemotherapy simultaneously with regorafenib, and 3) patients who received a 40 mg initial dose of regorafenib, because the minimal daily dose of regorafenib allowed per protocol

was 80 mg according to the results of the initial phase 1 studies [18, 19]. We separated the patients into 2 groups, a standard group (160 mg; recommended dose) and a reduced group (80 mg or 120 mg).

2.3 Outcome measures

The primary outcome measure of the trial was overall survival (OS), defined as the time from the start of regorafenib treatment to death from any cause. Secondary outcome measures included the total dose of regorafenib, duration of treatment, and proportion of adverse events. We defined the duration of treatment as last prescription day – first prescription day + number of days of supply at the last prescription day. We collected adverse events using ICD-10 codes (Supplemental Table B). If the registration date was during regorafenib treatment, we counted it as an adverse event. Additionally, information about disease-specific variables, including age, sex, body weight, BMI, comorbidity, primary site of disease, tumor sidedness, metastatic sites, previous systemic anticancer agents, department of prescribing physician, discontinuation after initial prescription, dose modification, and subsequent anticancer agents, was obtained. Tumor sidedness was collected by ICD-10 codes (right side: C180, C181, C182, C183, C184).

2.4 Statistical analysis

Continuous variables are presented as a median (range) and categorical variables are presented as a number and percentage (%). Continuous variables were compared using a Mann-Whitney U test and categorical

variables were compared using a chi-squared test. OS was compared using Cox's proportional hazard model. When the hazard curves for the 2 groups of observations intersected, OS was compared using a log-rank test. OS was also evaluated using the Kaplan-Meier method. Because of the exploratory nature of this study, a P-value <0.05 was considered statistically significant. To test the robustness of our results, we performed sensitivity analyses. For the first sensitivity analysis, we performed propensity score-matched analysis using 1:1 matching [20, 21]. In the statistical analyses, age, sex, body weight, BMI, comorbidity, previous systemic anticancer agents, and doctor's department were considered potential confounders. Propensity scores were calculated for each patient based on these potential confounders (Supplemental Table C). Each standard group patient was then matched to a reduced group patient using the propensity score. A caliper width of 0.1 standard deviations was used for matching. We discarded the remaining unmatched patients from the analysis. In this analysis, we performed complete-case analysis for missing data. We also separated patients into 3 groups (initial dose of 80 mg, 120 mg, and 160 mg) and compared OS. All statistical analyses were performed using SAS (Version 9.4; SAS Institute, Cary, NC).

3 Results

3.1 Patients

The flow diagram for the present study is shown in Figure 1, and patient characteristics are presented in Table 1.

The number of patients who met the inclusion criteria was 2585. The number of excluded patients was 209. Regorafenib was administered to 127 patients for conditions other than CRC. A lower initial dose (40 mg) was administered in 56 patients, and other chemotherapies were administered simultaneously with regorafenib in 30 patients. The number of eligible patients was 2376, including 1208 patients in the standard group and 1168 patients in the reduced group (120 mg: 717 patients and 80 mg: 451 patients). Patients in the reduced group were older and had a lower body weight than those in the standard group. The median intervals from the first diagnosis of metastases to start of treatment with regorafenib were 23.5 months (standard group) and 24.1 months (reduced group). Differences in administration of previous systemic anticancer agents ranged from 1% to 5% between the 2 groups. The proportion of previous trifluridine was significantly higher in the reduced group than in the standard group (26% vs. 22%, $p=0.011$). The mean numbers of previous anticancer agents were 4.5 for the standard group and 4.4 for the reduced group ($p=0.18$). The proportions of main regimens were not significantly different between the 2 groups.

More patients in the reduced group than in the standard group received regorafenib from the surgeon (66% vs. 53%, $p<0.001$). Other baseline characteristics were similar between the standard and reduced groups. There were some missing data. There were no height data for 111 patients, no body weight data for 150 patients, and no BMI data for 161 patients.

3.2 Efficacy

In the standard group, 679 (56%) patients died, and 621 patients (53%) died in the reduced group. The hazard curves for the 2 groups intersected; therefore, we used the log-rank test. There was no significant difference in OS between the standard group and the reduced group (p=0.41) (Fig. 2). The median OS in the standard group was 12.3 months (95% CI 11.0–13.3), and it was 12.6 months (95% CI 11.7–13.6) in the reduced group.

3.3 Treatment exposure and subsequent treatment

The median total dosage was higher in the standard group than in the reduced group (4480 mg vs. 3360 mg). Approximately half of the standard group patients and 21% of the reduce group patients had dose reduction over the course of treatment. In contrast, 13% of the patients in the reduced group underwent subsequent treatment with increased dosage. The rates of administration of subsequent anticancer agents were not similar between the 2 groups. Trifluridine was administered more frequently in the standard group (29% vs. 23%). Other anticancer agents were also administered more frequently in the standard group (24% vs. 20%).

3.4 Safety

Treatment-related adverse events were more frequently observed in the standard group (Table 2). Among the patients in the standard group, 13% discontinued treatment after initial prescription, whereas in the

reduced group, the discontinuation rate was 16%. In both groups, over one-third of patients who discontinued regorafenib (35% in the standard group and 36% in the reduced group) did so within 21 days of starting treatment.

3.5 Sensitivity analysis

We conducted 2 sensitivity analyses. First, 944 patients in each group were matched by propensity score. We excluded 161 patients who had missing data before propensity score matching for complete-case analysis. Patients' characteristics were balanced between the 2 groups (Table 3). No significant difference in OS was observed between the 2 groups (p=0.59) (Fig. 3). The median OS in the standard group was 11.9 months (95% CI 10.8–13.1), and it was 12.1 months (95% CI 11.3–13.2) in the reduced group.

Second, we separated patients into 3 groups by initial dose (80 mg, 120 mg, and 160 mg) and performed a sensitivity analysis (Fig. 4). There was no significant difference in OS (p=0.63). The median OS in the 120 mg group was 12.7 months (95% CI 11.5–14.0), and it was 12.5 months (95% CI 11.3–13.7) in the 80 mg group.

4 Discussion

Using a nationwide database, the present study showed no significant difference in OS between standard initial dose patients and reduced initial dose patients receiving regorafenib. However, the rates of most adverse effects were lower in the reduced group.

The CORRECT and CONCUR trials showed the efficacy of regorafenib, with an improvement of over best supportive care (median OS: 6.4 months vs. 5.0 months and 8.8 months vs. 6.3 months, respectively) [6, 7]. The present study showed longer OS (12.3 months in the standard group and 12.6 months in the reduced group). This might have occurred for several reasons. For patient background characteristics, the median time from the first diagnosis of metastases (23.5 months in the standard group and 24.1 months in the reduced group) was shorter than that in CORRECT (31.0 months in the regorafenib group) and similar to that in CONCUR (20.3 months in the regorafenib group). The mean numbers of previous anticancer agents were greater than 4 in both groups, and 70% to 80% of patients had previously received major anticancer agents, such as oxaliplatin and irinotecan. Additionally, if the patient receives treatment at multiple hospitals, treatment information from the previous hospital is unavailable on this database. Therefore, the time from the diagnosis of metastases and the proportion of previous anticancer agents would be underestimated. In such cases, patients were considered to be receiving adequate treatment as recommended in the guidelines. Subsequent anticancer agents, such as trifluridine, were administered to quite a few patients in the present study. Trifluridine was available from May 2014; therefore, patients did not receive trifluridine in the CORRECT and CONCUR trials. Moreover, there were many censored cases, which may affect the OS in either direction. It is necessary to conduct studies with better tracking to determine more accurate survival times.

Adverse events are observed in over 90% of patients receiving regorafenib, mainly within the first cycles

of therapy [6, 7, 22]. Therefore, dose adjustments are essential to reduce the occurrence of adverse events. All patients in the CORRECT and CONCUR trials started regorafenib at an initial dose of 160 mg. Several studies suggested the possibility of effectiveness of initial dose reduction [10- 14, 21], even though a cohort study in France showed a reduced initial dose as a risk factor for shortened survival [22]. The present study showed that around half of the patients received initial dose reduction in the real world setting in Japan, whereas a multicenter observational study in Japan showed that 15–35% of patients received initial dose reduction [12, 21, 25].

There was no significant difference in OS between the standard group and reduced group in the present study. Patient characteristics, such as age, sex, body weight, and previous systemic anticancer agents, were different between the 2 groups. Older patients and patients with lower body weight tended to receive a reduced initial dose. However, the OS was still similar after characteristics were matched according to the propensity score in sensitivity analysis. Subsequent anticancer therapy may be considered as one of the factors that influences OS [21]. A certain number of patients received trifluridine or other anticancer agents after regorafenib. It will be necessary to consider this point in future studies.

Most adverse events occurred less frequently in the reduced group. As it is important to consider not only prolonging survival but also increasing quality of life by decreasing adverse events for patients with refractory disease, this finding increases the advantage of initial dose reduction in this setting. We extracted adverse event data using ICD-10 codes that were registered after the first regorafenib prescription. The

present study showed a lower rate of adverse events (72% in the standard group and 65% in the reduced group) than a previous study (83% to 100% in the regorafenib group) [6, 7, 18, 26, 27]. In particular, the CORRECT study showed that the incidence of grade 3 or greater treatment-associated adverse events was higher in Japanese patients than in non-Japanese patients (80% vs. 51%) [8]. The reason was unclear; however, the median bodyweight was 10 kg lower in the Japanese patients (62.6 kg vs. 73.5 kg). In the present study, the median bodyweight was lower than in that study (58 kg in the standard group and 56 kg in the reduced group). In the CONCUR trial, patients were Asian and had a similar BMI to the Japanese patients in CORRECT. Adverse events in the CONCUR trial were similar to those in the CORRECT trial. However, the patients were younger (median, 57.5 years old) and had received fewer previous targeted treatments (60%) in the CONCUR trial. In our study, 90% of the patients in the standard group and 86% in the reduced group had received previous targeted treatments. Moreover, the patients were almost 10 years older in the present study (65 years old in the standard group and 68 years old in the reduced group). Therefore, the present study may have underestimated the occurrence of adverse events. We could not extract major adverse event data, such as anorexia and alopecia, because they were rarely registered in the ICD-10 code. A certain number of adverse events occurred before regorafenib treatment as a result of previous chemotherapies. For example, peripheral neuropathy and hand-foot syndrome were observed relatively frequently before regorafenib initiation. Symptoms such as pain, redness, and discomfort of the hand or foot overlap with those of a hand-foot skin reaction. If the same symptoms occurred after starting

regorafenib therapy, re-registration might have been omitted. Furthermore, if adverse events were unrelated to the medication or procedure, such as alopecia, low grade fatigue, and anorexia, registration might have been omitted. Adverse events data in the 2 groups were extracted under the same circumstances; therefore, that the rate of side effects was lower in the reduced group is acceptable.

We found a discontinuation rate of 13% in the standard group and 16% in the reduced group after initial prescription. Over one-third of the patients in both groups discontinued medication within 21 days (35% and 36%, respectively). Normally, disease progression is measured using computed tomography, and the examination is performed at least 1 month after the start of regorafenib. Therefore, discontinuation within 1 month might have been due to adverse events. Post-marketing surveillance showed that the median time to treatment failure (TTF) was 2.1 months (range 1.9–2.2 months) [23]. In contrast, the present study showed a shorter TTF (1.6 months in both groups). In our study, there was no relationship between early discontinuation and initial dose; therefore, there might be other factors involved, such as administration period and patient performance status.

This study has several limitations. First, there were some important unavailable data (e.g., performance status, grade of adverse events, time of diagnosis of metastatic disease, *KRAS* mutation, reasons for discontinuation, and therapeutic evaluation). Consequently, we could not evaluate progression-free survival and disease control rates. Although all patients treated with anti-EGFR drugs (cetuximab and panitumumab) would have wild-type KRAS, some patients with wild-type KRAS may not have received anti-EGFR drugs.

The proportion of anti-EGFR drug administration did not significantly differ between the 2 groups. When performance status is poor, patients tend to receive a reduced initial dose. Therefore, the result would be favorable for the standard group. Second, there were many censored cases in OS analysis. If patients change hospitals or decide to move to end-of-life care at home, it is impossible to determine the patient outcome. The rate of censored cases was similar in the 2 groups, regardless of follow-up period; therefore, the similarity in OS may not have been influenced. Third, most patients in the present study were Japanese. A previous study showed ethnic differences between Japanese and Western patients [8]. It concluded that regorafenib appears to be as effective in the Japanese subpopulation as in Western patients. However, more adverse events were observed in the Japanese patients. Japanese patients in the real-world setting were thinner and older than Western patients and were more likely to receive anticancer drug treatment from the surgeon [8]. Many surgeons are familiar with anti-cancer drug treatments and follow the guidelines for treatment in Japan. However, medical oncologists are experts in anti-cancer treatments and are likely to be better at managing adverse events than surgeons. Therefore, similar studies with a more heterogeneous population in another country are important.

5 Conclusion

We performed a comparative analysis of the standard initial dose and a reduced initial dose of regorafenib using a large nationwide cohort of patients with CRC. A reduced initial dose was associated with a similar

OS and fewer adverse events than the standard initial dose. The lower proportion of adverse events in the reduced group should be considered when deciding the starting dose in the refractory setting. Sensitivity analysis showed similar results. A reduced initial dose may be acceptable as a standard therapy, especially for patients who are frailer than those in previous phase III clinical trials. Further studies are needed to determine the optimal treatment with regorafenib.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to a contract with Medical Data Vision Co, Ltd. but are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflict of interest: K.K. receives honoraria from Shin Nippon Biomedical Laboratories, LTD.; research funds from: Olympus Corporation, Sumitomo Dainippon Pharma Co., Ltd., Bayer Yakuhin Ltd., Stella Pharma Corporation, Novartis Pharma K.K., CMIC Co., Ltd., Amgen Astellas BioPharma K.K., Suntory Beverage & Food Ltd., Medical Platform Co., Ltd.; and holds stocks of: School Health Record Center Co., Ltd. and Real World Data, Co., Ltd. There are no patent products under development or marketed products to declare, relevant to those companies. M.N. and K.I declare no conflicts of interest.

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Table 1. Comparison of patients' characteristics

Characteristic	Standard group (160 mg) (n=1208)	Reduced group (80 mg, 120 mg) (n=1168)	p value
Median age (range), years	65 (28–87)	68 (32–90)	<0.001
>65 years, n (%)	635 (53)	729 (62)	<0.001
Sex (male), n (%)	777 (64)	670 (57)	<0.001
Median body weight (range), kg	58 (31–111)	56 (27–112)	<0.001
Median body mass index (range), kg/m^2	22.0 (13.3–37.7)	21.8 (12.9–37.1)	0.025
≤18.5 kg/m^2, n (%)	177 (16)	186 (17)	0.27
Comorbidity, n (%)			
Hypertension	659 (55)	672 (58)	0.14
Diabetes mellitus	348 (29)	361 (31)	0.26
Hepatitis B	105 (9)	126 (11)	0.085
Hepatitis C	39 (3)	35 (3)	0.75
Peripheral neuropathy	425 (35)	441 (38)	0.19
Hand-foot syndrome	183 (15)	196 (17)	0.28
Primary site of disease, n (%)			0.84
Colon	666 (55)	657 (56)	
Rectum	382 (32)	357 (31)	
Colon and rectum	160 (13)	154 (13)	
Tumor sidedness (right side), n (%)	325 (27)	329 (28)	0.49
Metastatic sites, n (%)			
Liver	802 (66)	774 (66)	0.95
Lung	624 (52)	615 (53)	0.63
Lymph node	294 (24)	266 (23)	0.37
Peritoneum	310 (26)	288 (25)	0.57
Bone	200 (17)	185 (16)	0.64
Brain	92 (8)	64 (5)	0.036
Number of metastatic sites (≥3), n (%)	341 (28)	297 (25)	0.12
Time from diagnosis of metastases			
Median (months), (IQR)	23.5 (13.2-35.3)	24.1 (14.9-37.4)	0.14
≥ 18 months, n (%)	729 (64)	746 (66)	0.14
Missing metastatic diagnosis, n (%)	60 (5)	46 (4)	
Previous systemic anticancer agents, n (%)			

Fluorouracil	816 (68)	735 (63)	0.018
Capecitabine	431 (36)	408 (35)	0.70
Tegafur/gimeracil/oteracil	364 (30)	398 (34)	0.040
Tegafur	95 (8)	79 (7)	0.30
Oxaliplatin	897 (74)	819 (70)	0.025
Irinotecan	1028 (85)	940 (80)	0.003
Bevacizumab (anti-VEGF antibody)	971 (80)	896 (77)	0.029
Cetuximab (anti-EGFR antibody)	249 (21)	215 (18)	0.18
Panitumumab (anti-EGFR antibody)	373 (31)	327 (28)	0.12
Trifluridine	262 (22)	305 (26)	0.011
FOLFOX ± targeted therapy	526 (44)	492 (42)	0.48
FOLFIRI ± targeted therapy	695 (58)	637 (55)	0.14
FOLFOXIRI	10 (1)	3 (0)	0.059
XELOX ± targeted therapy	316 (26)	291 (25)	0.49
XELIRI ± targeted therapy	36 (3)	35 (3)	0.98
SOX ± targeted therapy	102 (8)	100 (9)	0.92
IRIS ± targeted therapy	232 (19)	230 (20)	0.76
Mean number of previous anticancer agents (SD)	4.5 (1.8)	4.4 (2.0)	0.18
Any previous targeted therapy, n (%)	1091 (90)	1004 (86)	0.001
Department, n (%)			<0.001
Medical oncology	136 (11)	112 (10)	
Internal medicine	426 (35)	291 (25)	
Surgery	646 (53)	765 (66)	

Abbreviations: EGFR=epidermal growth factor receptor; VEGF=vascular endothelial growth factor; IQR=interquartile range; SD=standard deviation; FOLFOX=fluorouracil, folinic acid and oxaliplatin; FOLFIRI=fluorouracil, folinic acid and irinotecan; FOLFOXIRI=fluorouracil, folinic acid, oxaliplatin and irinotecan; XELOX=capecitabine plus oxaliplatin; XELIRI=capecitabine plus irinotecan; SOX=tegafur/gimeracil/oteracil plus oxaliplatin; IRIS=tegafur/gimeracil/oteracil plus irinotecan.

Table 2. Comparison of drug exposure, adverse events, and subsequent anticancer agents between the 2 groups

Characteristic	Standard group (160 mg) (n=1208)	Reduced group (80 mg, 120 mg) (n=1168)	p value
Median total dosage (range), mg	4480 (320–79200)	3360 (80–59640)	<0.0001
Median time to treatment failure (range), days	49 (2–1080)	48 (1–911)	0.82
Discontinuation after initial prescription, n (%)	166 (13)	181 (16)	0.23
Discontinuation within 7 days	97 (8)	116 (10)	0.11
Discontinuation within 21 days	425 (35)	422 (36)	0.63
Dose modification, n (%)			
Increase	1 (0)	154 (13)	<0.001
≤ 1 week, n (%)	-	29 (2)	
≤ 2 weeks, n (%)	-	17 (1)	
≤ 4 weeks, n (%)	-	42 (4)	
≤ 8 weeks, n (%)	1 (0)	33 (3)	
> 8 weeks, n (%)	-	33 (3)	
Decrease	606 (50)	249 (21)	<0.001
≤ 1 week, n (%)	63 (5)	21 (2)	
≤ 2 weeks, n (%)	98 (8)	43 (4)	
≤ 4 weeks, n (%)	189 (16)	85 (7)	
≤ 8 weeks, n (%)	182 (15)	69 (6)	
> 8 weeks, n (%)	74 (6)	31 (3)	
Adverse events, n (%)			
Any adverse events	871 (72)	759 (65)	<0.001
Hand-foot skin reaction	443 (37)	364 (31)	0.005
Hypertension	406 (34)	343 (29)	0.026
Nausea	263 (22)	215 (18)	0.041
Diarrhea	189 (16)	139 (12)	0.008
Oral mucositis	189 (16)	124 (11)	<0.001
Rash/desquamation	151 (13)	76 (7)	<0.001
Fever	69 (6)	53 (5)	0.20
Hepatotoxicity	36 (3)	15 (1)	0.004
Fatigue	19 (2)	19 (2)	0.92
Subsequent anticancer agents, n (%)			

Trifluridine	345 (29)	269 (23)	0.002
Other anticancer agents	287 (24)	235 (20)	0.032
Fluorouracil	96 (8)	79 (7)	0.27
Capecitabine	52 (4)	46 (4)	0.65
Tegafur/gimeracil/oteracil	105 (9)	77 (7)	0.054
Tegafur	16 (1)	21 (2)	0.35
Oxaliplatin	88 (7)	83 (7)	0.87
Irinotecan	117 (10)	83 (7)	0.024
Bevacizumab (anti-VEGF antibody)	127 (11)	112 (10)	0.45
Cetuximab (anti-EGFR antibody)	49 (4)	32 (3)	0.077
Panitumumab (anti-EGFR antibody)	56 (5)	39 (3)	0.11

Abbreviations: EGFR=epidermal growth factor receptor; VEGF=vascular endothelial growth factor.

Table 3. Patients' characteristics after propensity score matching

Characteristic	Standard group 160 mg (n=944)	Reduced group 80 mg, 120 mg (n=944)	p value
Median age (range), years	66 (29–87)	66 (32–88)	0.12
>65 years, n (%)	548 (58)	553 (59)	0.82
Sex (male), n (%)	581 (61)	574 (60)	0.74
Median body weight (range), kg	57 (31–111)	56 (27–112)	0.15
Median body mass index (range), kg/m^2	22.0 (13.3–37.7)	21.9 (12.9–37.1)	0.41
≤ 18.5 kg/m^2, n (%)	155 (16)	158 (17)	0.85
Comorbidity, n (%)			
Hypertension	538 (57)	542 (57)	0.85
Diabetes mellitus	285 (30)	303 (32)	0.37
Hepatitis B	93 (10)	93 (10)	1.0
Hepatitis C	31 (3)	31 (3)	1.0
Peripheral neuropathy	350 (37)	352 (37)	0.92
Hand-foot syndrome	149 (16)	159 (17)	0.53
Primary site of disease, n (%)			0.89
Colon	531 (56)	521 (55)	
Rectum	288 (31)	293 (31)	
Colon and rectum	125 (13)	130 (14)	
Tumor sidedness (right side), n (%)	261 (28)	264 (28)	0.88
Metastatic sites, n (%)			
Liver	631 (67)	627 (66)	0.85
Lung	495 (52)	486 (51)	0.68
Lymph node	237 (25)	222 (24)	0.42
Peritoneum	241 (26)	241 (25)	1.0
Bone	155 (16)	150 (16)	0.75
Brain	69 (7)	51 (5)	0.090
Number of metastatic sites (≥3), n (%)	271 (29)	242 (26)	0.13
Previous systemic anticancer agents, n (%)			
Fluorouracil	633 (67)	625 (66)	0.70
Capecitabine	347 (37)	336 (36)	0.60
Tegafur/gimeracil/oteracil	301 (32)	308 (33)	0.73
Tegafur	72 (8)	75 (8)	0.80
Oxaliplatin	702 (74)	690 (73)	0.53

Irinotecan	793 (84)	789 (84)	0.80
Bevacizumab (anti-VEGF antibody)	741 (79)	741 (79)	1.0
Cetuximab (anti-EGFR antibody)	190 (20)	184 (19)	0.73
Panitumumab (anti-EGFR antibody)	288 (31)	281 (30)	0.73
Trifluridine	224 (24)	226 (24)	0.91
FOLFOX ± targeted therapy	418 (44)	426 (45)	0.71
FOLFIRI ± targeted therapy	536 (57)	551 (58)	0.48
FOLFOXIRI	10 (1)	2 (0)	0.021
XELOX ± targeted therapy	252 (27)	246 (26)	0.75
XELIRI ± targeted therapy	28 (3)	26 (3)	0.78
SOX ± targeted therapy	77 (8)	70 (7)	0.55
IRIS ± targeted therapy	193 (20)	184 (19)	0.60
Mean number of previous anticancer agents (SD)	4.5 (1.8)	4.5 (1.9)	0.92
Any previous targeted therapy, n (%)	848 (90)	822 (87)	0.06
Department, n (%)			0.23
Medical oncology	91 (10)	103 (11)	
Internal medicine	292 (31)	260 (28)	
Surgery	561 (59)	581 (62)	

Abbreviations: EGFR=epidermal growth factor receptor; VEGF=vascular endothelial growth factor receptor; IQR=interquartile range; SD=standard deviation; FOLFOX=fluorouracil, folinic acid and oxaliplatin; FOLFIRI=fluorouracil, folinic acid and irinotecan; FOLFOXIRI=fluorouracil, folinic acid, oxaliplatin and irinotecan; XELOX=capecitabine plus oxaliplatin; XELIRI=capecitabine plus irinotecan; SOX=tegafur/gimeracil/oteracil plus oxaliplatin; IRIS=tegafur/gimeracil/oteracil plus irinotecan.

Fig. 1 Patient flow diagram. [a] Four patients had 2 exclusion criteria

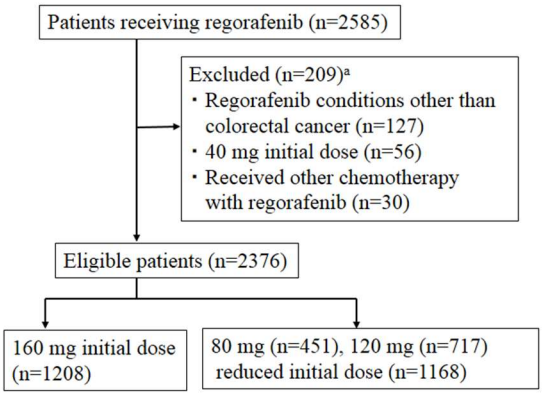


Fig. 2 Kaplan-Meier curves for overall survival (OS). The median OS were 12.3 months in the standard group and 12.6 months in the reduced group

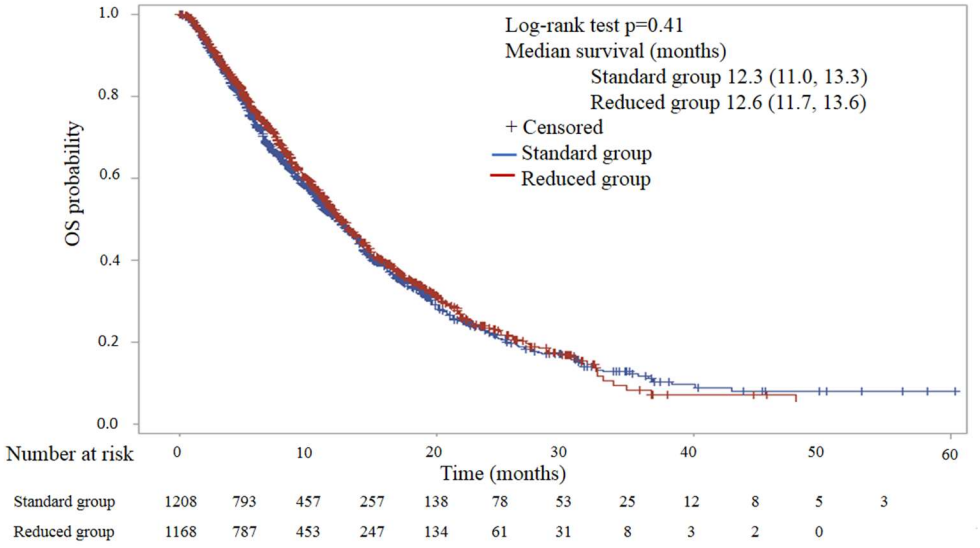


Fig. 3 Kaplan-Meier curves for overall survival (OS) after patient characteristics were matched by propensity score. The median OS were 11.9 months in the standard group and 12.1 months in the reduced group

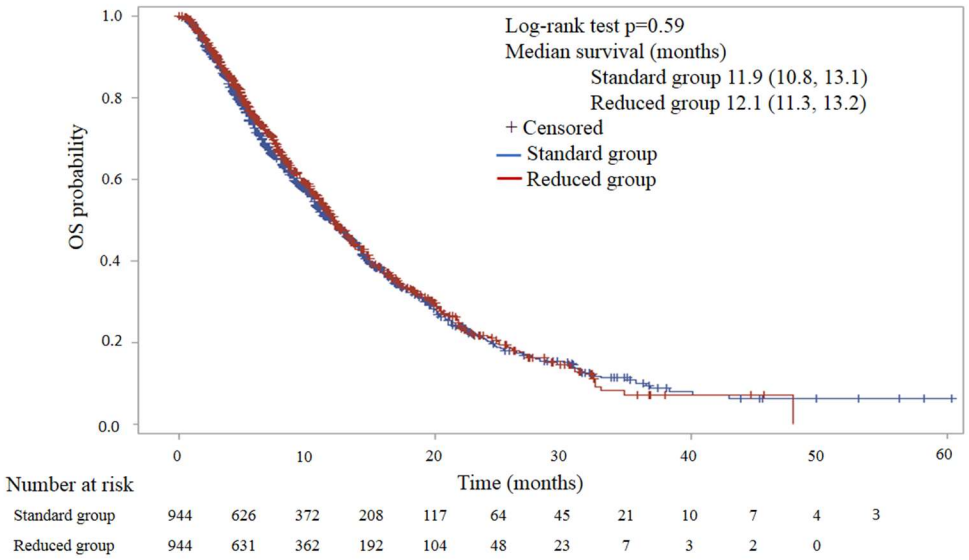
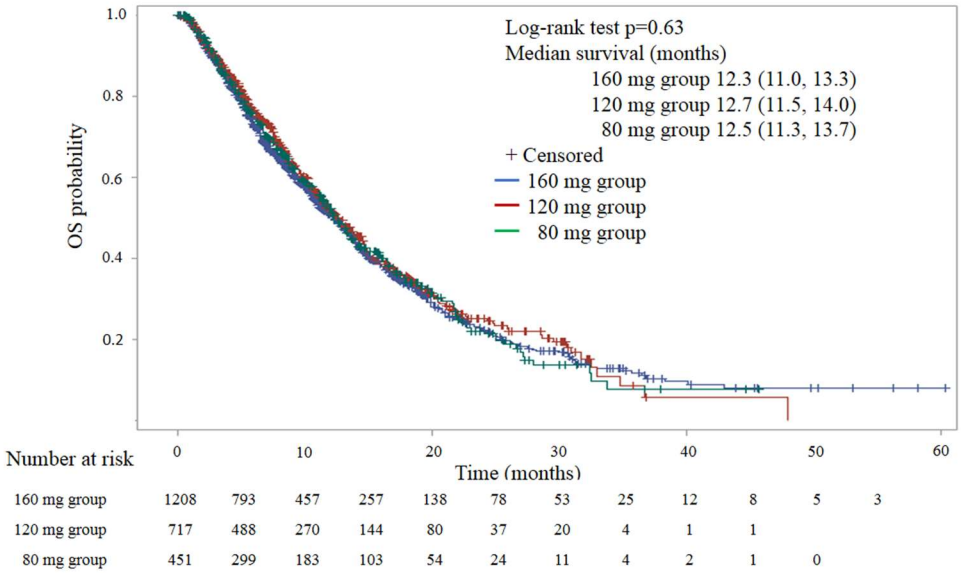


Fig. 4 Kaplan-Meier curves for overall survival (OS). The median OS were 12.7 months in the 120 mg initial dose group and 12.5 months in the 80 mg initial dose group



Electronic Supplemental Material

Table A. ICD-10 codes for colorectal cancer

	ICD-10 codes
Colorectal cancer	'C180' 'C181' 'C182' 'C183' 'C184' 'C185' 'C186' 'C187' 'C189' 'C19' 'C20'

Abbreviation: ICD-10=International Classification of Diseases, 10th revision.

Table B. ICD-10 codes for adverse events

Adverse events	ICD-10 codes
Hand-foot skin reaction	'G64' 'G98' 'G629' ‘L030’ 'L271' 'L309'
Hypertension	'I10' 'I110' 'I119' 'I129' 'I150' 'I151' 'I159
Nausea	'R11'
Diarrhea	'A099' 'K529' 'K521'
Oral mucositis	'K120' 'K121' 'K122' 'K130' 'K140'
Rash/Desquamation	'L500' 'L508' 'L509' 'L501' 'L270' 'L279'
Fever	'R509' 'R508'
Hepatotoxicity	'K711' 'K712' 'K716' 'K719' 'K720' 'K759'
Fatigue	‘R53’ ‘R464’

Abbreviation: ICD-10=International Classification of Diseases, 10th revision.

Table C. Variables used for calculating propensity score

Variable	Category
Sex	Male, Female
Age	≦65 years, >65 years
Body mass index	≦18.5 kg/m^2, >18.5 kg/m^2
Intolerant to trifluridine	Yes, No
Intolerant to fluorouracil	Yes, No
Intolerant to tegafur/gimeracil/oteracil	Yes, No
Intolerant to tegafur	Yes, No
Intolerant to capecitabine	Yes, No
Intolerant to oxaliplatin	Yes, No
Intolerant to irinotecan	Yes, No
Intolerant to bevacizumab	Yes, No
Intolerant to cetuximab	Yes, No
Intolerant to panitumumab	Yes, No
Department	Surgery, Internal medicine (oncology)
Hypertension	Yes, No
Diabetes mellitus	Yes, No
Peripheral neuropathy	Yes, No
Hand-foot syndrome	Yes, No
Hepatitis B	Yes, No
Hepatitis C	Yes, No