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Analysis of drug-induced hand–foot syndrome using a spontaneous reporting system database

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Abstract

Purpose: The aim of our study was to assess the clinical features of hand–foot syndrome (HFS) associated with certain systemic chemotherapeutic drugs in a real-world setting using the Japanese Adverse Drug Event Report (JADER) database.

Methods: HFS was defined using the preferred terms from the Medical Dictionary for Regulatory Activities. We used several indices, such as the reporting odds ratios (RORs) at 95% confidence interval (CI), the time-to-onset profile of HFS, and cluster analysis.

Results: Of 646,779 reports (submission period: April 2004 to September 2020), 1814 reported HFS events. The RORs (95% CI) for axitinib, capecitabine, lapatinib, regorafenib, sorafenib, and sunitinib were 14.9 (11.1–20.1), 54.6 (49.2–60.6), 130.4 (110.7–153.6), 63.3 (55.2–72.6), 29.0 (25.8–32.7), and 13.9 (11.7–16.5), respectively. The analysis of time-to-onset profiles revealed that the median values (interquartile range: 25.0–75.0%) of drug-induced HFS caused by capecitabine, cisplatin, docetaxel, everolimus, regorafenib, sorafenib, and trastuzumab were 21.0 (13.0–42.0), 15.0 (10.0–82.0), 6.0 (3.0–25.0), 86.5 (67.0–90.5), 9.0 (6.0–14.0), 9.0 (6.0–14.0), and 70.0 (15.0–189.0) days, respectively. The number of clusters was set to 4. Among these, one cluster, which included capecitabine, regorafenib, and lapatinib, exhibited a higher reporting ratio and ROR of drug-induced HFS than other drugs.

Conclusions: The RORs and results of time-to-onset analysis obtained in this study indicated the potential risk of HFS associated with chemotherapeutic drugs. Our results suggest that health care professionals must be aware of the potential onset of drug-induced HFS with docetaxel, regorafenib, and sorafenib for at least 4 weeks; therefore, careful observation is recommended.

Plain Language Summary

Elucidation of the relationship between cancer drugs and risk of hand–foot syndrome

Purpose: Hand–foot syndrome (HFS) is an adverse effect of some cancer drugs, which is characterized by symptoms such as redness, swelling, blistering, and pain in the area of palms and soles. HFS reduces the quality of life of patients and can sometimes interfere with anticancer treatment plans. It is important to understand the clinical manifestations of HFS and gain knowledge that will allow for early intervention by clinicians.

Methods: In this study, we used a large-scale side effect database of real-world cases for a comprehensive investigation of anticancer-drug-induced HFS. The database contained 646,779 adverse event reports from April 2004 to September 2020; among which, we identified 1814 HFS events. Using these data, we could obtain information on the relationship between 19 types of anticancer drugs and HFS, and the onset time of HFS and HFS prognosis related to each anticancer drug.

Results: Our results suggest that clinicians should monitor the risk of HFS with docetaxel, regorafenib, and sorafenib for at least the first 4 weeks after drug administration.

Conclusion: These findings are crucial for improving the management of the adverse effects caused by anticancer drugs.

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Introduction

Hand–foot syndrome (HFS) is a localized cutaneous adverse event (AE) caused by certain systemic chemotherapeutic drugs and is characterized by erythema, dysesthesia, pain, cracking, and desquamation on the palms and soles.[1–4] Many anticancer drugs such as capecitabine, fluorouracil, pegylated liposomal doxorubicin, and tyrosine kinase inhibitors are known to cause HFS.[4–9] Fluoropyrimidines and kinase inhibitors cause different initial skin findings and symptoms, and the onset time is different for each drug.[4,10] However, the detailed mechanism underlying drug-induced HFS (DIHFS) remains unclear.[4,11]

The tendency to develop AEs in actual clinical practice does not always correspond to that in clinical trials due to the complexity of the patients' characteristics. It is important to investigate the occurrence of AEs in clinical practice; clinical databases are useful resources for such an assessment. The Pharmaceuticals and Medical Devices Agency (PMDA), a major Japanese regulatory authority, collects data on AEs of pharmaceutical products reported after they are launched in Japan. Since 2004, the continuous operation of the Japanese Adverse Drug Event Report (JADER) database has created a large spontaneous reporting system (SRS) for data collection. The JADER is the largest publicly available database that reflects clinical practice in Japan.

Although DIHFS induced by anticancer drugs is not life-threatening, it can cause therapeutic modifications or even treatment discontinuation because of its dose-limiting toxicity and interference with the patient's daily activities and quality of life.[2,3] Therefore, it is important to detect abnormalities in the skin of limbs at an early stage and take immediate and appropriate measures during chemotherapy.

The time-to-onset profile of DIHFS remains unclear in actual clinical practice. The aim of this study was to assess the incidence and detailed onset profile of DIHFS by analyzing data from the JADER database. Furthermore, we revealed the patients' prognoses and classified drugs based on AE profiles using cluster analysis.

Materials and methods

Data source

Data regarding AE reports were collected and fully anonymized by the PMDA to form the JADER database. AE reports recorded in the database were downloaded from the PMDA website (www.pmda.go.jp). We assessed the database for reports submitted between April 2004 and September 2020. The structure of the database complies with international safety reporting guidelines [International Council on Harmonization (ICH) E2B]. It consists of four tables: patient demographic information such as sex, age, and height (DEMO), drug information (DRUG), AEs (REAC), and medical history and primary illness (HIST).

The DRUG table describes the presumed degree of involvement of a drug in AEs as follows: 'suspected drug', 'concomitant drug', or 'interacting drug'. In this retrospective pharmacovigilance study, data on 'suspected drugs' were extracted and analyzed. We integrated a relational database based on the four tables using FileMaker Pro 18 Advanced software (FileMaker, Inc. Santa Clara, CA, USA).

Definition of AE and drug selection

The AEs in the JADER database were defined as codes according to the terminology used in the Medical Dictionary for Regulatory Activities/Japanese version 21.0 (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php). We used the following preferred term (PT) for HFS: palmar-plantar erythrodysesthesia syndrome (PT code: 10033553).

In this study, we investigated 19 chemotherapeutic drugs with more than 10 reports of HFS cases in the JADER database. We used the Anatomical Therapeutic Chemical (ATC) Classification System described by the World

Table 1. Number of case, reporting ratio, and reporting odds ratio of hand–foot syndrome.

Drug classification (ATC code)	Drug name	Total	Cases	Noncases	Reporting Ratio (%)	Reporting Odds Ratio (95% confidence interval)
	Total	646,779	1814	644,965	0.3	
Pyrimidine analogues (L01BC)	Capecitabine	5576	545	5031	9.8	54.6 (49.2–60.6)
	Fluorouracil	16,989	36	16,953	0.2	0.8 (0.5–1.04)
	Tegafur–Gimeracil–Oteracil	9057	23	9034	0.3	0.9 (0.6–1.4)
	Tegafur–Uracil	2178	32	2146	1.5	5.4 (3.8–7.7)
Taxanes (L01CD)	Docetaxel	9455	55	9400	0.6	2.1 (1.6–2.8)
	Paclitaxel	12,092	10	12,082	0.1	0.3 (0.2–0.5)
Anthracyclines and related substances (L01DB)	Doxorubicin	7244	138	7106	1.9	7.4 (6.2–8.8)
Platinum compounds (L01XA)	Cisplatin	12,778	25	12,753	0.2	0.7 (0.5–1.03)
	Oxaliplatin	12,308	23	12,285	0.2	0.7 (0.4–0.998)
Monoclonal antibodies (L01XC)	Bevacizumab	13,669	60	13,609	0.4	1.6 (1.2–2.1)
	Trastuzumab	4105	23	4082	0.6	2.0 (1.3–3.1)
Protein kinase inhibitors (L01XE)	Axitinib	1167	46	1121	3.9	14.9 (11.1–20.1)
	Everolimus	4529	11	4518	0.2	0.9 (0.5–1.6)
	Lapatinib	848	208	640	24.5	130.4 (110.7–153.6)
	Lenvatinib	1905	22	1883	1.2	4.2 (2.8–6.4)
	Pazopanib	1865	31	1834	1.7	6.1 (4.3–8.7)
	Regorafenib	2072	273	1799	13.2	63.3 (55.2–72.6)
	Sorafenib	5893	364	5529	6.2	29.0 (25.8–32.7)
	Sunitinib	4309	150	4159	3.5	13.9 (11.7–16.5)

ATC, Anatomical Therapeutic Chemical Classification System.

Health Organization Collaborating Center for Drug Statistics Methodology (www.whocc.no/atc_ddd_index/) for defining these drugs. Nineteen drugs were linked to the corresponding ATC classification codes and categorized into six ATC-drug classes (Table 1).

Statistical analysis

To ascertain AE signals, we calculated the reporting odds ratio (RORs), which was established using a disproportionality analysis (Figure 1).[12,13] If the lower limit of the 95% confidence interval (CI) of the ROR was greater than one, the ROR was

	Adverse event of interest	All other adverse event of interest	Total
Drug of interest	a	b	a + b
All other drug of interest	c	d	c + d
Total	a + c	b + d	a + b + c + d

$$\text{Reporting Odds Ratio (ROR)} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$95\%\ \text{Confidence Interval (CI)} = e^{\ln(\text{ROR}) \pm 1.96\sqrt{1/a+1/b+1/c+1/d}}$$

Figure 1. Two-by-two contingency table for analysis.

considered an AE signal.[12,13] Two or more cases are necessary to positively identify such signals.[12,13]

Time-to-onset duration for each of the 19 drugs was calculated as the time from when the first dose of the drug was administered to the occurrence of DIHFS. Since DIHFS usually develops within a year, we analyzed a time-to-onset duration of up to 365 days to focus on the onset of AEs within a year.[4] Median duration, quartiles, and Weibull shape parameters (WSPs) were utilized while evaluating the time-to-onset data.[14,15] The WSP test is used for statistically analyzing time-to-onset data.[14] The scale parameter α of the Weibull distribution was used to determine the scale of the distribution function. A larger-scale value stretches the distribution, while a smaller-scale value shrinks the data distribution.[14] The shape parameter β of Weibull distribution indicated that the hazard did not possess a reference population. If $\beta = 1$, the hazard was estimated to remain constant over time, whereas if $\beta > 1$ and the 95% CI of β excluded the value 1, the hazard was considered to increase over time (wear-out failure type). When $\beta < 1$ and the 95% CI of β excluded 1, the hazards were estimated to decrease over time (initial-failure type).[14]

In addition, cluster analysis was used to analyze the association between the drugs that cause DIHFS. Clustering algorithms assign data to groups with similar properties.[16,17] In this study, we used agglomerative hierarchical clustering to classify 19 drugs and analyze the relationship between ROR, reporting ratio (RR), outcome (rate of 'recovered' and 'recovering', rate of 'not recovered', 'recovered with sequelae', and 'death'), and time-to-onset. Cluster analysis is performed to group several patterns into homogeneous clusters based on similarity.[16] Clusters are typically generated from standardized data using Ward's method with Euclidean distance. Cluster analysis is an 'unsupervised classification method' wherein the criteria for classification are not predetermined and no external criteria or evaluation are given.[16] Since this analysis is generally not associated with probabilistic evaluation, it is common for the researcher to make appropriate decisions about the number of clusters with the greatest perceived significance.[16]

All data analyses were performed using JMP 14.0 (SAS Institute Inc., Cary, NC, USA).

Results

The JADER database contains 646,779 reports submitted from April 2004 to September 2020, from which we identified 1814 (0.3%) DIHFS events. The drugs with the top five RR values of DIHFS were capecitabine (9.8%), lapatinib (24.5%), regorafenib (13.2%), sorafenib (6.2%), and sunitinib (3.5%) (Table 1). The drugs with RORs greater than 10 were axitinib [ROR: 14.9 (95% CI: 11.1–20.1)], capecitabine [ROR: 54.6 (95% CI: 49.2–60.6)], lapatinib [ROR: 130.4

(95% CI: 110.7–153.6)], regorafenib [ROR: 63.3 (95% CI: 55.2–72.6)], sorafenib [ROR: 29.0 (95% CI: 25.8–32.7)], and sunitinib [ROR: 13.9 (95% CI: 11.7–16.5)] (Table 1).

Time-to-onset analysis revealed the median values [interquartile range (days) 25.0–75.0%] of DIHFS. The drugs with the top five reported case numbers were capecitabine [21.0 (13.0–42.0) $n = 361$], doxorubicin [14.0 (7.0–21.0) $n = 107$], lapatinib [32.0 (16.0–43.0) $n = 176$], regorafenib [9.0 (6.0–14.0) $n = 227$], and sorafenib [9.0 (6.0–14.0) $n = 320$] (Table 2). Docetaxel, regorafenib, and sorafenib were the three drugs with the shortest onset time. Everolimus and trastuzumab were the two drugs with the longest onset time.

The WSP β (95% CI) for docetaxel, doxorubicin, everolimus, fluorouracil, oxaliplatin, and tegafur–gimeracil–oteracil were 0.77 (0.60–0.96), 1.53 (1.30–1.77), 7.01 (2.43–15.45), 0.59 (0.34–0.92), 0.66 (0.45–0.91), and 1.48 (1.02–2.03), respectively (Table 2). The upper limits of the 95% CI of the WSP β value for docetaxel, fluorouracil, and oxaliplatin were less than 1. The lower limits of the 95% CI of the WSP β value for doxorubicin, everolimus, and tegafur–gimeracil–oteracil were greater than 1.

In the mosaic plot, outcomes after the onset of AEs with each drug are shown in Figure 2. The percentage of 'recovered' and 'recovering' patients who received bevacizumab (94.3%), doxorubicin (92.7%), lenvatinib (95.0%), oxaliplatin (90.0%), sorafenib (90.7%), and tegafur–gimeracil–oteracil (91.3%) were 90% or more. The total percentages of the 'not recovered', 'recovered with sequelae', and 'death' patients who received cisplatin, fluorouracil, paclitaxel, sunitinib, and trastuzumab were 22.2%, 22.2%, 40.0%, 20.0%, and 20.0%, respectively.

The dendrogram summarizing the data, and each target molecule of monoclonal antibodies,[18–28] is shown in Figure 3. The number of clusters was set to 4 based on the characteristics of each cluster. Cluster 1 included sunitinib, fluorouracil, and cisplatin, which tended to have high rates of 'not recovered', 'recovered with sequelae', and 'death' outcomes. Cluster 2 included trastuzumab and everolimus, which tended to have longer times to DIHFS onset than other drugs. Cluster 3 included capecitabine, regorafenib, and lapatinib, which tended to have higher rates of RR and ROR of DIHFS than other drugs. Cluster 4 included drugs such as doxorubicin, sorafenib, lenvatinib, tegafur–gimeracil–oteracil, and bevacizumab, for which the rates of 'recovered' and 'recovering' were high. Paclitaxel was not used for cluster analysis because of the lack of data regarding its time-to-onset profile.

Discussion

In this study, we evaluated the plausible relationship between chemotherapeutic drugs and DIHFS using data from an SRS database. We summarized the incidence of DIHFS, ROR values, and time-to-onset profiles from the JADER database. Our findings are considered of complementary value on the occurrence of DIHFS reflecting real-world setting than has been published previously.

In our analysis, AE signals were detected in many of the drugs that induce HFS as reported by clinicians and patients according to the Manual for Handling Disorders due to Adverse Drug Reactions issued by the Ministry of Health, Labor and Welfare (MHLW) in Japan (DIHFS manual).[4] Pyrimidine analogues, such as capecitabine, tegafur–gimeracil–oteracil, tegafur–uracil, and fluorouracil, are listed in the DIHFS manual as typical drugs that may cause HFS.[4] The risk of DIHFS for fluorouracil and capecitabine is listed under the section concerning serious side effects in their package inserts. The frequency of DIHFS caused by tegafur–gimeracil–oteracil or tegafur–uracil is less than 0.1–5.0% or is unknown. This information is listed under other side effects in their package inserts. It has been reported that capecitabine is more likely to induce HFS than other fluoropyrimidine drugs.[20–31] In our analysis, ROR signals for capecitabine and tegafur–uracil were detected, and the RR for capecitabine was 9.8%. Therefore, the onset of DIHFS by capecitabine should be monitored carefully. In contrast, the signals for fluorouracil and tegafur–gimeracil–oteracil were not detected.

According to the DIHFS manual, there is a high possibility of sorafenib and regorafenib causing HFS.[4] The RRs of lapatinib and regorafenib were 24.5% and 13.2%, respectively; therefore, thorough monitoring is required to prevent DIHFS induced by these drugs. In our previous study based on data collected from 2004 to 2014, the RR of regorafenib was found to be 28.2%.[10] The

Table 2. Parameters of Weibull distribution for hand–foot syndrome.

Drug classification (ATC code)	Drug name	Cases	Median (interquartile range, day)	Scale parameter, α (95% confidence interval)	Shape parameter, β (95% confidence interval)
Pyrimidine analogues (L01BC)	Capecitabine	361	21.0 (13.0–42.0)	42.28 (37.60–47.46)	0.99 (0.91–1.07)
	Fluorouracil	10	19.5 (2.0–82.0)	37.15 (10.42–121.43)	0.59 (0.34–0.92)
	Tegafur–Gimeracil –Oteracil	20	15.0 (12.5–34.5)	25.26 (18.00–34.74)	1.48 (1.02–2.03)
	Tegafur–Uracil	17	31.0 (14.0–83.0)	55.37 (32.01–92.69)	1.003 (0.67–1.41)
Taxanes (L01CD)	Docetaxel	39	6.0 (3.0–25.0)	14.62 (9.18–22.81)	0.77 (0.60–0.96)
	Paclitaxel	0	–	–	–
Anthracyclines and related substances (L01DB)	Doxorubicin	107	14.0 (7.0–21.0)	18.44 (16.02–21.16)	1.53 (1.30–1.77)
Platinum compounds (L01XA)	Cisplatin	14	15.0 (10.0–82.0)	41.49 (22.63–73.01)	1.02 (0.65–1.48)
	Oxaliplatin	18	21.0 (5.0–28.0)	35.54 (15.99–75.61)	0.66 (0.45–0.91)
Monoclonal antibodies (L01XC)	Bevacizumab	20	39.0 (16.0–59.5)	40.53 (25.67–62.42)	1.10 (0.74–1.55)
	Trastuzumab	6	70.0 (15.0–189.0)	93.15 (34.92–233.95)	1.08 (0.50–1.95)
Protein kinase inhibitors (L01XE)	Axitinib	10	12.0 (5.0–39.0)	36.22 (16.22–76.63)	1.08 (0.58–1.76)
	Everolimus	4	86.5 (67.0–90.5)	84.94 (68.64–104.60)	7.01 (2.43–15.45)
	Lapatinib	176	32.0 (16.0–43.0)	49.49 (42.34–57.67)	1.04 (0.93–1.15)
	Lenvatinib	13	21.0 (2.0–37.0)	35.75 (19.77–62.36)	1.28 (0.72–2.03)
	Pazopanib	17	35.0 (17.0–46.0)	50.71 (27.21–91.62)	0.90 (0.61–1.24)
	Regorafenib	227	9.0 (6.0–14.0)	14.12 (12.34–16.14)	1.04 (0.96–1.13)
	Sorafenib	320	9.0 (6.0–14.0)	16.09 (14.20–18.20)	0.97 (0.90–1.04)
	Sunitinib	58	17.0 (10.0–23.0)	25.48 (19.20–33.57)	0.99 (0.83–1.16)

ATC, Anatomical Therapeutic Chemical Classification System.

decline in RR was 28.2% in the previous study and 13.2% in this study. Spontaneous reporting is notably influenced by external factors such as the time since the drug was launched. Regorafenib was approved by the PMDA in 2013. The Weber effect is an epidemiological phenomenon, which suggests that spontaneous reporting of AEs increases substantially when a drug is first approved, then plateaus, and eventually declines with time.[32–34] The decrease observed in this study could be explained by the Weber effect.

The ROR signals were detected in all protein kinase inhibitors except everolimus. It has been reported that HFS is an uncommon toxicity induced by everolimus, and according to its package insert, everolimus has a lower incidence of DIHFS than other protein kinase inhibitors.[35] In

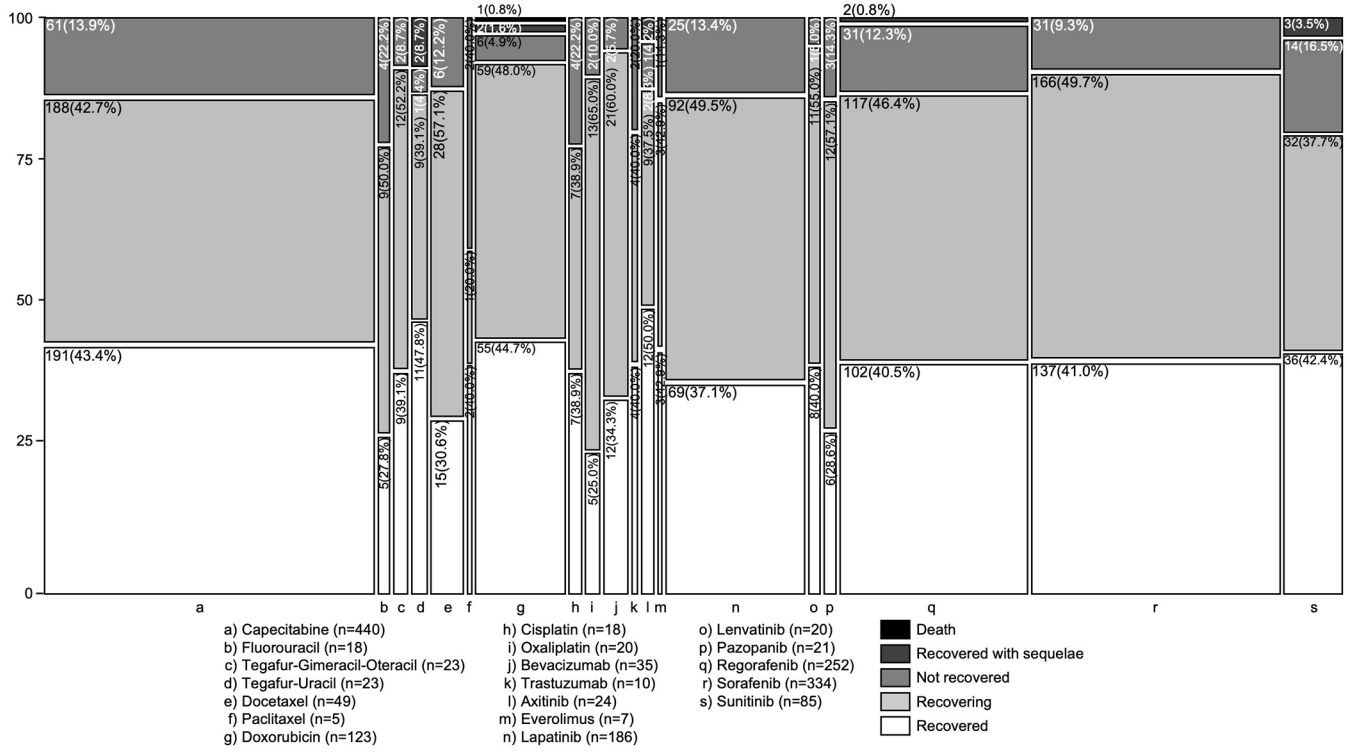
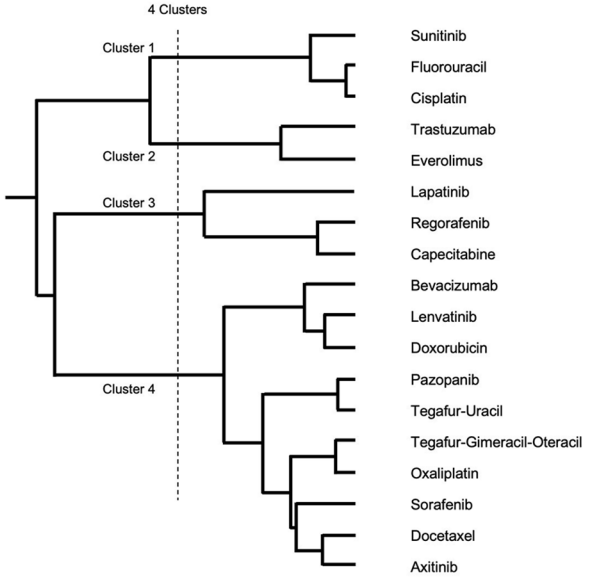


Figure 2. Mosaic plot of outcomes of drug-induced hand–foot syndrome. The plot is divided into rectangles where each vertical length represents the proportion of each level of the Y variable within each level of the X variable.



Cluster	ATC Classification (ATC code)	Target molecule
1	Protein kinase inhibitors (L01XE)	VEGFR, PDGFR, KIT, RET, FLT3, CSF1
1	Pyrimidine analogues (L01BC)	-
1	Platinum compounds (L01XA)	-
2	Monoclonal antibodies (L01XC)	HER2
2	Protein kinase inhibitors (L01XE)	mTOR (VEGF)
3	Protein kinase inhibitors (L01XE)	HER2, EGFR
3	Protein kinase inhibitors (L01XE)	VEGFR1-3, PDGFRβ, KIT, RET, BRAF, TIE2, FGFR
3	Pyrimidine analogues (L01BC)	-
4	Monoclonal antibodies (L01XC)	VEGF
4	Protein kinase inhibitors (L01XE)	VEGFR1-3, PDGFRα, KIT, RET, FGFR1-4
4	Anthracyclines and related substances (L01DB)	-
4	Protein kinase inhibitors (L01XE)	VEGFR, PDGFR, FGFR, KIT
4	Pyrimidine analogues (L01BC)	-
4	Pyrimidine analogues (L01BC)	-
4	Platinum compounds (L01XA)	-
4	Protein kinase inhibitors (L01XE)	VEGFR2,3, PDGFRβ, KIT, RET, BRAF, CRAF, FLT3
4	Taxanes (L01CD)	-
4	Protein kinase inhibitors (L01XE)	VEGFR

Characteristics of each cluster

Cluster 1: tend to have high rates of "not recovered," "recovered with sequelae," and "death"

Cluster 2: tend to have long onset times of DIHFS than other drugs

Cluster 3: tend to have high rates of RR and ROR

Cluster 4: tend to have high rates of "recovered" and "recovering"

Figure 3. Dendrogram representing the clusters and each target molecule of monoclonal antibodies (cluster 1: tend to have high rates of 'not recovered', 'recovered with sequelae', and 'death'; cluster 2: tend to have long onset times of DIHFS than other drugs; cluster 3: tend to have high rates of RR and ROR; cluster 4: tend to have high rates of 'recovered' and 'recovering').
CSF, colony-stimulating factor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factors receptor; FLT, FMS-like tyrosine kinase; HER, human epidermal growth factor receptor; KIT, KIT proto-oncogene receptor tyrosine kinase; mTOR, mechanistic target of rapamycin; PDGFR, platelet-derived growth factor receptor; RAF, RAF proto-oncogene serine-threonine protein kinase; RET, rearranged during transfection; TIE, tyrosine kinase with immunoglobulin-like and EGF-like domains; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

addition, unlike other drugs, everolimus does not inhibit the vascular endothelial growth factor receptor (VEGFR) itself. Instead, it inhibits the production of VEGF and mainly acts as a selective immunosuppressant.[21] These differences in the mechanism of action may have influenced the expression of DIHFS.

The ROR of the trastuzumab signal was detected in this study. Trastuzumab monotherapy rarely causes DIHFS.[36] Trastuzumab is generally used concomitantly with taxanes or other drugs such as capecitabine. In our study, the rate of concomitant use of trastuzumab with capecitabine was 78% (18/23 cases). Thus, it is suggested that the ROR signal is influenced by co-administered anticancer drugs such as capecitabine. Further consideration was difficult because detailed information about the chemotherapy protocol is not included in the JADER database. In contrast, recently, an unusual complication of DIHFS with trastuzumab monotherapy has been reported as a case report.[37] Clinicians should be watchful of the early signs of DIHFS such as dermatologic desquamation in trastuzumab monotherapy.

According to the DIHFS manual, DIHFS caused by capecitabine, doxorubicin, and sunitinib develops in most cases within 16 weeks (92.7%, 255/275), 8 weeks (86.2%, 50/58), and 12 weeks (92.3%, 24/26), respectively.[4] For sorafenib, HFS often develops within 3 weeks (59.7%, 43/72), and typically develops within 9 weeks (91.7%, 66/72).[4] In our analysis, the time-to-onset median durations (25.0–75.0%) of capecitabine, doxorubicin, sunitinib, and sorafenib was 21.0 (13.0–42.0) days [3.0 (1.9–6.0) weeks], 14.0 (7.0–21.0) days [2.0 (1.0–3.0) weeks], 17.0 (10.0–23.0) days [2.4 (1.4–3.3) weeks], and 9.0 (6.0–14.0) days [1.3 (0.9–2.0) weeks], respectively. There is almost no contradiction in the 75.0% quartile time-to-onset duration of these four drugs in our results compared with those in the manual.[4]

DIHFS is a well-known cutaneous AE of multiple tyrosine kinase inhibitors.[4–8,18] In our analysis, regorafenib and sorafenib had shorter time to onset than other protein kinase inhibitors, which was corroborated by a previous study.[10] Regorafenib and sorafenib are small molecule biaryl urea compounds with similar structures and are both multiple protein kinase inhibitors that inhibit VEGFR, platelet-derived growth factor receptor (PDGFR), KIT proto-oncogene receptor tyrosine kinase (c-KIT), rearranged during transfection (RET), and B-RAF proto-oncogene serine/threonine protein kinase (BRAF).[21,22,38,39,40] It has been suggested that sorafenib is secreted in high concentrations from eccrine sweat glands.[41] However, another study showed that the direct mechanism of action of sorafenib was unlikely to be the cause of skin-related side effects because the expression of VEGFR and FMS-like tyrosine kinase (FLT) 3 in keratinocytes is not well known.[42,43] Interestingly, sorafenib acts through another mechanism involving inflammatory cells which may be associated with skin-related AEs.[43] This analysis suggests that the mechanism of action of protein kinase inhibitors may be related not only to the onset of HFS but also to the number of reports and the ROR value.

Although the exact mechanism remains unknown, the pathogenic mechanism of DIHFS is presumed for some drugs. DIHFS by pyrimidine analogues causes paresthesia and relatively diffuse redness of the skin in the early stages of onset, and as it progresses, the skin surface becomes glossy and pain is observed following the disappearance of fingerprints. Capecitabine, whose AEs were often reported according to our study, is a prodrug of fluorouracil. In the liver, capecitabine is metabolized by enzymes such as thymidine phosphorylase and dihydropyrimidine dehydrogenase and is finally metabolized to α-fluoro-β-alanine, which is a degradation product of fluorouracil. As these enzymes present in the keratinocytes of the skin are highly active in the palms and soles, it has been suggested that an inflammatory reaction may occur due to the accumulation of α-fluoro-β-alanine in these areas.[4,29,44]

In our study, docetaxel also exhibited an early onset, and docetaxel-induced HFS was likely to be of the initial-failure type. Docetaxel-induced HFS is a rare and dose-dependent AE.[45] However, docetaxel package inserts do not clearly state when this DIHFS is expressed, and the exact mechanism of this side effect remains unknown.[46] Our results suggest that health care professionals must be made aware about the potential of DIHFS onset with docetaxel, regorafenib, and sorafenib occurring within at least the first 4 weeks after administration. Therefore, careful observation is recommended.

Pegylated liposomal doxorubicin is delivered to the skin surface with sweat and accumulates in the palms and soles where eccrine sweat glands are distributed abundantly. Hydrophilic coating of liposomes facilitates the delivery of doxorubicin to eccrine sweat glands.[47,48] However, DIHFS induced by protein kinase inhibitors often causes localized erythema and blisters in areas exposed to high pressure such as the finger pulp, joints, and areas of physical stimulation such as the heels. The mechanism of DIHFS caused by protein kinase inhibitors has not been fully elucidated.

Protein kinase inhibitors are known to cause severe symptoms. Careful monitoring is required. A difference in clinical symptoms occurs due to a difference in the pathogenic mechanism of each drug.[49]

Although SRS collects big data on valuable AE reports that reflect actual clinical practice, some limitations should be considered, including underreporting, overreporting, missing data, biases, confounders, and lack of control population as a reference group.[12,13] Therefore, ROR cannot be applied to inferences of comparative degrees of causality. It can provide only a rough indication of the signal strength.

Ideally, the covariates should be assessed with respect to various patients' backgrounds. Multiple logistic analysis is a method for adjusting covariates partially.[50,51] Similarly, propensity score is statistical method used to adjust covariates in observational studies to estimate causal effects that are difficult to randomize and are prone to various confounders.[52–54] However, at present, there is no standard and widely accepted method to adjust covariates for SRS data. Therefore, our results require careful interpretation that takes all existing confounding factors into consideration.

In the JADER database, duplicate cases may exist because of follow-up reports on the same patient. However, the JADER database has no keycode to identify duplicate reports, making it difficult to exclude duplicate reports. Although the PMDA has introduced a method for estimating duplicate reports by matching scores,[55] this method has not been widely accepted yet. Therefore, we did not consider duplicate reports this time.

The JADER database does not contain detailed information on the patient's background such as medical history and chemotherapy regimens. Although DIHFS is classified as grade 1 to grade 3 according to clinical aspects such as symptoms, skin-related clinical characteristics, and functional areas that determine the degree of restriction on daily activities, it was not possible to analyze the effect of DIHFS severity using the JADER database.[4,10] The study findings on several drugs did not match the results from the manual. The daily burden on the limbs, such as physical stimuli through friction, pressure, and heat, might have affected the onset of DIHFS. In Japan, sorafenib was first sold on April 18, 2008, while regorafenib was first sold in May 2013. Therefore, future studies should investigate whether corporate alerts regarding the onset of HFS affected AE reporting (Weber effect). Although epidemiological studies may be needed for confirmation, our results, based on JADER's assessment, are consistent with previous reports and are believed to provide practical information to better understand this issue.

The most effective way to manage HFS is through dose delay, dose reduction, treatment discontinuation, or switching to other tolerated regimens.[56] In addition, urea and steroidal creams are commonly used to treat HFS along with chemotherapy regimens. Information on the time to onset of AEs is useful for alerting health care professionals and patients and for maintaining the quality of life of patients with AEs such as DIHFS.

Conclusions

The JADER database, in which health care professionals report potential AE concerns, is recognized as a useful tool for pharmacovigilance that reflects the reality of clinical practice. Using this database, we demonstrated the potential risks of HFS associated with chemotherapeutic drugs based on RORs and time-to-onset analysis in this study. Our results are consistent with those previously reported. Consequently, it is suggested that clinicians must be aware of the risk of DIHFS onset with docetaxel, regorafenib, and sorafenib within at least the first 4 weeks. Therefore, careful follow-up and pertinent measures are essential.

Ethics approval

Ethical approval was not sought for this study because it was a retrospective observational study without any research subjects.

Author contribution(s)

Yu Yoshida: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing – original draft.

Sayaka Sasaoka: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Writing – review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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