






# Factors Associated With Regorafenib Adherence With Metastatic Colorectal Cancer

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**Introduction:** Regorafenib is an oral multikinase inhibitor for the treatment of metastatic colorectal cancer (mCRC). The clinical factors that may affect adherence to regorafenib remain unclear. The aim of this study was to evaluate adherence to regorafenib with mCRC and to identify factors that might affect adherence to regorafenib.

**Methods:** A total of 108 consecutively enrolled Japanese patients with mCRC received regorafenib. Adherence was measured by pharmacists using pill counts and a self-reported treatment diary for patients at a pharmaceutical outpatient clinic. The median relative dose intensities of regorafenib and the factors adversely affecting adherence were retrospectively surveyed. Logistic regression analysis was then performed using patient socio-demographic factors and clinical factors.

**Results:** A total of 96 patients were included in the analysis. The median adherence rate was 61.7% in the first cycle. The median relative dose intensity was 57.1%. The most common reason for non-adherence was a hand-foot-skin reaction (35.6%). On multivariate analysis, increased non-adherence to regorafenib was significantly associated with sex (female) [odds ratio (OR) = 4.36; 95% confidence interval (CI): 1.43–13.22,  $p = 0.01$ ].

**Discussion:** Hand-foot-skin reactions and female sex were associated with lower adherence to regorafenib. Since these factors could be associated with lower adherence to regorafenib, it would be useful to consider these factors when assessing adherence.

**Keywords:** adherence, regorafenib, colorectal cancer, hand-foot-skin reactions

## Introduction

Due to the availability of rapidly growing numbers of new oral anticancer agents directed towards specific tumor cell targets, medication adherence is becoming an increasingly important issue in oncology.<sup>1</sup> In addition, over 80% of patients would prefer oral anticancer agents to intravenous administration.<sup>2</sup> The development of new oral anticancer therapies has not only prolonged survival, but also improved cancer patients' quality of life by decreasing the need for hospitalization.<sup>3</sup>

On the other hand, poor medication adherence could worsen treatment outcomes.<sup>4,5</sup> Adherence rates to anticancer agents vary from 16% to 100%.<sup>6</sup> Research on adherence to protein kinase inhibitor treatment in patients with chronic myeloid leukemia showed an association between the missing of only a small number of doses per month (5%) and a less favorable clinical outcome.<sup>7</sup> According to published data from the World Health Organization, non-adherence to medication has become a global problem of striking magnitude.<sup>8</sup> Therefore, maintaining good adherence is an important issue, particularly with oral anticancer agents.

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Regorafenib is an oral multi-kinase inhibitor that blocks the activity of several protein kinases involved in the multiple biological processes of progression and development of cancer; these kinases include vascular endothelial growth factor receptor (VEGFR) 1–3 and tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2) involved in tumor angiogenesis.<sup>9</sup> Treatment with regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle has shown significant benefits for overall survival and progression-free survival in patients with previously treated metastatic colorectal cancer (mCRC) in two placebo-controlled phase 3 trials, CORRECT<sup>10</sup> and CONCUR.<sup>11</sup>

A previous study reported that the average regorafenib adherence was 82% in southern Italy, and patients' level of education, other concomitant oral medications, and patients' general clinical condition may affect regorafenib adherence.<sup>12</sup> However, there are no available data regarding the regorafenib adherence rate in every cycle and the factors reducing regorafenib adherence. Additionally, very little has been published on adherence and persistence to oral molecular targeted therapies in solid malignancies.<sup>13</sup> The purpose of this retrospective analysis was to evaluate adherence and patient profiles that can help predict poor adherence in mCRC patients receiving regorafenib.

## Patients And Methods

### Patients

This was a retrospective observational study to examine the clinical factors that may affect regorafenib adherence. Data from 108 consecutive Japanese patients with mCRC who received regorafenib between May 18, 2013 and March 31, 2015 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research were enrolled. Patients received regorafenib (Bayer, Leverkusen, Germany) 160 mg once daily for the first three weeks of each 4-week cycle until disease progression or unacceptable toxicity. To prevent hand-foot-skin reactions, heparinoid ointment was applied to the hands and feet, and clobetasol propionate was applied at the time of symptom onset. Patients treated with regorafenib were followed-up on day 1, day 8, and day 15 until the end of the 3<sup>rd</sup> cycle.

### Data Collection

Adherence to regorafenib was assessed using pill counts and patient-reported treatment diaries, and non-adherents were interviewed about the reasons for not taking regorafenib at a pharmaceutical outpatient clinic at every patient

visit. The pill count was performed by counting the number of regorafenib pills remaining unused whenever the patient visited the outpatient clinic. All participants in this study visited a pharmaceutical outpatient clinic and completed the study. The adherence rate in a cycle was calculated as the number of times a patient took regorafenib/21.

Median relative dose intensities<sup>14</sup> of regorafenib and factors associated with reduced adherence were retrospectively collected from electronic patient records. The study protocol was reviewed and approved by the clinical research ethics review committee at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (approval no: 2015–1042). The all patients provided written informed consent in compliance with the Declaration of Helsinki.

### Pharmaceutical Outpatient Clinic

In our hospital, proactive intervention by pharmacists to check adherence and side effects (which are one cause of non-adherence) is considered necessary, and a pharmaceutical outpatient clinic is helpful for patients undergoing oral chemotherapy treatment.<sup>15,16</sup> The main tasks of the pharmaceutical outpatient clinic were: to check the regorafenib treatment diary (Bayer) for regorafenib adherence and leftover medication; to propose prescription support for regorafenib and supportive pharmacotherapy; and assessment of side effects such as the hand-foot-skin reaction and hypertension. In practice, prescription support for regorafenib consists of a pharmacist recording the regorafenib dose and administration period required for the next cycle in the electronic medical record. This is then checked and authorized by a physician to enable the prescription to be issued. If any regorafenib is left over from the previous cycle, the prescribed amount is adjusted accordingly.

### Statistical Analysis

The primary endpoint was adherence, dichotomized according to success defined as an adherence rate  $\geq 90\%$  in the first cycle. Univariate analyses were then performed using socio-demographic factors (sex, age ( $\geq 70$  years vs.  $< 70$  years), living status (alone vs. with others), and marital status) and clinical factors (Eastern Cooperative Oncology Group (ECOG) performance status, adverse events (Grade  $\geq 3$ ), and number of systemic medications ( $\geq 6$ )). The factors that were significant on univariate analysis were entered into the multivariate analysis. Significance levels for uni- and multivariate analyses

were set at  $p < 0.2$  and  $p < 0.05$ , respectively. Odds ratios and  $p$ -values were computed for the variables in logistic regression models. All analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL).

## Results

### Patients And Characteristics

A total of 108 patients were extracted from the outpatient pharmacy information systems in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Among them, 12 patients were excluded. The reasons for exclusion were no data collected ( $n=10$ ) and change in hospital during the first cycle ( $n=2$ ) (Figure 1). Clinical characteristics and socio-demographic data for the 96 patients analyzed are reported in Table 1. The median age of the patients was 62.5 years (range, 34–83 years), and more than half of the patients were female. The majority of the patients had an ECOG performance status of 0. In terms of living status, 82 patients (85.4%) were living with family, and 14 patients (14.6%) were living alone. In almost 90% of patients, regorafenib was administered as 3<sup>rd</sup>-line or later. The total number of regorafenib treatments was 185 cycles.

### Adherence Rate

Figure 2 shows the regorafenib adherence rate determined at the pharmaceutical outpatient clinic using the pill count and patient-reported treatment diaries. No cases of over-adherence (defined as adherence rate  $> 100\%$ ) were found. The rate of patients who completed regorafenib to the third cycle was 4.2% (4 patients). The median adherence rate was 61.7% ( $n=96$ ) in the first cycle, 77.5% ( $n=68$ ) in the second cycle, and 84.3% ( $n=34$ ) in the third cycle. The median relative dose intensity of regorafenib in this study was 57.1%.

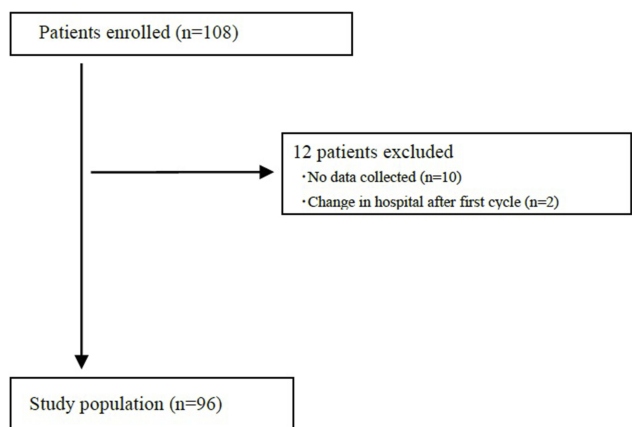


Figure 1 Flow chart of patients and reasons for exclusion.

Table 1 Clinical And Socio-Demographic Characteristics Of The Study Population

Characteristic	No. Patients (n=96)	%
Median age, years (range)	62.5 (34–83)	
Gender		
Male/Female	46/50	47.9/52.1
ECOG performance status		
0/1/2	61/35/0	63.5/36.5/0
Primary tumor site		
Colon/Rectal/Others	60/31/5	62.5/32.3/5.2
Living status		
With family/Alone	82/14	85.4/14.6
Marital status		
Married/Not married	74/22	77.1/22.9
ECOG performance status		
PS 1/PS 2	61/35	63.5/36.5
Grade $\geq 3$ adverse events		
Yes/No	56/40	58.3/41.7
Number of internal medications		
$< 5/\geq 6$	74/22	77.1/22.9
Number of prior regimens		
2	4	4.2
3	29	30.2
4	56	58.3
5	7	7.3
Duration of use (cycles)		
Total	185	

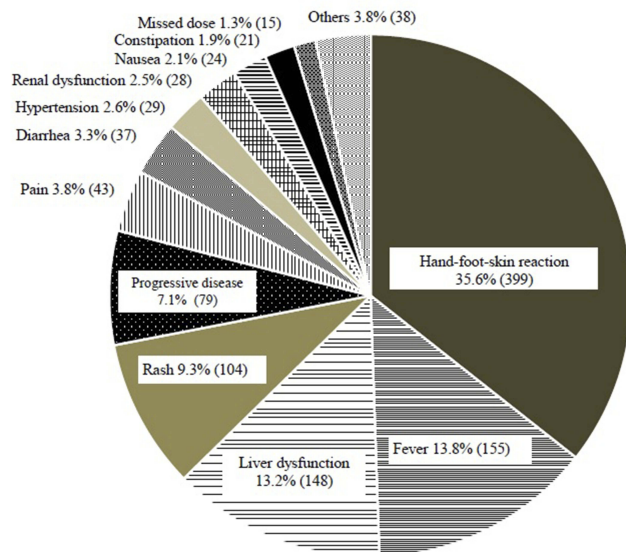
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

### Factors Reducing Regorafenib Adherence

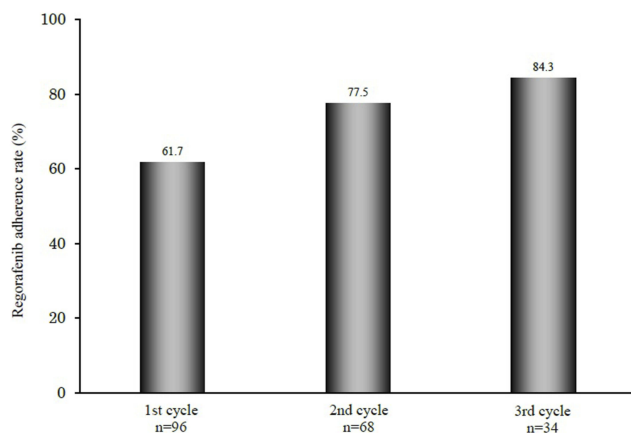
In total, non-adherence was seen in 92 patients (95.8%), with 1120 instances. The most common reasons for non-adherence were hand-foot-skin reactions (35.6%, 399 instances), fever (13.8%, 155 instances), liver dysfunction (13.2%, 148 instances), and rash (9.3%, 104 instances) (Figure 3).

### Multivariate Model Of Factors Associated With Adherence

The results of the multivariate analysis are shown in Table 2. Univariate analyses identified sex, living status, and adverse events (Grade  $\geq 3$ ) as possible risk factors for predicting a  $< 90\%$  adherence rate within the 1st cycle. A significant association was found for sex (female) [odds ratio (OR) = 4.36; 95% confidence interval (CI) = 1.43–13.22;  $p = 0.01$ ] on logistic regression analysis.



**Figure 3** Factors reducing adherence to regorafenib treatment (n=1120 instances). Progression disease discontinued regorafenib treatment during its course, and these instances were counted as progression disease.



**Figure 2** Regorafenib adherence rate in Japanese patients with metastatic colorectal cancer during cycles 1–3. The adherence rate was calculated as the median adherence rate for each cycle from pill counts and a self-reported treatment diary for patients at a pharmaceutical outpatient clinic.

## Discussion

In many previous studies, the dose intensity of oral anticancer agents was determined only by the amount of medicine prescribed.<sup>17</sup> Thus, whether patients were adherent at home was not known. The present study examined not only the median relative dose intensity of regorafenib but also the median adherence rate determined by pharmacists by pill counts and patient-reported treatment diaries. Moreover, female sex was found to be a factor decreasing regorafenib adherence. To the best of our knowledge, this is the first report of a clinical factor that affects adherence to regorafenib with mCRC.

In the present study, the median regorafenib adherence rate was 61.7% in Japanese patients. However, it was reported that the average regorafenib adherence rate was 82.0% in a previous study that was conducted in Italy.<sup>12</sup> These data suggest that the regorafenib adherence rate is lower in Japanese patients than in non-Japanese patients. Accumulated data from clinical trials have suggested that there are ethnic differences in the incidence of regorafenib treatment-related adverse events, with a higher incidence of serious adverse events in the Japanese subpopulation compared with the non-Japanese subpopulation.<sup>10,11,18</sup> In the CORRECT trial, regorafenib treatment-related adverse events were clearly higher in the Japanese subpopulation than in the non-Japanese subpopulation, including hand-foot-skin reaction (80 vs 42%) and hypertension (60 vs 23%) of any grade.<sup>19</sup> The median dose intensity of regorafenib was 71.4% (range 9.5–100.0%) in the Japanese subpopulation, while it was 83.3% (range 9.5–114.3%) in the non-Japanese subpopulation.<sup>19</sup> The present data are consistent with the previous reports, and ethnic difference may cause lower adherence in Asians.

The present study showed that female sex was significantly associated with lower regorafenib adherence in mCRC patients. In general, female sex has been associated with lower adherence not only in cancer, but also in other diseases.<sup>20,21</sup> It has been reported that female sex was associated with lower imatinib adherence in adult chronic myeloid leukemia.<sup>22</sup> Adverse effects of imatinib include rash, edema, and weight gain. Because women are more concerned with their appearance, this issue may be related to the lower adherence in females. Interestingly, in the present study, Grade  $\geq 2$  rash/desquamation occurred in 5 patients, all of whom were female. All of them stopped taking regorafenib immediately. These data support the finding that females have lower regorafenib adherence than males.

The present study identified the factors for non-adherence to regorafenib. The major reasons for lower regorafenib adherence were subjective symptoms such as hand-foot-skin reaction, fever, rash, and pain. The relative dose intensity represents the ratio of the amount of drug prescribed to the amount planned for a fixed time period. On the other hand, adherence represents patients' actual medication-taking behavior. This concept contains the actual amount of drug taken. Therefore, it is important to assess not only the relative dose intensity of regorafenib, but also the adherence.<sup>23</sup>

Several limitations of this paper should be taken into consideration. In this study, relevant patient-related factors that might be related to adherence, such as education, were not examined.<sup>24,25</sup> In general, highly educated patients are

**Table 2** Logistic Regression Analysis Of Socio-Demographic And Clinical Factors For An Adherence Rate < 90% In The First Cycle

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Socio-demographic factors				
Gender (female)	4.36 (1.43–13.22)	0.01*	4.36 (1.43–13.22)	0.01*
Age (≥70 years)	0.76 (0.26–2.15)	0.60		
Living Status (Living alone)	3.92 (0.48–31.94)	0.17		
Marriage (Not married)	1.89 (0.50–7.16)	0.27		
Clinical factors				
ECOG performance status (≥1)	1.44 (0.50–4.17)	0.50		
Adverse events (Grade ≥3)	3.37 (1.20–9.46)	0.02*		
Number of systemic medications (≥6)	3.21 (0.68–15.1)	0.10		

Note: \*P < 0.05.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

more adherent.<sup>26,27</sup> Another limitation of this study include its retrospective nature and small sample size from a single institute. These limitations make firm conclusions difficult. Nevertheless, the present data are important for demonstrating the clinical factors that may affect adherence to regorafenib in Japanese patients with mCRC.

In conclusion, the median regorafenib adherence rate was 61.7% in the first cycle, and the most common reason for non-adherence was a hand-foot-skin reaction. Female sex was associated with lower regorafenib adherence, careful dose reduction and interruption of regorafenib are required for female patients.

## Availability Of Data And Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval And Consent To Participate

This study was approved by the Ethics Committee of the Cancer Institute Hospital, Japanese Foundation for Cancer Research. All the participants gave their written consent to be included in this study.

## Disclosure

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