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Regorafenib-Induced Hand–Foot Skin Reaction Is More Severe on the Feet Than on the Hands

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Regorafenib is a multikinase inhibitor for the treatment of metastatic colorectal cancer. Regorafenib-induced hand–foot skin reaction (HFSR) is a common side effect during treatment. The reported frequency of HFSR was 80% (grade 3: 28%) in the Japanese subpopulation in the CORRECT trial; however, more detailed data regarding HFSR in terms of onset and sites of susceptibility are unclear. Additionally, the risk factors for regorafenib-induced severe HFSR are unknown. The aim of this study was to compare HFSR between the hands and feet and identify preexisting risk factors for severe HFSR in Japanese patients receiving regorafenib. We retrospectively examined the onset and severity of HFSR on the hands and feet of patients with metastatic colorectal cancer treated with regorafenib from May 2013 to October 2015 in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. In addition, we examined the possible association between preexisting clinical factors and severe HFSR. Our results showed that no significant difference in the incidence of HFSR of any grade was observed between the hands (71%) and feet (74%) ($p = 0.63$). The incidence of grade 3 HFSR was more frequent on the feet (33%) than on the hands (8%) ($p < 0.01$). The onset of grade 3 HFSR was earlier on the feet than on the hands ($p < 0.001$). No preexisting risk factor was identified. Our findings indicate that severe HFSR was more prevalent on the feet than on the hands, suggesting the need for appropriate screening for early detection and treatment of regorafenib-induced HSFR.

Key words: Regorafenib; Hand–foot skin reaction (HFSR); Pharmaceutical outpatient clinic; Risk factors

INTRODUCTION

Regorafenib is an orally administered multikinase inhibitor that targets the activity of several protein kinases that are associated with tumor angiogenesis [i.e., vascular endothelial growth factor receptors 1 to 3 (VEGFR1 to 3) and tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domain-2] and oncogenesis [i.e., platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor, proto-oncogene tyrosine protein kinase, rearranged during transfection receptor tyrosine kinase, rapidly accelerating fibrosarcoma proto-oncogene serine–threonine protein kinase, and v-raf murine sarcoma viral oncogene homolog B1][1]. The CORRECT trial demonstrated that, compared with placebo, regorafenib prolonged overall survival and progression-free survival in patients with metastatic colorectal cancer (mCRC)[2]. Hand–foot skin reaction (HFSR) is the most common adverse event of regorafenib. In the CORRECT trial, the incidence of HFSR of any grade was 47% (233/500 patients), and that of grade 3 was 17% (83/500 patients)[2]. Moreover, in a subanalysis of the CORRECT trial, the frequency of HFSR was higher in the Japanese subpopulation (all grades = 80%, grade 3 = 28%) than in the non-Japanese (all grades = 42%, grade 3 = 15%). These findings suggested the presence of an ethnic difference in the incidence of HFSR[3]. The incidence of HFSR caused by multikinase inhibitors has been indicated by various clinical trials. However,

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detailed data such as the sites of susceptibility of each inhibitor-induced HFSR have not been analyzed.

Severe HFSR impairs quality of life and leads to interruption and/or discontinuation of regorafenib. Therefore, a more detailed understanding of regorafenib-induced HFSR and the ability to predict its occurrence would be useful for the management of patients undergoing regorafenib treatment. Previous studies using sunitinib and capecitabine clarified that the risk factors for development of treatment adverse effects were anemia, female sex, renal dysfunction, and diabetes for capecitabine and low Eastern Cooperative Oncology Group (ECOG) performance status (PS) and liver metastasis for sunitinib[4–7]. However, these risk factors have not been evaluated in Japanese patients receiving regorafenib.

In this study, we examined the onset and severity of regorafenib-induced HFSR in Japanese patients with mCRC. Moreover, the preexisting risk factors for regorafenib-induced severe HFSR were evaluated to promote a more effective and safer management of regorafenib treatment.

MATERIALS AND METHODS

Pharmaceutical Outpatient Clinic

In the Pharmaceutical Outpatient Clinic (POC) of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR), patients undergo proactive intervention by pharmacists before examination by physicians[8]. In particular, the pharmacists play two important roles of confirmation and suggestion. Confirmation involves checking the patients' adherence and grading the side effects of medications. Suggestion involves proposing to physicians through the electronic medical records the most effective prescription for supportive pharmacotherapy, the timing of the next dose, and administration period (Fig. 1).

Study Design and Treatment

In this study, Japanese patients with mCRC who received regorafenib at the Cancer Institute Hospital of JFCR between May 2013 and October 2015 were included. Patients who were not treated in the POC were excluded from this study. Informed consent was obtained from all participants. In principle, the patients initially received regorafenib (Bayer, Leverkusen, Germany) at 160 mg once daily for the first 3 weeks of each 4-week cycle, along with a prescription of heparinoid cream as moisturizer and clobetasol propionate ointment to suppress HFSR-induced inflammation.

Data Collection

Using the pharmacists' records, the incidence and grade of HFSR, dose of regorafenib, and baseline clinical factors were collected separately for the hands and feet and were evaluated as possible preexisting risk factors for

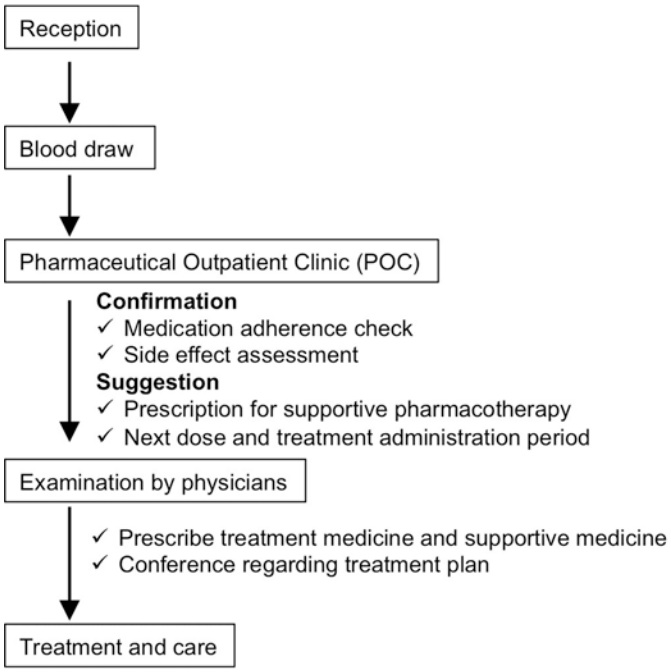

Figure 1. Outline of the pharmaceutical outpatient clinic.

severe HFSR. The grade of HFSR was determined by the pharmacists according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The pharmacists checked the condition of the HFSR every week during the first treatment cycle and every 1 to 2 weeks thereafter until discontinuation. This study was approved by the Clinical Research Ethics Review Committee of the Hospital (approval number: 2015-1123).

Statistical Analyses

Comparison of the incidence of HFSR between the hands and feet was performed with the chi-square test. The cumulative incidence of HFSR was evaluated using Kaplan–Meier analysis, and statistical significance was analyzed using the log-rank test. The risk factors for regorafenib-induced severe HFSR were assessed in two patient groups, which were classified based on the presence (i.e., moderate to severe or grade 2 HFSR) and absence (i.e., none or grade 1 HFSR) of exacerbation of HFSR. Univariate analysis was then performed using the patients' clinical factors and blood examination findings as the explanatory variables and grade 2 HFSR exacerbation as the objective variable. The resulting significant variables were then entered into a multivariate analysis. The significance levels for the univariate and multivariate analyses were $p<0.2$ and $p<0.05$, respectively. Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 98 patients were eligible for this study (Table 1). The study included 51 men and 47 women, with an overall median age of 62.5 years (range, 34–83 years). The ECOG PS was 0 in 58 patients (59%) and 1 in 40 patients (41%). A total of 17 (17%) and 19 (19%) patients had a history of grade 2 HFSR and diabetes, respectively, before regorafenib treatment. The median number of treatment cycles was 2 (range, 0–25).

Separate analyses of the hands and feet showed that HFSR of any grade occurred on the hands in 71% and on the feet in 74%, whereas grade 3 HFSR occurred on the hands in 8% and on the feet in 33% (Fig. 2). Grade 3 HFSR occurred more frequently on the feet than on the hands ($p<0.01$). In the first cycle of regorafenib treatment, the onset of grade 3 HFSR was significantly earlier on the feet than on the hands ($p<0.001$) (Fig. 3). Moreover, the median period for development of HFSR of any grade was 7 days (range, 1–84 days) and 14 days (range, 1–112 days) for the hands and 10 days (range, 1–96 days) for the feet; that for grade 3 HFSR was 15 days (range, 3–423 days) and 17 days (range, 11–116 days) for the hands and 15 days (range, 3–423 days) for the feet.

Table 1. Baseline Patient Characteristics ($n=98$)

Characteristics	*n*
Age, years	
Median	63
Range	34–83
Sex	
Male	51 (52.0%)
Female	47 (48.0%)
ECOG performance status	
0	58 (59.2%)
1	40 (40.8%)
Primary tumor site	
Colon	63 (64.3%)
Rectum	30 (30.6%)
Appendix	2 (2.0%)
Cecum	3 (3.1%)
Body mass index	
<25 kg/m^2	80 (81.6%)
25 kg/m^2	18 (18.4%)
Liver metastasis	
Yes	71 (72.4%)
No	27 (27.6%)
History of diabetes	
Yes	19 (19.4%)
No	79 (80.6%)
Creatinine clearance rate	
<60 ml/min	11 (11.2%)
60 ml/min	87 (88.8%)
Albumin level	
<3 g/dl	4 (4.1%)
3 g/dl	94 (95.9%)
Aspartate aminotransferase level	
<30 IU/L	48 (49.0%)
30 IU/L	50 (51.0%)
Alanine aminotransferase level	
<30 IU/L	75 (76.5%)
30 IU/L	23 (23.5%)
Prior grade 2 HFSR	
Yes	17 (17.3%)
No	74 (75.5%)
Unknown	7 (7.1%)
Median treatment cycles [*n* (range)]	2 (0–25)

HFSR, hand–foot skin reaction; ECOG, Eastern Cooperative Oncology Group.

The univariate analysis revealed the presence of liver metastasis, creatinine clearance of <60 ml/min, hemoglobin level of <10 g/dl, and aspartate aminotransferase level of 30 IU/L as possible risk factors for grade 2 HFSR within the first cycle of regorafenib treatment. However, these four variables were not independent risk factors for severe HFSR in the multivariate analysis (Table 2).

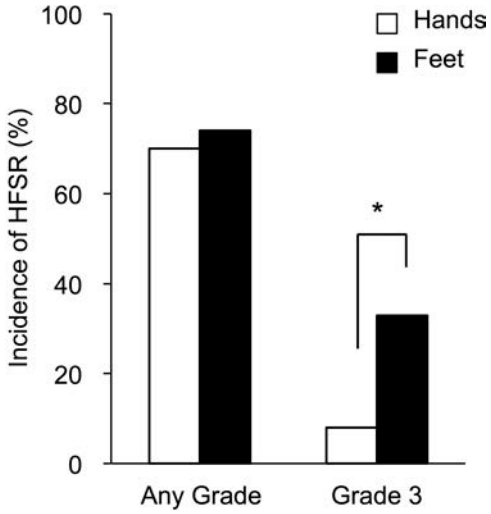

Figure 2. Incidence of hand–foot skin reaction (HFSR) in patients within the entire cycle of regorafenib treatment. The incidence of any grade or grade 3 HFSR was separately assessed on the hands and feet. *$p < 0.01$.

DISCUSSION

Our results indicated that Japanese patients are likely to develop regorafenib-induced HFSR, in agreement with the findings of the CONCUR and the CORRECT trials. In addition, we observed that severe HFSR was more prevalent on the feet than on the hands. In the CONCUR trial, the incidence of HFSR in Asian patients was higher than that in non-Asian patients[9]. In the CORRECT trial, HFSR occurred more frequently in the Japanese subpopulation than in the non-Japanese subpopulation[3]. Additionally, Asian patients were likely to develop HFSR with sunitinib or sorafenib, which are multikinase inhibitors similar to regorafenib[10,11]. However, the reasons for these ethnic differences were not clear. Nevertheless, our results implied that Japanese patients undergoing regorafenib treatment must be monitored for the development of side effects, including HFSR.

Compared with the CORRECT trial in which follow-up was performed every 2 weeks, this study, which performed follow-up every week at the POC, allowed earlier identification of the patients' symptoms. Our results showed that HFSR on the feet became severe within the first cycle of regorafenib treatment and that early observation of symptoms at the POC was important to prevent HFSR exacerbation. Moreover, a positive correlation between HFSR and better survival has been reported[12]. We propose that pharmacists should observe for development of symptoms every week in order to allow modification of the regorafenib dose and prescription of supportive medicines as necessary.

HFSR is a skin disorder that can develop with the use of multikinase inhibitors. Regorafenib inhibits various

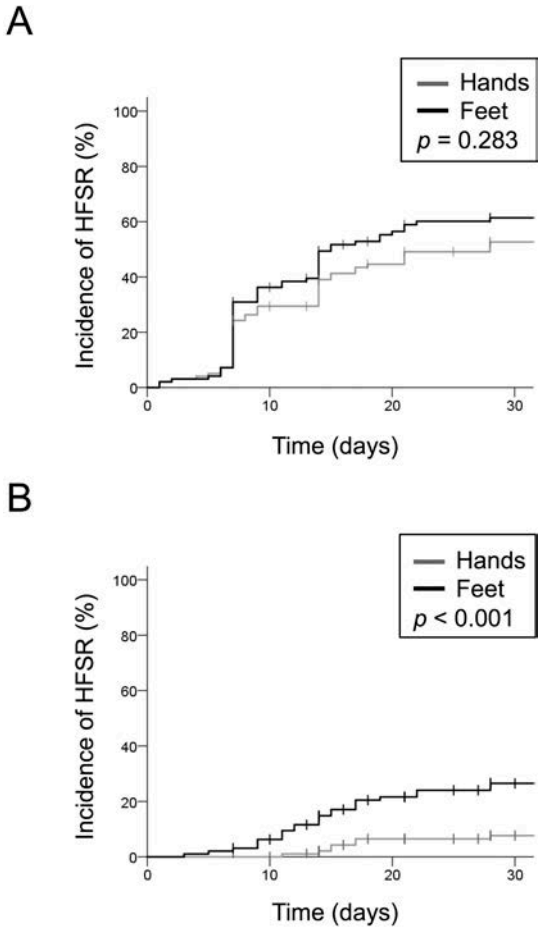

Figure 3. Onset of HFSR in patients within the first cycle of regorafenib treatment. The onset of (A) any grade and (B) grade 3 HFSR is indicated.

kinases, such as EGFR, which is present in the epidermal basal layer of normal skin and is known to be involved in the proliferation and differentiation of keratinocytes. Inhibition of EGFR signaling induces apoptosis in keratinocytes[13]. Furthermore, among the multikinase inhibitors, sorafenib was reported to have a higher incidence of HFSR than sunitinib[14]. This difference in the incidence of HFSR is considered to be affected by the presence or absence of Raf kinase inhibition. Raf is located downstream of EGFR in the signaling pathway. Moreover, several genes that are associated with cell proliferation are located downstream of Raf. Therefore, Raf kinase inhibitors increase not only tumor suppression but also the expression of HFSR. Aside from EGFR, VEGFR and PDGFR are associated with the onset of HFSR. VEGFR and PDGFR are involved in endothelial cell survival[15]; their inhibition reduces the density of capillary vessels and diminishes the epithelial cell repair function. Therefore, combined inhibition of these receptors enhances the development of HFSR[16]. In fact, one study showed that the incidence of

Table 2. Risk Factors for Exacerbation of HFSR

	Univariate Analysis		Multivariate Analysis	
Factors	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (<65 years)	1.58 (0.70–3.56)	0.261		
Sex (female)	0.83 (0.37–1.85)	0.654		
ECOG performance status (0)	1.40 (0.61–3.16)	0.418		
Body mass index (25 kg/m^2)	0.74 (0.26–2.10)	0.571		
Liver metastasis (yes)	0.55 (0.22–1.35)	0.191	0.61 (0.23–1.59)	0.311
History of diabetes (yes)	0.66 (0.23–1.85)	0.432		
Creatinine clearance rate (<60 ml/min)	0.23 (0.04–1.16)	0.055	0.28 (0.05–1.44)	0.128
Albumin level (<3 g/dl)	1.23 (0.16–9.16)	0.610		
Hemoglobin level (<10 g/dl)	0.32 (0.06–1.62)	0.139	0.39 (0.07–2.18)	0.283
Aspartate aminotransferase level (30 IU/L)	0.56 (0.25–1.26)	0.161	0.61 (0.26–1.43)	0.256
Alanine aminotransferase level (30 IU/L)	0.57 (0.21–1.52)	0.265		
Prior grade 2 HFSR	1.97 (0.68–5.71)	0.204		

OR, odds ratio; CI, confidence interval; HFSR, hand–foot skin reaction; ECOG, Eastern Cooperative Oncology Group.

HFSR was higher in patients treated with a combination of the VEGFR inhibitor bevacizumab and sorafenib than in patients treated with sorafenib alone[6]. A previous meta-analysis showed that the incidence of HFSR induced by sorafenib and regorafenib was 34% and 61%, respectively[17]. All of these findings indicated that regorafenib was an effective agent in cancer treatment, but had a high incidence of side effects, including HFSR. Moreover, from the viewpoint of the mechanism of inhibition, it is considered that not only regorafenib but also other multikinase inhibitor-induced HFSR may be more likely to become severe on the foot than on the hand. Consequently, medication counseling by the pharmacist is important.

In this study, we showed that HFSR was more severe on the feet than on the hands. However, one report indicated worsening of symptoms on the fingertip with the use of a mobile phone[18]. Therefore, the incidence and exacerbation of HFSR on the feet may be affected by physical stimulation, such as working[19]. A previous study showed that body mass index and body surface area were not associated with the incidence of HFSR[3]. On the other hand, young age, female sex, anemia, hypoalbuminemia, renal dysfunction, and liver metastasis were reported as possible risk factors for HFSR in patients treated with capecitabine and sorafenib[4–7]. However, in this study, we did not identify these factors to significantly predispose to HFSR, probably because the study was underpowered.

There were three major limitations of our study. The first was the small number of patients ($n = 98$) enrolled in our study, which might have caused us to overlook some risk factors for HFSR because of the insufficient statistical power. Another study with a larger number of patients should be performed to overcome this issue[20]. The second limitation was the patients' background. Some patients who developed severe HFSR on the hands might have used their hands frequently, such as when playing the piano. Therefore, future studies need to take into account the patients' lifestyles and occupations in order to come up with more definitive statements regarding this point. The third limitation was the evaluation point. It is impossible to evaluate the impact of HFSR in patient's quality of life in this study. Our study focused on the onset of regorafenib-induced HFSR, and whether there would be any differences in susceptibility of regorafenib-induced HFSR by site, hand or foot. Therefore, we did not consider the impact of HFSR on patient's quality of life. In addition, we did not plan to include the compliance/adherence for heparinoid cream and clobetasol as suppression of inflammation by HFSR. Therefore, we were unable to examine the preventive effect of these drugs on HFSR.

In conclusion, the incidence of regorafenib-induced HFSR was 81%, with grade 3 HFSR being more frequent and occurring earlier on the feet than on the hands.

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