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Body Weight–Guided Regorafenib Dosing Optimizes Clinical Outcomes in Metastatic Colorectal Cancer

Laura Keller[1]*, Thomas Lehmann[1], Simon Brunner[2], Christoph Meier[3], David Thompson[4]

[1]Department of Colorectal Cancer and Body Weight–Guided Dosing, Faculty of Medicine, ETH Zurich, Zurich, Switzerland.

[2]Department of Regorafenib Pharmacokinetics and Clinical Outcomes, Faculty of Medicine, EPFL Lausanne, Lausanne, Switzerland.

[3]Department of Dose Optimization and Metastatic Colorectal Cancer, Faculty of Medicine, University of Bern, Bern, Switzerland.

[4]Department of Personalized Dosing and Clinical Pharmacology, Faculty of Medicine, University of Basel, Basel, Switzerland.

***E-mail** ✉ laura.keller@pharma.ethz.ch

Abstract

Earlier randomized clinical trials demonstrated that regorafenib improves survival in patients with unresectable colorectal cancer, yet it is also linked to a substantial frequency of adverse reactions. To minimize toxicity and enhance patient tolerance, this investigation evaluated body weight–based regorafenib dosing to determine an appropriate regimen. Data were drawn from a comprehensive national claims database in Japan. We assessed the effectiveness and safety profile of regorafenib among individuals with metastatic colorectal cancer, categorizing participants by body weight (60 kg cutoff) and median average dose (120 mg), for treatments administered between 2013 and 2018. Comparisons of overall survival (OS) and adverse event rates were performed across the defined groups. A total of 2530 Japanese patients were included (heavy weight/high dose: 513; light weight/low dose: 921; heavy weight/low dose: 452; light weight/high dose: 644). After adjustment with inverse probability treatment weighting (IPTW), the heavy-weight/high-dose group and the light-weight/low-dose group showed no meaningful differences in adverse events or OS (hazard ratio, HR = 0.97). Within the light-weight subgroup, administration of a higher average dose was associated with reduced OS (IPTW-adjusted HR = 1.21, 95% CI: 1.05–1.39). By comparison, heavy-weight patients exhibited no significant OS difference between high- and low-dose categories (IPTW-adjusted HR = 1.14, 95% CI: 0.95–1.37). The results imply that light-weight patients receiving a lower dose of regorafenib can attain safety and efficacy outcomes equivalent to those observed in heavy-weight patients given higher doses. Prospective research is required to refine individualized dosing protocols that account for each patient's body composition and overall clinical status.

Keywords: Regorafenib, Reduced dose, Colorectal cancer, Cohort study, Drug therapy

Introduction

Regorafenib is an orally administered multikinase inhibitor that targets protein kinase pathways involved in angiogenesis, tumor development, and the tumor microenvironment. It is authorized as monotherapy for metastatic colorectal cancer (CRC) in patients who have not responded to previous lines of treatment, with a standard initial dose of 160 mg taken once daily for the first 21 days of a 28-day cycle [1, 2]. Randomized studies such as CORRECT and CONCUR have confirmed its therapeutic benefit relative to placebo [3, 4]. However, the agent is frequently accompanied by notable treatment-related toxicities, including hand-foot skin reaction, fatigue, and rash. Grade 3–5 adverse events

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most commonly comprised hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%) [3, 4], with serious adverse events occurring in 9% of cases.

Observational data from routine clinical practice have likewise revealed elevated rates of adverse reactions, often resulting in early dose reductions, subsequent adjustments, or complete cessation of therapy [5-7]. Determining the optimal dose therefore necessitates careful balancing of anticancer activity against potential harm. Several prior efforts have tested reduced starting doses to limit toxicity [8-11]. One phase II trial by Suzuki *et al*. [10] initiated treatment at 120 mg/day and escalated to 160 mg/day on day 15, yet the achieved disease control rate fell short of the target threshold. Another randomized phase II trial (ReDOS) implemented a gradual dose-escalation protocol beginning at 80 mg/day and increasing by 40 mg weekly up to 160 mg/day; this strategy produced similar therapeutic activity with fewer adverse events than the conventional approach [11]. Despite these advances, research specifically examining personalized dose adaptation for regorafenib remains limited.

Establishing individualized dosing recommendations for regorafenib is critical to maximize antitumor efficacy while preserving patient well-being. Diverse strategies must be explored to identify optimal regimens tailored to patient attributes. A secondary analysis of the CORRECT trial found comparable efficacy of the 160 mg daily dose across Japanese and non-Japanese participants, although Japanese patients experienced adverse events at higher rates [12].

Japanese patients typically weigh about 10 kg less than non-Japanese patients. This disparity suggests that body weight may influence both treatment response and toxicity. Hence, customizing regorafenib dosage based on body weight is a valuable direction for further inquiry. The present nationwide Japanese claims database study tested the hypothesis that light-weight CRC patients treated with a reduced dose of regorafenib would experience survival outcomes and adverse event profiles comparable to those of heavy-weight patients receiving higher doses.

Materials and Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13]. Approval was obtained from the Ethics Committee of the Graduate School and Faculty of Medicine at Kyoto University (approval number: R2719, issued November 18, 2020). Because the dataset contained only de-identified information, the committee waived the need for informed consent.

Data sources

Analyses were performed using a large-scale medical claims database curated by Medical Data Vision Co., Ltd. (MDV; Tokyo, Japan). This resource provides comprehensive patient-level details, including demographic variables, diagnoses recorded according to the International Classification of Diseases, 10th revision (ICD-10), discharge status, and detailed prescription records including dosage, duration of supply, and quantity. The database aggregates information from both inpatient and outpatient services across 269 hospitals spanning multiple geographic areas in Japan, accounting for roughly 17% of the country's acute care hospital capacity. Age and sex profiles in the database align closely with national census figures, and the resource has supported numerous published investigations [14-16].

Study cohort

We identified patients older than 20 years with colorectal cancer (CRC) diagnosed between June 2013—the month regorafenib was introduced in Japan—and September 2018 through ICD-10 coding. Inclusion required regorafenib administration in individuals without documented metastatic disease but with a primary tumor judged unresectable. Exclusion criteria comprised: (1) regorafenib use for non-CRC malignancies such as gastrointestinal stromal tumor, small bowel cancer, or hepatic cancer; (2) absence of recorded body weight; (3) initial dosing outside the acceptable range (under 80 mg or over 160 mg); (4) simultaneous administration of other chemotherapeutic agents alongside regorafenib; (5) repeated courses of regorafenib; and (6) follow-up duration shorter than one year. Body weight was dichotomized at 60 kg, while the median average dose throughout the observation period was set at 120 mg. The 60 kg cutoff was chosen because it approximated the median observed weight (56.7 kg) and facilitated straightforward interpretation. The average dose was used to assess both the suitability of starting and ongoing dosing. The high-average-dose category (> 120 mg) included patients who initiated therapy at 160 mg and those who began at 120 mg and subsequently escalated to 160 mg. Four distinct subgroups were formed by

crossing weight and dose levels: heavy weight/low average dose group (heavy/low group), heavy weight/high average dose group (heavy/high group), light weight/high average dose group (light/high group), and light weight/low average dose group (light/low group).

Outcome measures

The main outcome was overall survival (OS), comparing the heavy/high group with the light/low group, with adjustment by inverse probability of treatment weighting (IPTW). OS was measured from the date of regorafenib initiation to death due to any reason. Data were censored at the last recorded visit for patients lost to follow-up or alive at the end of the study period in September 2018. Extracted covariates included age, body weight, body mass index (BMI), comorbid conditions, primary tumor site, metastasis locations, prior lines of systemic anticancer treatment, physician specialty, and subsequent anticancer therapies. Comorbidities were ascertained from ICD-10 codes documented before the first regorafenib prescription.

Statistical analysis

Demographic information, clinical features of the disease, and previous cancer treatment records for the heavy/high and light/low groups are summarized. Continuous variables are reported as means accompanied by their standard deviations. Categorical variables are expressed as frequencies and corresponding percentages. Group comparisons regarding drug exposure, adverse event incidence, and subsequent anticancer therapy utilization between the heavy/high and light/low groups employed the two-sample t-test or Mann-Whitney U test for continuous data and Fisher's exact test for categorical data.

To minimize confounding due to differences in patient profiles, inverse probability of treatment weighting (IPTW) was implemented. Propensity scores representing the probability of assignment to the heavy/high versus light/low group were derived using logistic regression. Covariates included in the model were age, sex, primary tumor site, comorbidities, prior systemic anticancer treatments, and the treating physician's specialty. When comparing within the heavy-weight (heavy/high vs. heavy/low) or light-weight (light/high vs. light/low) subgroups, body weight was also included as a covariate. These propensity scores served as the basis for weighting individual patients to achieve balance in baseline characteristics between the contrasted groups (e.g., heavy/high vs. light/low). Standardized differences (SD) [17] were calculated to quantify the degree of imbalance in the unweighted and weighted populations. An SD value below 0.1 was interpreted as indicating minimal imbalance.

IPTW-adjusted Kaplan–Meier estimates and corresponding log-rank tests were used to compare overall survival (OS) distributions across groups. Furthermore, an IPTW-weighted Cox proportional hazards model with only the dose group variable was applied to estimate the adjusted hazard ratio (HR) reflecting the impact of the high versus low dose. The robustness of the findings was examined through a sensitivity analysis using the cohort's median body weight (56.7 kg) as the cutoff. Subgroup-specific analyses were also conducted to determine the IPTW-adjusted HR comparing high versus low dose separately among light-weight and heavy-weight patients. Statistical significance was defined as a two-sided P value below 0.05. All analyses were carried out using SAS software (Version 9.4; SAS Institute, Cary, NC) and R statistical software (version 4.03; https://www.r-project.org/).

Results and Discussion

Patients

A total of 4205 individuals received regorafenib during the study period. After applying the exclusion criteria, 1675 cases were removed. The analytic sample comprised 513 patients in the heavy/high group, 921 in the light/low group, 579 in the heavy/low group, and 577 in the light/high group. The process of participant selection is presented in **Figure 1**. **Table 1** provides an overview of demographic details, disease characteristics, and cancer treatment background for the heavy/high and light/low groups, including both unadjusted and IPTW-adjusted standardized differences. In comparison with the heavy/high group, patients in the light/low group were generally older, included a higher proportion of females, were more often managed by surgeons, exhibited lower rates of diabetes mellitus, and had reduced prior exposure to systemic agents such as fluorouracil, tegafur/gimeracil/oteracil, and irinotecan. IPTW weighting resulted in effective balance between the heavy/high and light/low groups, as evidenced by standardized differences below 0.1 for nearly all covariates in the weighted sample.

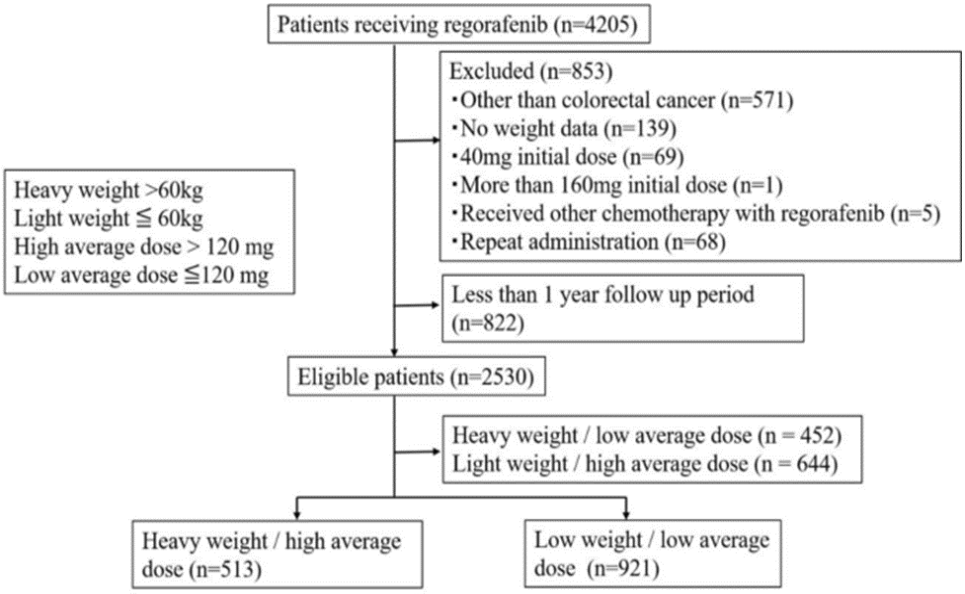

Figure 1. Participant selection flowchart for the study cohort.

Table 1. Patient characteristics.

Variable	Standardized difference (Post-IPTW)	Standardized difference	Light/Low-dose group (n = 921)	Heavy/High-dose group (n = 513)
Age, mean (SD), years	0.013	0.604	67.9 (9.6)	61.8 (10.3)
≥ 65 years, n (%)	0.040	0.506	583 (62)	199 (39)
Male sex, n (%)	0.106	1.037	411 (45)	452 (88)
Body weight, mean (SD), kg	NA	2.708	49.9 (6.8)	69.6 (7.7)
Body mass index, mean (SD), kg/m²	NA	1.635	20.3 (2.7)	24.9 (2.9)
Missing BMI data	—	—	3	5
BMI ≤ 18.5 kg/m², n (%)	NA	0.808	256 (28)	7 (1)
Initial regorafenib dose, n (%)	NA	2.539		
160 mg			114 (12)	466 (91)
120 mg			489 (53)	34 (7)
80 mg			318 (35)	13 (3)
Comorbidities, n (%)				
Hypertension	0.194	0.007	533 (58)	295 (58)
Hyperlipidemia	0.033	0.036	169 (18)	87 (17)
Diabetes mellitus	0.023	0.228	249 (27)	193 (38)
Hepatitis B	0.077	0.002	92 (10)	51 (10)
Hepatitis C	0.069	0.006	26 (3)	14 (3)
Peripheral neuropathy	0.125	0.053	343 (37)	178 (35)
Hand–foot syndrome	0.086	0.059	87 (9)	40 (8)
Primary tumor location, n (%)	0.070	0.069		
Colon			517 (56)	273 (53)
Rectum			247 (27)	153 (30)
Colon and rectum			157 (17)	87 (17)
Metastatic involvement, n (%)				
Liver	0.031	0.062	618 (67)	359 (70)
Lung	0.050	0.071	485 (53)	252 (49)
Lymph nodes	0.003	0.002	229 (25)	127 (25)
Peritoneum	0.153	0.077	276 (30)	136 (27)
Bone	0.010	0.052	142 (15)	89 (17)

Brain	0.008	0.022	63 (7)	38 (7)
Other metastatic sites	0.012	0.146	127 (14)	47 (9)
Three or more metastatic sites, n (%)	0.143	0.093	309 (34)	150 (29)
Time since metastatic diagnosis				
Mean (SD), months	0.088	0.034	27.6 (22.0)	26.9 (21.0)
≥18 months, n (%)	0.040	0.044	572 (65)	305 (63)
Missing metastatic diagnosis, n (%)	—	—	36 (4)	25 (5)
Previous systemic anticancer treatments, n (%)				
Trifluridine	0.140	0.024	263 (29)	141 (28)
Fluorouracil	0.154	0.121	579 (63)	352 (69)
Capecitabine	0.104	0.037	334 (36)	177 (35)
Tegafur/gimeracil/oteracil	0.001	0.112	308 (33)	145 (28)
Tegafur	0.074	0.019	62 (7)	37 (7)
Oxaliplatin	0.211	0.021	672 (73)	379 (74)
Irinotecan	0.169	0.137	741 (81)	439 (86)
Bevacizumab (anti-VEGFR antibody)	0.091	0.006	716 (78)	400 (78)
Cetuximab (anti-EGFR antibody)	0.023	0.077	159 (17)	104 (20)
Panitumumab (anti-EGFR antibody)	0.025	0.130	242 (26)	165 (32)
Ramucirumab (anti-VEGFR antibody)	0.018	0.026	28 (3)	18 (4)
Mean number of prior anticancer therapies (SD)	0.198	0.072	4.5 (1.9)	4.6 (1.9)
Any prior targeted therapy, n (%)	0.036	0.075	794 (86)	455 (89)
Treating department, n (%)	0.106	0.221		
Medical oncology			87 (9)	52 (10)
Internal medicine			235 (26)	180 (35)
Surgery			599 (65)	281 (55)

Abbreviations: EGFR = Epidermal growth factor receptor, VEGFR = Vascular endothelial growth factor receptor, SD = Standard deviation.

Effectiveness

Overall survival (OS) did not differ significantly between the heavy/high group and the light/low group in the IPTW-adjusted analysis (HR = 0.97; 95% CI: 0.79–1.20, P = 0.81) **(Figure 2)**. Details regarding drug exposure, safety outcomes, and use of subsequent anticancer treatments for these groups appear in **Table 2**. Patients in the heavy/high group experienced a slightly extended treatment course (51 days versus 49 days, P = 0.043) and a markedly higher cumulative dose (5600 mg versus 3160 mg, P < 0.001). Adverse event frequencies showed no substantial differences. When repeating the analysis with the median body weight threshold of 56.7 kg, the OS results remained consistent, indicating no significant difference (IPTW-adjusted HR = 0.89; 95% CI: 0.73–1.08, P = 0.19) **(Figure 3)**.

Within the light-weight patient category, receipt of a higher average dose was associated with poorer OS (IPTW-adjusted HR = 1.21, 95% CI: 1.05–1.39, P = 0.01) **(Table 3)**. Among heavy-weight patients, however, OS outcomes were comparable across dose levels (IPTW-adjusted HR = 1.14, 95% CI: 0.95–1.37, P = 0.17) **(Table 3)**. In this subgroup, the light/low group had a longer average treatment duration. In contrast, the light/high group had higher rates of specific toxicities, including oral mucositis, rash/desquamation, and hepatotoxicity.

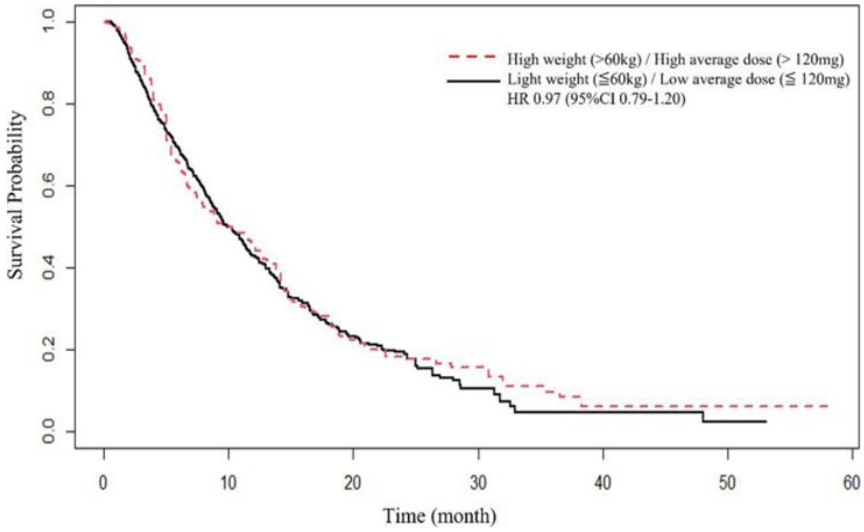

Figure 2. Kaplan–Meier plots of overall survival comparing the heavy weight (> 60 kg)/high average dose (> 120 mg) group with the light weight (≤ 60 kg)/low average dose (≤ 120 mg) group following IPTW adjustment.

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

Parameter	P-value	Light/Low-dose group (n = 921)	Heavy/High-Dose Group (n = 513)
Treatment duration			
Mean treatment duration (SD), days	0.043	82 (106)	89 (109)
Median treatment duration (IQR), days	0.043	49 (20–103)	51 (21–106)
Median cumulative dose (IQR), mg	< 0.001	3160 (1680–6160)	5600 (3360–11200)
Treatment-related adverse events, n (%)			
Hand–foot skin reaction	0.67	279 (30)	161 (31)
Hypertension	0.15	216 (23)	138 (27)
Nausea	0.42	108 (11)	53 (10)
Diarrhea	0.084	69 (7)	52 (10)
Oral mucositis	0.48	76 (8)	48 (9)
Rash/desquamation	0.94	71 (8)	39 (8)
Fever	0.69	27 (3)	17 (3)
Hepatic toxicity	0.21	9 (1)	9 (2)
Fatigue	0.59	14 (2)	6 (1)
Subsequent systemic anticancer therapy, n (%)			
Any anticancer treatment	0.017	399 (43)	256 (50)
Trifluridine/tipiracil	0.054	281 (31)	182 (35)
Fluorouracil	0.039	80 (9)	62 (12)
Capecitabine	0.26	43 (5)	31 (6)
Tegafur/gimeracil/oteracil	0.008	59 (6)	53 (10)
Tegafur	0.47	18 (2)	13 (3)
Oxaliplatin	0.013	67 (7)	57 (11)
Irinotecan	0.032	85 (9)	66 (13)
Bevacizumab (anti-VEGF antibody)	0.062	105 (11)	76 (15)
Cetuximab (anti-EGFR antibody)	0.074	25 (3)	23 (5)
Panitumumab (anti-EGFR antibody)	0.12	37 (4)	30 (6)
Aflibercept (anti-VEGF antibody)	0.64	10 (1)	7 (1)
Ranibizumab (anti-VEGF antibody)	0.34	38 (4)	16 (3)

Abbreviations: TFTD = Trifluridine/tipiracil, IQR = Interquartile range, EGFR = Epidermal growth factor receptor, VEGF = Vascular endothelial growth factor receptor, SD = Standard deviation, IQR = Interquartile range

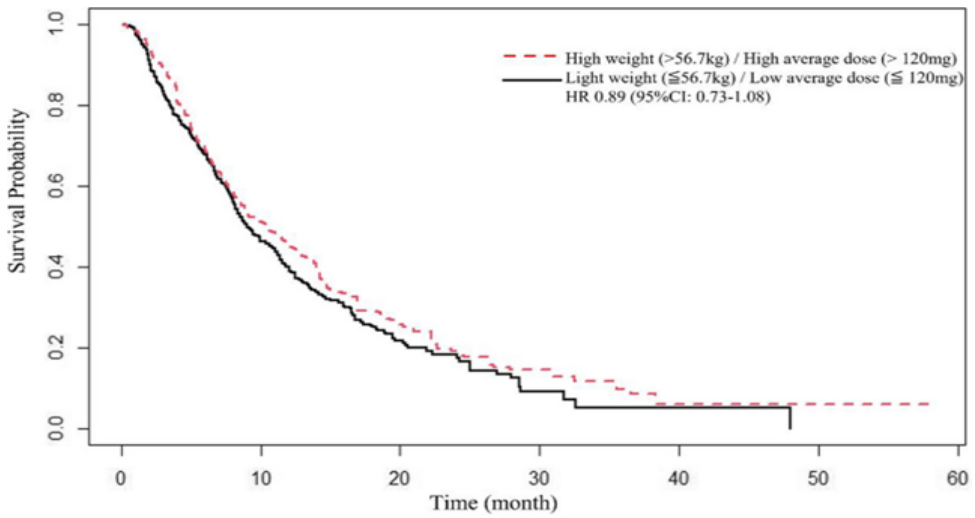

Figure 3. Kaplan–Meier plots of overall survival comparing the heavy weight (> 56.7 kg)/high average dose (> 120 mg) group with the light weight (≤ 56.7 kg)/low average dose (≤ 120 mg) group following IPTW adjustment

Table 3. Comparison of OS between high- and low-dose groups in light-weight and heavy-weight patients.

Comparison	IPTW-adjusted hazard ratio (95% CI)	Hazard ratio (95% CI)
Light-weight/high-dose vs. light-weight/low-dose	1.21 (1.05–1.39)	1.17 (1.03–1.33)
Heavy-weight/high-dose vs. heavy-weight/low-dose	1.14 (0.95–1.37)	1.21 (1.02–1.44)

Abbreviations: OS = overall survival, CI = confidence interval.

This nationwide claims database study represents the first evaluation of body-weight–guided regorafenib dosing to optimize survival outcomes. The findings indicate that light-weight patients with colorectal cancer (CRC) receiving a lower average dose experienced comparable overall survival and adverse event rates to heavy-weight patients given a higher average dose. Notably, use of a higher average dose in light-weight individuals was associated with inferior OS. In heavy-weight patients, dose reduction of regorafenib yielded efficacy similar to that of the conventional 160 mg once-daily regimen.

Previous randomized trials in CRC have established that regorafenib provides meaningful clinical benefit while also carrying a considerable risk of adverse reactions [3, 4]. Because toxicities tend to emerge predominantly during the early treatment cycles [4, 5], multiple investigations have explored strategies involving reduced starting doses [8-11]. These reports generally found that lower initial doses reduced treatment-related toxicity without compromising effectiveness compared with the standard 160 mg starting dose. Nevertheless, limited attention has been paid to adjustments in maintenance dosing.

For conventional cytotoxic anticancer drugs, optimal initial and maintenance doses are typically established through Phase I trials, where the maximum tolerated dose (MTD) is identified due to the clear dose-toxicity relationship. In contrast, most orally targeted agents, such as regorafenib, exhibit substantial interpatient variability in pharmacokinetics and a narrow therapeutic index [18]. Consequently, dosing for these targeted therapies should be individualized according to patient-specific factors [19]. As regorafenib is generally administered late in the treatment sequence, prioritizing patient quality of life makes it particularly important to identify the lowest effective dose that maintains antitumor activity while minimizing toxicity. However, the approved initial dose was derived from traditional Phase I studies based on MTD and may therefore be suboptimal [2, 20, 21]. Although personalization using predictive biomarkers or therapeutic drug monitoring would be ideal, reliable methods for this purpose are currently unavailable [22]. In the present analysis, the median treatment duration was less than 2 months, suggesting that a notable subset of patients discontinued therapy due to adverse effects. Adverse event rates and treatment duration were similar between the heavy/high and light/low groups, yet total cumulative dose was markedly greater in the heavy/high group. Within the light-weight subgroup, the light/low group achieved longer treatment duration, potentially reflecting better

tolerability. These observations support more proactive implementation of reduced dosing—both initial and average—for light-weight patients.

Several limitations should be acknowledged given the characteristics of the claims database. First, certain clinically relevant details were unavailable, including performance status, severity grading of adverse events, KRAS mutation status, reasons for discontinuation, and response assessments. Progression-free survival and disease control rates could not be evaluated. Second, the OS analysis contained a high proportion of censored observations, as patients who transferred to other facilities or received end-of-life care at home or in hospice could not be followed. Third, the study population was composed almost exclusively of Japanese patients and may not reflect global demographics. Prior research in Japan has noted that patients tend to be older, have lower body weight, and experience higher rates of adverse events [12]. Therefore, analogous investigations involving more geographically and ethnically diverse populations are warranted.

Conclusion

This study provides the first comparative evaluation of high-average-dose regorafenib in heavy-weight CRC patients versus low-average-dose regorafenib in light-weight CRC patients within a large nationwide cohort. No significant survival differences were observed, supporting the suitability of reduced doses for light-weight individuals. Furthermore, heavy-weight patients appeared to derive a comparable survival benefit from lower doses compared with the standard regimen. These findings offer valuable insights for guiding individualized regorafenib dosing decisions in patients with CRC.

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Ethics Statement: None

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