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ORIGINAL ARTICLE

Associations among regorafenib concentrations, severe adverse reactions, and ABCG2 and OATP1B1 polymorphisms

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Abstract

Purpose The ability of predicting severe adverse reactions caused by regorafenib is important. We evaluated regorafenib concentrations for adverse reaction risks and assessed the relevance of laboratory values and gene polymorphisms.

Methods A total of 28 Japanese cancer patients who were treated with regorafenib were evaluated for the steady state of serum regorafenib concentrations and adverse reactions for 28 days. In addition, we determined the association of regorafenib concentrations with ABCG2 and OATP1B1 polymorphisms, which are regorafenib transporters.

Results Regorafenib concentrations were significantly higher in the group with Grade 2 or higher total bilirubin elevation and thrombocytopenia compared with the group with grades 0 or 1 [3.45 (2.18–7.31) vs. 1.76 (0.26–2.77) μg/mL, $P = 0.01$ and 3.45 (2.12–7.31) vs. 1.76 (0.26–2.77) μg/mL, $P = 0.02$, respectively]. A strong association was noted between serum regorafenib concentrations and total bilirubin levels, but the physical and genetic factors predicting regorafenib pharmacokinetics could not be clarified.

Conclusions Regorafenib concentrations were associated with total bilirubin elevation and thrombocytopenia. Total serum bilirubin could be a useful marker when estimating regorafenib pharmacokinetics.

Keywords Adverse reactions · Bilirubin · Pharmacokinetics · Regorafenib · OATP1B1 · SLCO1B1

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Introduction

Regorafenib is an oral multikinase inhibitor which prolongs survival for patients with colorectal cancer and gastrointestinal stromal tumors. However, the drug causes severe adverse reactions, such as hand–foot skin reactions, diarrhea, hypertension, thrombocytopenia, and hepatic injury [1]. Adverse reactions to chemotherapy are known to vary among individuals, depending on physical (e.g., age, sex, body surface area, and organ function) and genetic factors. Adverse reactions induced by regorafenib are considered to be dose-dependent [2], but the relevance of serum regorafenib concentrations to adverse reactions has not been fully clarified. In clinical practice, it is difficult to measure serum concentrations of regorafenib, because measurement systems are not commercialized, and the factors influencing these concentrations are also unclear. Regorafenib treatment should begin at doses lower than the usual 160 mg/day to minimize adverse reaction risk, with tolerance confirmed as the dose is increased [3].

Therefore, if factors associated with adverse events are related to regorafenib concentrations, we can also clinically predict the appropriate concentration for the patient and adjust the dose. Understanding this relationship can help in managing adverse reactions.

Regorafenib is transported by organic anion transporting polypeptide (OATP) 1B1, which contributes to its uptake from the blood into the liver, and by ATP binding cassette superfamily G member 2 (ABCG2), which is a polymorphic efflux transporter protein [4, 5]. In our previous study, we investigated the association of these polymorphisms with adverse reactions to regorafenib and found that there was a high frequency of liver dysfunction in the S SLCO1B1*1b (388G/521T) haplotype non-carrier [6]. Serum regorafenib concentrations might be elevated due to the influence of a genetic polymorphism of SLCO1B1 521T>C, which has decreased uptake capability into the liver.

In this study, we evaluated the association between regorafenib concentrations and adverse reactions, and the usefulness of laboratory values and gene polymorphisms as pharmacokinetic predictive markers of regorafenib in patients whose serum concentration could be measured [6].

Materials and methods

Patients

This was a prospective, observational study conducted at Aichi Cancer Center Hospital from December 2013 to December 2014. Patients were recruited based on the following inclusion criteria: (1) at least 20 years of age; (2) sufficient food intake; and (3) naïve to treatment with regorafenib. All the patients were Japanese and provided written informed consent. This study was approved by the Ethics Committee of Aichi Cancer Center Hospital and was conducted in accordance with the Declaration of Helsinki.

Procedures

All the enrolled patients received regorafenib (Bayer Yakuhin, Ltd., Osaka, Japan) at a starting dose prescribed by the attending physician. The following information was prospectively collected during cycle 1 (within 28 days): any changes in laboratory values (hematology and clinical chemistry) and vital signs and the occurrence of adverse events, which were reported according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Cancer Therapy Evaluation Program; National Cancer Institute, National Institutes of Health, Bethesda, MD, USA).

Methods and measurements

We collected one-point blood samples at steady state after regorafenib administration on days 7–22 from participants who had been taking regorafenib longer than a week. The adverse events were evaluated using the maximum CTCAE grade for one cycle.

Regorafenib was purchased from Toronto Research Chemicals, Inc. (Toronto, Ontario, Canada). Gefitinib-D6 was supplied by the Cayman Chemicals Co. (Ann Arbor, MI, USA). Ultrapure water was obtained using an RFU554CA ultrapure water system (Advantec, Kyoto, Japan). The ethanol, acetonitrile, and formic acid were purchased from Nacalai Tesque (Kyoto, Japan).

Serum regorafenib concentration measurement

Regorafenib concentrations in serum samples were determined using a previously reported method [7] with some modifications. A serum sample was added to a twofold concentration of acetonitrile, including gefitinib-D6 (100 ng/mL) as internal standard (IS), to precipitate proteins. After vortexing and centrifugation (25 °C, 10,000×*g* for 10 min), a 1 µL supernatant was injected into a liquid chromatography tandem mass spectrometry system, which comprised the 1260 LC system (Agilent, Waldbronn, Germany) and a QTRAP 4500 triple quadrupole mass spectrometer (AB Sciex, Framingham, MA, USA). The mobile phase (0.1% formic acid: acetonitrile = 3:7, v/v) was pumped at a flow rate of 0.2 mL/min, and the chromatography was performed at 40 °C, using an InertSustainSwift C18 analytical column (3 µm, 2.1 × 50 mm, GL Sciences, Tokyo, Japan). A multiple reaction monitoring transition of regorafenib and the gefitinib-D6 (IS) was selected with m/z 482.8 → 269.9 and 452.8 → 134.0, respectively.

Peak area ratios of regorafenib (analyte) to that of the IS were used for all calculations. A least squares linear regression ($1/x^2$ weighting factor) was used to define the calibration curve.

ABCG2 and SLCO1B1 genotyping

DNA was determined according to a previously reported method [6].

Statistical analysis

The different regorafenib serum concentrations between the two groups were analyzed using the Mann–Whitney *U* test and among the three groups using the Kruskal–Wallis test. The variation of bilirubin was analyzed using Wilcoxon

signed-rank test. The correlation was calculated as a Pearson correlation coefficient. The data were expressed as median (range) and mean values ± standard deviation. *P* values < 0.05 were considered statistically significant. All calculations were performed using EZR version 1.37 software [8].

Results

Of the 37 patients who were enrolled, 28 patients were able to take regorafenib for 7 days before we analyzed their blood samples. Of the 11 patients who started treatment at 120 mg, 10 patients' blood samples were analyzed. However, of the 26 patients who started taking doses at 160 mg, 8 patients could not continue the treatment for more than 7 days due to adverse reactions; thus, only 18 patients could be analyzed. The characteristics and genotypes of the 28 patients analyzed in this study are summarized in Table 1. The median of serum regorafenib concentrations measurement days was day 7 (7–21), and 21 (75%) patients were measured in 7–9 days. The trough concentrations were 1.92 (0.26–7.31) and 1.82 (0.28–3.45) μg/mL in the 120-mg and 160-mg dose groups, respectively; there was no statistically significant difference ($P = 0.87$) between the two groups. In addition, no significant correlation was observed between the serum regorafenib concentration and body weight (120-mg group: $r = 0.47$, $P = 0.17$; 160-mg group: $r = -0.31$, $P = 0.22$) (Fig. 1).

Adverse reactions

The relationship between adverse drug reactions and serum concentrations of regorafenib during cycle 1 (day 28) is shown in Table 2. The trough concentrations were significantly higher in the group with grade 2 or higher total bilirubin elevation and thrombocytopenia compared to the group with grades 0 or 1. The correlation between platelet count reduction rate in cycle 1 and serum regorafenib concentrations was determined ($r = -0.52$, $P = 0.0046$).

Statistical analysis revealed that regorafenib concentrations increased total serum bilirubin levels (Fig. 2). In addition, a strong correlation was observed between total bilirubin levels and serum regorafenib concentrations ($r = 0.78$, $P = 0.0001$). The total bilirubin value recovered to pretreatment levels within 2–8 days after discontinuing the drug (Fig. 3).

Polymorphisms

The background characteristics were not significantly different between genotype groups. The regorafenib concentration-to-dose ratio (CDR) was shown to be higher in *SLCO1B1* 521 T>C and *SLCO1B1*1b* non-carriers than in the other polymorphisms, and was reported to reduce the ability of drug transport via OATP1B1. However, these differences were not statistically significant. The regorafenib CDR was significantly higher in the group with lower than an estimated creatinine clearance of 60 mL/min compared to those with 60 mL/min or more (Table 3).

Table 1 Patient characteristics

Patients (*n*)	28
Diagnosis	
Colon cancer[a]	26
GIST	2
Age, median (range)	63 (37–87)
Male *n*, (%)	19 (68)
BSA (/m^2)	1.61 (1.20–2.11)
ECOG-PS (*n*)	
0/1/2	5/20/3
Regorafenib dose	
120/160	10/18
AST (U/L)	33.8 ± 25.7
ALT (U/L)	24.7 ± 27.2
T.bil (mg/dL)	0.67 ± 0.25
SCr (mg/dL)	0.74 ± 0.24
eCCr (mL/min)	91.3 ± 39.5
Liver metastasis	
Yes/no/unknown	11/14/3
ABCG2 421C>A	
C/C	13
C/A	11
A/A	4
SLCO1B1 388 A>G	
A/A	9
A/G	12
G/G	7
SLCO1B1 521 T>C	
T/T	25
C/T	3
SLCO1B1 haplotype	
*SLCO1B1*1b* (+)	18
*SLCO1B1*1b* (−)	10

Data are presented as the means ± standard deviation. SLCO1B1*1b (+) and *SLCO1B1*1b* (−) are defined as *SLCO1B1*1b* allele carrier and non-carrier, respectively

GIST gastrointestinal stromal tumor, *BSA* body surface area, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T.bil* total bilirubin, *SCr* serum creatinine, *eCcr* estimated creatinine clearance (Cockcroft–Gault)

[a]Colon cancer included one patient with appendiceal cancer

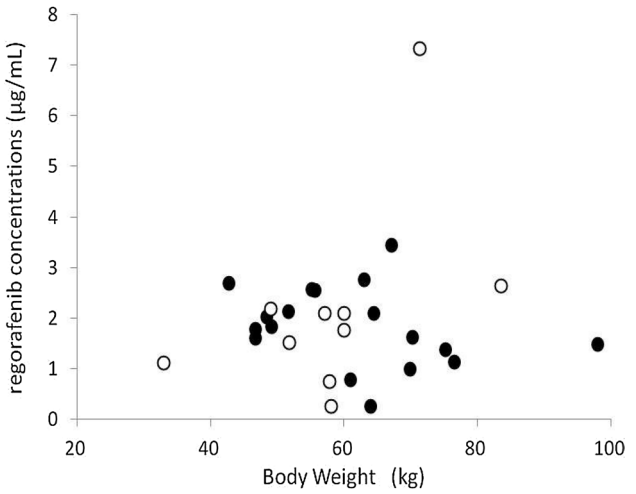

Fig. 1 Correlation between serum regorafenib concentrations and body weight. The plot presents correlation between serum regorafenib concentration and body weight in each patient; regorafenib 120 mg (open circle), 160 mg/kg (filled circle)

Table 2 Comparison of adverse events in cycle 1 and trough serum concentrations

Grade	*n*	Conc. (μg/mL)	*P* value
AST increased			
0, 1	24	1.78 (0.26–7.31)	0.64
≥ 2	4	2.09 (1.51–2.18)	
ALT increased			
0, 1	26	1.79 (1.51–2.09)	0.89
≥ 2	2	1.83 (0.26–7.31)	
Blood bilirubin increased			
0, 1	24	1.76 (0.26–2.77)	0.01
≥ 2	4	3.45 (2.18–7.31)	
Neutropenia			
0, 1	25	1.76 (0.26–7.31)	0.11
≥ 2	3	2.14 (2.12–3.45)	
Anemia			
0, 1	20	1.70 (0.26–7.31)	0.28
≥ 2	8	2.09 (1.11–3.45)	
Thrombocytopenia			
0, 1	25	1.76 (0.26–2.77)	0.02
≥ 2	3	3.45 (2.12–7.31)	
Hypertension			
0, 1	10	1.80 (0.26–7.31)	0.94
≥ 2	18	1.92 (0.28–3.45)	
Hand–foot skin reaction			
0, 1	11	2.04 (0.26–7.31)	0.61
≥ 2	17	1.76 (0.28–2.77)	
Anorexia			
0, 1	22	1.83 (0.27–7.31)	0.98
≥ 2	6	1.90 (0.26–2.70)	

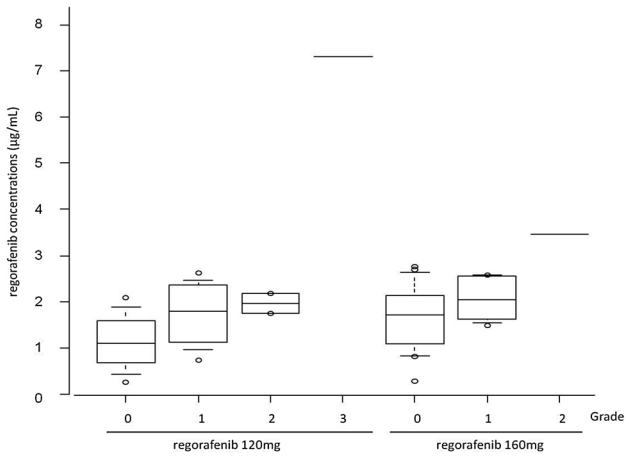

Fig. 2 Relationship between regorafenib concentrations and grade of total serum bilirubin increased at blood sampling point. The lines within the boxes represent the median values, the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively, and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. Grade = blood bilirubin increased

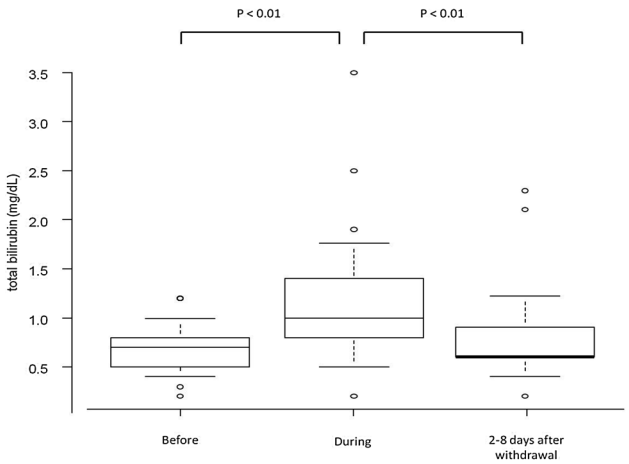

Fig. 3 Variation in total bilirubin by treatment with regorafenib. The lines within the boxes represent the median values, the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively, and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively

Discussion

In this study, we investigated the relationship between the pharmacokinetic properties of regorafenib and its associated adverse reactions as well as the factors influencing regorafenib pharmacokinetics using steady state trough values. Given that the half-life of regorafenib is approximately 20–30 h, serum concentration was considered to reach a steady state on and after day 7 of blood sampling

Table 3 Comparison of CDR in patient physical and genetic factors

	All patients (n = 28)		
	n	Conc. (ng/mL)/dose (mg)	*P* value
ABCG2 421C>A			
C/C	13	12.6 (1.73–60.9)	0.606
C/A	11	10.3 (2.17–21.5)	
A/A	4	16.7 (8.73–17.4)	
SLCO1B1 388 A>G			
A/A	9	13.4 (7.26–60.9)	0.641
A/G	12	11.1 (1.73–21.6)	
G/G	7	12.6 (5.06–21.9)	
SLCO1B1 521T>C			
T/T	25	11.5 (1.73–60.9)	0.167
C/T	3	17.3 (12.6–21.9)	
SLCO1B1 haplotype			
*SLCO1B1*1b* (+)	18	12.1 (1.73–21.9)	0.226
*SLCO1B1*1b* (−)	10	14.0 (7.26–60.9)	
BSA ($/m^2$)			
≤ 1.6	12	13.1 (9.23–18.2)	0.28
≧ 1.6	16	9.81 (1.73–60.9)	
ECOG-PS			
0	5	10.3 (6.17–60.9)	0.987
1	20	12.7 (1.73–21.9)	
2	3	13.4 (2.17–17.4)	
Age			
≤ 60	14	11.4 (1.73–60.9)	0.603
≧ 60	14	13.0 (2.17–21.9)	
Sex			
Male	19	10.3 (1.73–60.9)	0.223
Female	9	13.4 (9.23–21.5)	
CCr (mL/min)			
≤ 60	7	16.1 (11.3–60.9)	0.0418
≧ 60	21	10.3 (1.72–21.9)	

[9]. Therefore, trough serum concentration values were used to estimate in vivo exposure to regorafenib. Trough values in this study were similar to those recorded in previous clinical studies [10].

The present study results indicate that the serum regorafenib concentration is associated with grade 2 or higher thrombocytopenia. Thrombocytopenia was the primary hematological toxicity caused by regorafenib in prior large-scale clinical trials focusing on colon cancer [1]. A relationship between serum regorafenib concentration and thrombocytopenia was considered possible given the rate of change in platelet count during cycle 1 compared to the start of treatment.

Serum regorafenib concentrations in the group of patients who developed grade 2 or higher total bilirubin elevation during cycle 1 were significantly higher than those in other patient groups, and a statistically significant correlation with total bilirubin was observed in the same serum samples used to measure serum regorafenib concentrations. Indirect (unconjugated) bilirubin is produced in the reticuloendothelial system, is taken up by the liver via OATP1B1, and becomes direct (conjugated) bilirubin by glucuronic acid [11, 12]. Given that serum bilirubin levels are elevated as a competitive inhibition via OATP1B1 and that regorafenib inhibits the process of bilirubin uptake into the liver [13], bilirubin could be a useful indicator of a patient's exposure to regorafenib. Liver disorders involving elevated aspartate transaminase (AST)/alanine transaminase (ALT) and bilirubin values were reported as adverse reactions [14]. In this study, elevated total bilirubin was not related to elevated AST or ALT levels, and the increased total bilirubin following the administration of regorafenib returned rapidly to pretreatment levels after stopping administration. As such, this phenomenon may be distinct from cytotoxic liver injury. If total bilirubin increases as a result of competition with the OATP1B1 hepatic uptake process, then predominantly indirect bilirubin may also be increased. In contrast, it was reported that patients with Rotor syndrome, who are genetically deficient in OATP1B1 and OATP1B3, exhibit increased concentrations of indirect and direct bilirubin in plasma, because both indirect and direct bilirubin are transported by OATP1B1 [15]. In the nine patients whose direct bilirubin levels were measured in this study, indirect and direct bilirubin levels significantly increased from 0.5 (0.4–0.8) and 0.1 (0.1–0.4) before regorafenib administration to 0.8 (0.6–1.1) and 0.3 (0.1–0.7) after administration ($P = 0.009$ and 0.03), respectively. It was not possible to sufficiently examine this fluctuation for direct and indirect bilirubin levels associated with the interaction between regorafenib and bilirubin, because all cases of elevated bilirubin were lower than grade 2. Therefore, the detailed mechanism of competition between regorafenib and bilirubin with respect to OATP1B1 requires further evaluations.

Elevated serum concentrations of SN-38, an active irinotecan metabolite, and angiotensin receptor antagonist (ARB) have been reported in clinical trials [16] and by pharmaceutical companies as a result of pharmacokinetic interactions with regorafenib. The causes of these interactions are reported to be the inhibition of UDP-glucuronosyltransferase 1A1 and regorafenib's inhibition of the breast cancer resistance protein; however, there is a possibility of competitive inhibition via OATP1B1 as well, given SN-38 and ARB are also OATP1B1 substrates [17–20]. Further studies of the interactions between regorafenib and OATP1B1 are necessary.

Estimating serum concentrations and pharmacokinetics of regorafenib before administration was difficult. A correlation between patient body weight and serum regorafenib concentration was not detected, and serum concentrations may vary because of individual differences in clearance ability

and genetic factors rather than distribution. Although we investigated the influence on regorafenib concentrations of the pharmacokinetics of the polymorphisms ABCG2 and OATP1B1 among the transporters acting as substrates for regorafenib, we found no effect of the *ABCG2* gene polymorphism on serum regorafenib concentrations. However, serum regorafenib concentrations in patients who have *SLCO1B1* 521 T>C, which reduces OATP1B1's function, were found to be higher than in the T/T group, although no statistically significant difference was observed. On the other hand, the effect of the *SLCO1B1* gene polymorphism on the pharmacokinetics of oral drugs has a large impact on C_{max} [21–23]. As such, one should calculate the AUC and clearance when examining the pharmacokinetic effects of these gene polymorphisms, and further investigation of their influence is needed.

Serum concentrations in the patient group with creatinine clearance lower than 60 mL/min were significantly higher than those in patients with 60 mL/min or higher. Pharmaceutical companies report that kidney function does not influence regorafenib excretion; however, based on the present results, further data on regorafenib pharmacokinetics in patients with low renal function are needed.

Conclusion

Regorafenib concentrations were significantly higher in the groups with grade 2 or higher total bilirubin elevation and thrombocytopenia. Total serum bilirubin has validated the relationship with trough serum concentrations of regorafenib and could be a useful marker in estimating the regorafenib pharmacokinetics. This usefulness will be validated by further investigations of regorafenib and a detailed analysis of its pharmacokinetics. On the other hand, genetic factors affecting the pharmacokinetics of regorafenib could not be clarified.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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