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Effectiveness of Topical Steroid Therapy for Prevention of Regorafenib-associated Hand-foot Skin Reaction

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Abstract

Introduction: Hand-foot Skin Reaction (HFSR) often hinders completion of Regorafenib therapy. No established prophylaxis exists against multikinase inhibitor-associated HFSR and further improvement of prophylaxis for HFSR is needed. Therefore, we offer multiagent therapy to prevent Regorafenib-associated HFSR comprising topical steroid (0.05% difluprednate) ointment and 20% urea-based cream.

Methods: Subjects were unresectable or recurrent colorectal cancer patients who started Regorafenib therapy between May 2013 and March 2014 at the Shizuoka Cancer Center. Electronic medical records were retrospectively examined for HFSR incidence, CTCAE v3.0 grade of severest HFSR, time of HFSR onset, rate of therapy termination, delay and dose reduction.

Results: Subjects were 55 patients and median treatment time 7.1 weeks. Overall and grade 3 HFSR incidence rate in this study (73 and 22%, respectively) was lower than in the CORRECT study Japanese subpopulation (80 and 28%, respectively). HFSR (grade ≥ 2) occurred in the first cycle or later in 42 and 11% of patients, respectively. HFSR accounted for 33 and 61% of first-cycle Regorafenib delay and dose reductions, respectively, and HFSR accounted for 40 and 53% in any cycle, respectively.

Conclusion: Effectiveness of prophylactic topical steroids against Regorafenib-associated HFSR was shown in this study. Therefore, this prophylaxis is applicable in clinical settings.

Keywords: Regorafenib; Hand-Foot Skin Reaction (HFSR); Multikinase inhibitors; Topical steroids; Prophylaxis

Introduction

Regorafenib is the world's first multikinase inhibitor with confirmed efficacy in patients with metastatic colorectal cancer. In the international, phase III, randomized, double-blind CORRECT trial, Regorafenib significantly prolonged Overall Survival (OS) versus placebo in patients with metastatic colorectal cancer that had progressed after all approved standard therapies [1,2]. One of the most common adverse events associated with Regorafenib is Hand-foot Skin Reaction (HFSR). In the CORRECT study, HFSR occurred at a rate of 44.6% overall and 16.6% at grade 3[2], and showed higher proportions (80 and 27.7%, respectively) in the Japanese subpopulation [3]. HFSR is not life-threatening adverse event, but may cause considerable deterioration of patients' Quality of Life (QOL), resulting in discontinuation of treatment. Therefore, adequate management for Regorafenib-induced HFSR is needed in order to continue treatment in safe.

The underlying mechanisms how Tyrosine Kinase Inhibitors (TKIs) cause HFSR remain unclear, but are suspected to be related to combined inhibition of several receptors such as vascular endothelial growth factor receptors and platelet-derived growth factor receptors [4]. Although HFSR is also caused by other TKIs, such as Sorafenib, Sunitinib, Axitinib, Pazopanib and Lenvatinib, the incidence rate of Regorafenib-induced HFSR seems to be higher than that of other TKIs especially for a Japanese population. HFSR associated with TKIs occurs earlier compared with cytotoxic anticancer agents (fluoropyrimidines or taxanes). Patients with TKIs-associated HFSR often present with erythema, swelling, bullae, and hyperkeratosis, especially in pressure-bearing skin surface such as plams or soles [3-11]. Although there are no established therapeutic options available for TKIs-associated HFSR, it has recommended that pressure bearing should be avoided in daily life [4]. Maintaining moisture in affected skin surface is crucial, and prophylactic use of a urea-based cream is recommended in TKIs therapy [12,13]. However, despite the prophylactic use of moisturizing agents, HFSR occurred in a considerable proportion of patients in the CORRECT study [2]. Therefore further improvement of prophylaxis for HFSR is needed.

In general, topical steroid in addition to a urea-based preparation is recommended to use for grade 2 HFSR associated with TKIs. Histologic findings in this reaction showed inflammatory cells infiltration within the epidermis, topical steroid is considered an effective treatment to prevent from exacerbation of HFSR [14,15]. Therefore we have used topical steroid ointment and urea-based cream from the beginning of Regorafenib therapy for further improvement of HFSR compared with the start of steroid from getting worse of HFSR.

In this study, we retrospectively evaluated the effectiveness of this prophylactic therapy against HFSR in patients with colorectal cancer who had started Regorafenib therapy.

Methods

Patient

Subjects were unresectable or recurrent colorectal cancer patients who started regorafenib therapy between May 2013 and March 2014 at the Shizuoka Cancer Center. The patients with contraindications to topical steroids, such as ringworm, were excluded. And the patients who didn't use topical steroids when the Regorafenib therapy started were excluded. This study was approved by the institutional review committee of the Shizuoka Cancer Center (Shizuoka, Japan) and met the standards set forth in the Declaration of Helsinki. Written informed consent was obtained from all patients in this study.

Treatment

From the beginning of Regorafenib therapy, 20% urea-based cream and topical steroid (0.05% difluprednate) ointment were applied to palms and sole both in the morning and evening. The patients received 160 mg of Regorafenib once daily for the first 21 days of each 28 day cycle. Dose reduction of Regorafenib was adapted at grade 2 HFSR and administration was temporarily discontinued at grade 3 HFSR.

Evaluation

The following parameters were retrospectively investigated using electronic medical records: HFSR incidence rate, HFSR severity (most severe grade), time of HFSR onset, completion rate of Regorafenib therapy (without delay and dose reduction), the relative dose intensity (RDI: delivered total dose for 28 days/160 mg × 21 days × 100) in the first cycle, rate of and reasons for termination and delay of therapy and dose reduction in the first cycle and in any cycle, and overall median duration of treatment (weeks). Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results

Sixty patients were treated with Regorafenib for colorectal cancer at the Shizuoka Cancer Center between May 2013 and March 2014. Of these, five patients were excluded from this study for the following reasons: No use of topical steroid from the beginning of Regorafenib therapy (n=3) and foot ringworm (n=2). Baseline characteristics are shown in Table 1.

n=55	
Median age (range)	64(38-78)
Sex (male/female)	36/19
PS* (0/1/2/3)	21/34/0/0
KRAS status (wild type/mutant/not examined)	32/22/1
Primary lesions (colon/rectum)	31/24
Primary lesion removal (yes/no)	39/16
Median number of prior regimens (range)	3(1-6)
*Eastern Cooperative Oncology Group Performance Status	

Table 1: Patient characteristics.

The incident rates of HFSR were 73% in any grade and 22% in grade 3, respectively (Table 2). The cumulative incidence of ≥ grade 2 HFSR was 42% during the first cycle and was 11% during the second and subsequent cycle, respectively (Figure 1).

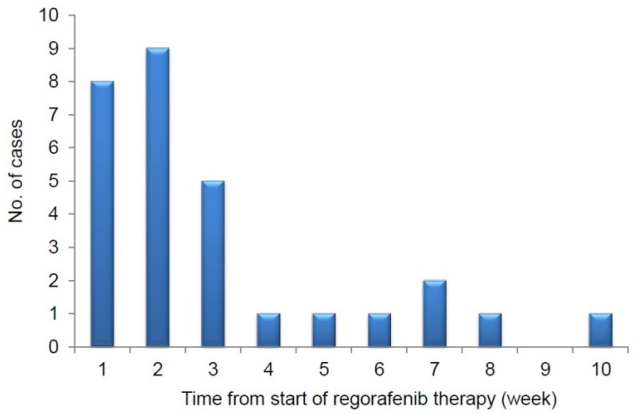

Figure 1: Time of the first onset of HFSR (≥ grade 2).

Median treatment time was 7.1 weeks. Main adverse events except for HFSR were anorexia (47%), fatigue (47%), thrombocytopenia (45%), hoarseness (44%), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increased (40%) and hypertension (33%) (Table 2). Topical steroid ointment with urea-based cream did not cause any adverse events in all 55 patients.

Adverse events	Any Grade	Grade ≥ 3
HFSR	73%	22%
Anorexia	47%	2%
Fatigue	47%	2%
Thrombocytopenia	45%	4%
Hoarseness	44%	0%
AST/ALT	40%	7%
Hypertension	33%	2%
Proteinuria	27%	5%
Rash	15%	2%
Nausea	15%	0%
Diarrhoea	13%	0%
Anaemia	7%	2%
Leukopenia	5%	0%
Neutropenia	4%	0%
CTCAE v3.0		

Table 2: Adverse events.

Eleven patients (20%) received Regorafenib without delay and dose reduction in the first cycle (RDI was 72%). Eighteen patients (33%) were delayed and 34 patients (61%) were reduced Regorafenib due to HFSR in the first cycle (Table 3). Twenty two (40%) were delayed and 29 patients (53%) were reduced Regorafenib due to HFSR during the all cycles. Four patients were discontinued due to AST/ALT increased (n=1), anorexia (n=1), fatigue (n=1), or proteinuria (n=1). There was no patient who discontinued Regorafenib due to HFSR.

Therapy completion rate†			20%		
Relative dose intensity (RDI)‡			72%		
*Duration of first cycle: 28 days					
†Therapy completion rate: Rate of cases without delay and dose reduction					
‡RDI: Delivered total dose for 28 days/160 mg × 21 days × 100					
Delay			Dose reduction		
Rate	76% (42/55)		Rate	38% (21/55)	
Reasons	HFSR	33%	Reasons	HFSR	61%
	Proteinuria	20%		Proteinuria	14%
	Fever	13%		Rash	11%
	Fatigue	9%		Anorexia	8%
	Thrombocytopenia	9%		Fatigue	8%

Table 3: Treatment compliance (During the first cycle*).

Discussion

Regorafenib-associated HFSR occurred early in a considerable proportion of patients and we investigated the prophylactic effect of the topical steroid from the beginning of the Regorafenib therapy. We showed the incident rates of overall HFSR (73% vs. 80% for the CORRECT study in the Japanese sub-population and this study, respectively) [3]. Especially grade 3 HFSR was apparently lower (22% vs 28%, respectively). There was no patient who discontinued Regorafenib due to HFSR. Furthermore, we did not find any adverse events related to use of topical steroid.

In general, it is recommended to apply a steroid at the time of HFSR appearances more than grade 2. However, the HFSR incidence rate was markedly higher in the first cycle of Regorafenib than in the second and subsequent cycle (Figure 1), suggesting a crucial role of early prophylaxis. Therefore, starting a twice-daily prophylactic regimen using a topical steroid ointment and a urea-based cream at the beginning of Regorafenib therapy might be effective. Moreover, HFSR was a major cause of delay and dose reduction of Regorafenib, suggesting that adequate control of HFSR considerably influences compliance of Regorafenib therapy, patients' QOL and survival. Therefore, this preventive method could have a major impact on patients who receive Regorafenib therapy.

Conclusion

In conclusion, the use of a topical steroid is a viable option in actual clinical settings. Although this study has limitations, such as a small number of patients, use of retrospective data and performance at a single center, this is the first report to evaluate the efficacy of topical steroid ointment and a urea-based cream in patients with colorectal cancer who received Regorafnib therapy. Therefore, our observations should be confirmed with a prospective investigation.

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