Risk of hand-foot skin reaction associated with vascular endothelial growth factor–tyrosine kinase inhibitors: A meta-analysis of 57 randomized controlled trials involving 24,956 patients

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Background: Multiple randomized controlled trials have assessed hand-foot skin reaction (HFSR) caused by vascular endothelial growth factor receptor–tyrosine kinase inhibitors (VEGFR-TKIs).

Objective: We performed a meta-analysis to determine the incidence and the relative risk (RR) of HFSR associated with these agents.

Methods: Databases were searched for relevant studies. Statistical analyses were conducted to calculate the summary incidences, RR, and 95% confidence intervals (CIs) by using random-effects or fixed-effects models according to the heterogeneity of the included studies.

Results: A total of 24,956 patients from 57 studies were included. The overall incidence of all-grade and high-grade HFSR associated with VEGFR-TKIs was 35.0% (95% CI, 28.6%-41.6%) and 9.7% (95% CI, 7.3%-12.3%), respectively. The use of VEGFR-TKIs significantly increased the risk of developing all-grade (RR, 5.09; 95% CI, 3.52-7.35; $P < .001$) and high-grade (RR, 9.42; 95% CI, 5.59-15.90; $P < .001$) HFSR. Subgroup analyses revealed that the risk of HFSR was significantly increased according to tumor type, VEGFR-TKI, trial phase, treatment regimen, and control therapy. No evidence of publication bias was observed.

Limitation: High heterogeneity in most studies.

Conclusion: High risk of HFSR is prone to develop in cancer patients receiving VEGFR-TKIs. (J Am Acad Dermatol 2020;83:788-96.)

Key words: cancer; hand-foot skin reaction; meta-analysis; VEGFR-TKIs.

Vascular endothelial growth factor (VEGF) plays an important role in tumor growth, progression, and metastasis by promoting angiogenesis.[1] In recent decades, several angiogenesis inhibitors that target the VEGF signaling pathway have shown clinical efficacy against various solid tumors and have been approved for use by the United States Food and Drug Administration and the European Medicines Agency. However, the VEGF pathway is not only essential for normal growth and

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development but also critical to physiologic response and homeostasis.[2]

A variety of adverse effects are therefore expected with pharmacologic blockage of this pathway. Hand-foot skin reaction (HFSR) is considered the most clinically significant dermatologic adverse event. HFSR associated with VEGFR-TKIs is a distinct localized cutaneous reaction characterized by numbness, dysesthesia, paresthesia, and tingling affecting the palms, soles, or both.[3] The reported incidences of HFSR associated with VEGFR-TKIs are different in previously randomized clinical trials (RCTs). To determine the risk of HFSR associated with the clinical use of VEGFR-TKIs, we investigated the incidence and the relative risk (RR) of these events in patients treated with VEGFR-TKIs and then performed a systematic review and a meta-analysis.

CAPSULE SUMMARY

- This meta-analysis shows the incidence of hand-food skin reaction in patients with cancer receiving vascular endothelial growth factor receptor—tyrosine kinase inhibitors reaches 35%, which is controversial in multiple randomized controlled trials.
- Dermatologists should pay particular attention to hand-food skin reaction associated with vascular endothelial growth factor receptor—tyrosine kinase inhibitors.

MATERIALS AND METHODS

Data sources

Study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[4] An independent review was performed of citations from PubMed between January 1, 1966, and December 30, 2017. Key words were sorafenib, BAY 43-9006, nexavar, sunitinib, sutent, SU11248, pazopanib, votrient, GW786034, vandetanib, ZD6474, caprelsa, ZD6474, axitinib, AG-013736, cediranib, AZD2171, regorafenib, BAY 73-4506, linifanib, ABT-869, motesanib, AMG 706, cabozantinib, dovitinib, nintedanib, brivanib, cancer, and randomized controlled trials. We performed independent searches using the Embase and Web of Science databases between January 1, 1966, and December 30, 2017 to ensure that no clinical trials were overlooked. We additionally searched the clinical trials registration website, American Society of Clinical Oncology, and the European Society of Medical Oncology for relevant trials. When duplicate or subgroup studies were encountered, the most up-to-date or thorough report of a clinical trial was incorporated.

To ensure clinical significance, phase I trials were omitted from the analysis owing to variations in dosage and limited sample sizes. Studies that met the following criteria were analyzed: (1) patients with cancer, (2) participants assigned to treatment with VEGFR-TKIs (alone or in combination and at any dosage or frequency) or control treatments, (3) safety data available for HFSR, and (4) prospective, randomized, controlled phase II and III trials.

Data extraction

Data abstraction was conducted independently by 2 investigators (B.L. and F.D.), and any discrepancy between the reviewers was resolved by consensus. Clinical end points were selected from the safety profile of each trial. Adverse events were recorded according to versions 2, 3, or 4 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (Table I). The incidence of all-grade or high-grade (grade ≥3) HFSR was included in the analysis. The quality of each eligible study was assessed by using the 5-point Jadad scale.[5]

Statistical analysis

All statistical analyses were performed using Stata 12.0 software (StataCorp LLC, College Station, TX). To calculate the incidence and RR of HFSR, the number of patients with HFSR and the number of patients receiving VEGFR-TKIs were extracted from individual clinical trials. For trials that reported 0 events in the treatment or control arms, a classic half-integer continuity correction was used to calculate the incidence and RR and their variance.[6] Statistical heterogeneity between trials was estimated using the χ^2-based Q statistic.[7] Heterogeneity was considered statistically significant when P for heterogeneity was $<.1$.

Data were analyzed using a random-effects or fixed-effects model based on heterogeneity. A statistical test with a P value of $<.05$ was considered significant. The following prespecified subgroup analyses were also undertaken to identify potential effect modifiers for HFSR: tumor type, type of VEGFR-TKI, trial phase, treatment regimen, and control therapy. To examine the stability of the results, sensitivity analysis was performed by sequential omission of individual studies. Finally, we also performed meta-regressions with differences in the median length of experimental

Abbreviations used:

CI:	confidence interval
HFSR:	hand-foot skin reaction
RCT:	randomized controlled trial
RR:	risk ratio
VEGFR-TKIs:	vascular endothelial growth factor receptor–tyrosine kinase inhibitors

treatments (expressed in days) as a predictor and the risk ratio as a dependent variable. Publication bias was evaluated using funnel plots and Egger tests.

RESULTS

Systematic literature search

Our search yielded 1942 clinical studies relevant to VEGFR-TKIs (Fig 1), and 24,956 patients from 57 RCTs were finally included in the meta-analysis.[8-64] Criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate hematologic, cardiac, and renal function, and a variety of cancers: non-small cell lung cancer (8 trials), breast cancer (8 trials), hepatocellular carcinoma (9 trials), renal cell carcinoma (7 trials), thyroid cancer (2 trials), pancreatic cancer (3 trials), metastatic colorectal cancer (4 trials), ovarian cancer (3 trials), gastrointestinal stromal tumor (3 trials), melanoma (2 trials), pancreatic neuroendocrine tumors (1 trial), prostate cancer (2 trials), cervical cancer (1 trial), gastric cancer (1 trial), urothelial carcinoma (1 trial), and acute myeloid leukemia (2 trials).

Incidence of all-grade HFSR

A total of 9707 patients, who were treated with VEGFR-TKIs in 46 RCTs, were available for analysis, 3536 of whom experienced all-grade HFSR. The highest incidence (90.2%; 95% CI, 83.3%-94.4%) occurred in a phase II trial of breast cancer, and the lowest incidence (1.4%; 95% CI, 0.2%-7.3%) occurred in a phase II trial of cervical cancer. A random-effects model (χ^2-based Q statistic test = 2054.98; $P < .001$; $I^2 = 97.81\%$) revealed that the summary incidence of all-grade HFSR in patients receiving VEGFR-TKIs was 35.0% (95% CI, 28.6%-41.6%) (Table II).

Incidence of high-grade HFSR

There were 13,241 patients from 57 RCTs available for analysis, 1595 of whom experienced high-grade HFSR. The highest incidence (66.1%; 95% CI, 56.9%-74.2%) was observed in a phase II trial for breast cancer, whereas the lowest incidence was observed in 3 trials that reported no high-grade HFSR: 1 phase II trial for breast cancer, 1 phase II trial for renal cell carcinoma, and 1 phase II trial for cervical cancer. A random-effects model (χ^2-based Q statistic test = 1255.29; $P < .001$; $I^2 = 95.54\%$) revealed that the summary incidence of high-grade HFSR in patients receiving VEGFR-TKIs was 9.7% (95% CI, 7.3%-12.3%) (Table II).

RR of HFSR

A total of 18,127 patients in 46 RCTs were included when calculating the RR of all-grade HFSR. The combined results demonstrated that VEGFR-TKIs significantly increased the risk of developing all-grade HFSR: a random-effects model ($I^2 = 95.5\%$, $P < .001$) yielded an RR of 5.09 (95% CI, 3.52-7.35; $P < .001$) (Table II). There were 24,191 patients in 57 RCTs included when calculating the RR of high-grade HFSR. The combined RR based on a random-effects model ($I^2 = 84.2\%$, $P < .001$) revealed that VEGFR-TKIs significantly increased the risk of high-grade HFSR (RR, 9.42; 95% CI, 5.59-15.90; $P < .001$) (Table II).

Furthermore, we also performed a sensitivity analysis to examine the stability and reliability of the pooled RRs by sequentially omitting individual studies. The results indicated that the significance estimate of the pooled RRs was not significantly influenced by omitting any single study. In addition, we performed a meta-regression analysis to test whether the RR of HFSR varied as a function of the difference in treatment time. The analysis included the studies that reported data on the length of treatment. The results indicated that the RR tended to be higher in studies in which the experimental treatment was longer and that this effect was statistically significant.

Risk of HFSR according to tumor type, VEGFR-TKI, trial phase, treatment regimen, and control therapy

We examined the RR of VEGFR-TKI–associated HFSR according to tumor type. The highest RRs of all-grade and high-grade HFSR were observed in patients with thyroid cancer (all-grade: RR, 12.62; 95% CI, 3.57-44.60; high-grade: RR, 52.90; 95% CI, 7.81-358.27), and the RR of all-grade and high-grade events varied significantly according to tumor type ($P < .001$). The RR of HFSR caused by VEGFR-TKIs might be different. The highest RR of all-grade HFSR was observed in patients receiving cabozantinib (RR, 12.10; 95% CI, 3.01-48.54). The highest RR in high-grade HFSR was observed in patients receiving regorafenib (RR, 36.89; 95% CI, 7.41-183.72), and the differences among VEGFR-TKIs were statistically significant ($P < .001$) (Table II).

Next, we executed a subgroup analysis according to trial phase. The RRs of all-grade and high-grade HFSR were significantly higher in phase III trials than

Table I. National Cancer Institute Common Terminology Criteria for Adverse Events for hand-foot skin reaction

Grade	Version 2.0	Version 3.0	Version 4.0
1	Skin changes or dermatitis without pain (eg, erythema, peeling)	Minimal skin changes or dermatitis (eg, erythema) without pain	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain
2	Skin changes with pain, not interfering with function	Skin changes (eg, peeling, blisters, bleeding. edema) or pain, not interfering with function	Skin changes (eg, peeling, blisters, bleeding. edema, or hyperkeratosis) with pain, limiting instrumental ADL
3	Skin changes with pain, interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	Severe skin changes (eg, peeling, blisters, bleeding. edema, or hyperkeratosis) with pain, limiting self-care ADL
4	…	…	…
5	…	…	…

ADL, Activities of daily living.

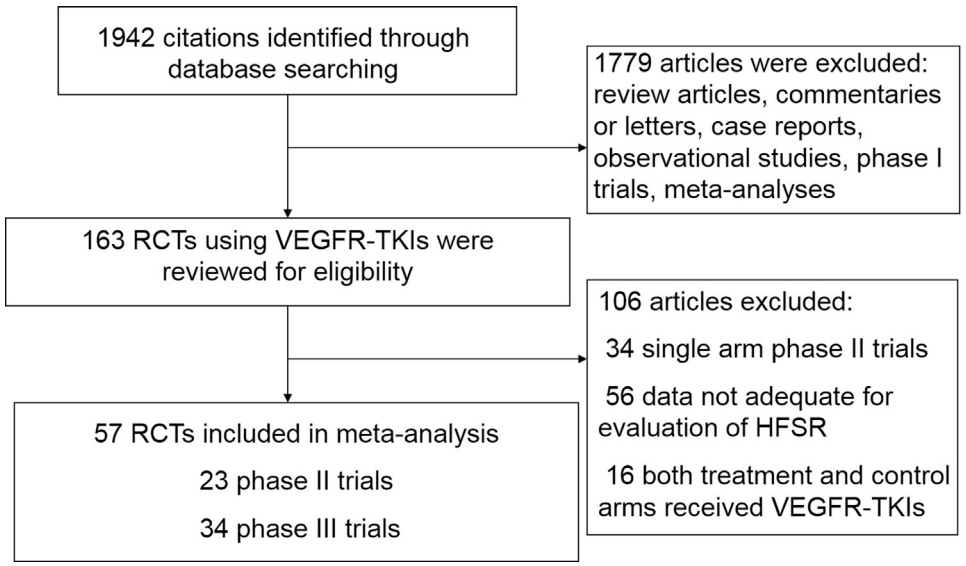

Fig 1. Selection process for randomized controlled trials (*RCTs*) included in the meta-analysis. *HFSR*, Hand-foot skin reaction; *VEGFR-TKIs*, vascular endothelial growth factor—tyrosine kinase inhibitors.

in phase II trials (all-grade: 5.75 vs. 3.68; high-grade: 13.76 vs. 6.57). This difference in the risk of all-grade and high-grade HFSR at different test phases was statistically significant ($P < .001$). We also performed a subgroup risk analysis stratified according to treatment regimen. The RRs of all-grade and high-grade HFSR were significantly higher in patients receiving VEGF-TKI monotherapy than those receiving combination therapy (all-grade: 6.43 vs 3.87; high-grade: 10.39 vs 8.56). The difference in the risk of all-grade and high-grade HFSR according to treatment regimen was statistically significant ($P < .001$).

Finally, we performed subgroup analysis according to the control therapy. The combined results showed that the use of VEGFR-TKI was associated with a significantly higher RR of all-grade and high-grade HFSR than placebo or nonplacebo therapy (all-grade: 7.45 vs 3.90; high-grade: 24.77 vs 7.20). These differences were statistically significant ($P < .001$) (Table II).

Publication bias

Evidence of publication bias was detected with respect to the RR of HFSR by funnel plots and the Egger test ($P < .001$). We therefore adopted an iterative method to evaluate the number of deficient studies (trim-and-fill method) and then performed a new meta-analysis after adding in some hypothetical trials.[65] The combined results also demonstrated that

Table II. Incidence and relative risk of hand-foot skin reaction with VEGFR-TKIs according to tumor type, VEGFR-TKI, trial phase, treatment regimen, and control therapy

Groups	Studies, No.	All-grade hand-foot skin reaction, No. (%)		RR (95% CI)*	*P* value	Studies, No.	High-grade hand-foot skin reaction, No. (%)		RR (95% CI)†	*P* value
		VEGFR-TKI	Control				VEGFR-TKI	Control		
Overall	46	3536 (35.0)	807 (7.5)	5.09 (3.52-7.35)	<.001	57	1595 (9.7)	161 (0.5)	9.42 (5.59-15.90)	<.001
Tumor type										
NSCLC	6	469 (25.1)	76 (4.9)	4.37 (2.54-7.55)	<.001	8	143 (4.9)	10 (0.2)	6.66 (2.04-21.74)	.002
Breast cancer	8	555 (45.5)	403 (25.4)	1.92 (1.04-3.54)	.038	8	251 (19.5)	121 (7.1)	2.65 (0.95-7.40)	.063
HCC	8	938 (42.6)	82 (4.5)	8.47 (5.52-12.99)	<.001	9	331 (12.0)	9 (0.2)	25.50 (14.41-45.10)	<.001
RCC	5	495 (28.0)	65 (3.4)	8.10 (4.84-13.55)	<.001	7	414 (6.7)	10 (0)	20.51 (11.74-35.82)	<.001
Thyroid cancer	2	265 (63.5)	22 (6.3)	12.62 (3.57-44.60)	<.001	2	69 (16.2)	0 (0)	52.90 (7.81-358.27)	<.001
Pancreatic cancer	3	52 (36.5)	21 (8.4)	5.69 (0.60-53.81)	.130	3	18 (13.1)	1 (0.3)	9.66 (2.29-40.71)	.002
mCRC	3	408 (40.9)	86 (11.0)	3.67 (1.28-10.47)	.015	4	148 (10.6)	7 (0.5)	12.93 (3.41-49.01)	<.001
Ovarian cancer	3	158 (34.6)	25 (3.6)	6.14 (4.16-9.05)	<.001	3	61 (13.4)	2 (0.1)	24.30 (6.95-84.95)	<.001
GIST	3	117 (22.6)	12 (4.0)	4.88 (2.80-8.51)	<.001	3	43 (7.9)	0 (0)	14.96 (2.96-75.58)	.002
Melanoma	…	…	…	…	…	2	56 (10.5)	1 (0.1)	37.96 (7.54-191.10)	<.001
PNET	1	19 (22.9)	2 (2.4)	9.39 (2.26-39.01)	.002	1	5 (6.0)	0 (0)	10.87 (0.61-193.45)	.104
Prostate cancer	1	2 (10.5)	0 (0)	5.25 (0.27-102.74)	.274	2	39 (5.5)	0 (0)	23.23 (2.80-192.61)	.073
Cervical cancer	1	1 (1.4)	0 (0)	3.16 (0.13-76.37)	.479	1	0 (0)	0 (0)	1.05 (0.02-52.41)	.979
Urothelial carcinoma	…	…	…	…	…	1	2 (7.7)	0 (0)	5.37 (0.27-106.88)	.271
Gastric cancer	1	30 (53.6)	10 (20.4)	2.63 (1.43-4.80)	.002	1	3 (5.4)	0 (0)	6.14 (0.33-116.01)	.226
AML	1	27 (20.1)	3 (2.3)	8.93 (2.78-28.74)	<.001	2	12 (4.9)	0 (0)	12.60 (1.67-94.84)	.020
VEGFR-TKI										
Sorafenib	21	2067 (48.5)	312 (7.9)	6.17 (4.25-8.95)	<.001	26	1029 (16.3)	49 (0.5)	16.20 (9.65-27.21)	<.001
Sunitinib	11	519 (26.0)	351 (11.6)	2.97 (1.50-5.89)	.002	17	325 (6.5)	109 (1.1)	4.69 (1.83-12.03)	.001
Cediranib	3	153 (15.2)	70 (8.0)	1.67 (1.29-2.16)	<.001	4	25 (1.8)	5 (0.2)	3.22 (1.34-7.72)	.012
Pazopanib	3	81 (6.3)	8 (1.0)	8.40 (4.17-16.95)	<.001	3	11 (1.0)	1 (0)	5.08 (1.16-22.28)	.061
Regorafenib	2	307 (48.6)	28 (8.5)	5.53 (3.85-7.94)	<.001	2	109 (17.2)	1 (0.2)	36.89 (7.41-183.72)	<.001
Cabozantinib	2	246 (45.1)	21 (4.6)	12.10 (3.01-48.54)	<.001	2	55 (10.0)	3 (0.5)	12.49 (4.09-38.07)	<.001
Vandetanib	1	2 (10.5)	0 (0)	5.25 (0.27-102.74)	.274	1	1 (5.3)	0 (0)	3.15 (0.14-72.89)	.474
Axitinib	1	45 (33.8)	4 (5.9)	5.75 (2.16-15.33)	<.001	1	20 (15)	0 (0)	21.11 (1.30-343.84)	.032
Brivanib	2	116 (22.4)	13 (3.1)	6.12 (0.92-40.80)	.061	2	20 (3.7)	0 (0)	16.76 (2.49-112.73)	.011
Phases of trials										
Phase II	17	605 (35.5)	166 (7.9)	3.68 (2.48-5.46)	<.001	23	292 (10.2)	35 (0.7)	6.57 (4.84-8.91)	<.001
Phase III	29	2931 (34.6)	641 (7.3)	5.75 (3.47-9.53)	<.001	34	1303 (9.3)	126 (0.5)	13.76 (6.27-30.19)	<.001
Treatment regimen										
VEGFR-TKIs alone	25	2183 (31.9)	385 (5.3)	6.43 (3.53-11.73)	<.001	30	996 (8.5)	63 (0.2)	10.39 (4.45-24.28)	<.001
Combinations	21	1353 (38.7)	422 (10.7)	3.87 (2.51-5.95)	<.001	28	599 (10.7)	98 (0.9)	8.56 (4.41-16.63)	<.001
Control therapy										
Placebo	17	1724 (36.0)	177 (4.3)	7.45 (5.56-9.99)	<.001	21	818 (9.8)	16 (0.1)	24.77 (16.61-36.94)	<.001
Nonplacebo	29	1812 (34.5)	630 (9.8)	3.90 (2.54-5.99)	<.001	36	777 (9.6)	145 (1.0)	7.20 (3.92-13.22)	<.001

AML, Acute myeloid leukemia; *CI*, confidence interval; *GIST*, gastrointestinal stromal tumor; *HCC*, hepatocellular carcinoma; *mCRC*, metastatic colorectal cancer; *NSCLC*, non-small cell lung cancer; *PNET*, pancreatic neuroendocrine tumors; *RCC*, renal cell carcinoma; *RR*, relative risk; *VEGFR-TKI*, vascular endothelial growth factor−tyrosine kinase inhibitor.

*P <.001 for variation in RR according to tumor type, VEGFR-TKI, trial phase, treatment regimen, and control therapy.

†P <.001 for variation in RR according to tumor type, VEGFR-TKI, trial phase, treatment regimen, and control therapy.

VEGFR-TKIs significantly increased the risk of developing all-grade and high-grade HFSR, indicating that the results are unlikely to be affected by publication bias.

DISCUSSION

To the best of our knowledge, this is the largest meta-analysis evaluating the risk of HFSR associated with VEGFR-TKIs. Previous meta-analyses have demonstrated that several VEGFR-TKIs (eg, regorafenib[66] and sorafenib[67]) are associated with a significantly increased risk of developing HFSR. However, the small sample size and heterogeneity of included studies in these meta-analyses could affect the reliability of results. In addition, the nonrandom or single-arm studies in their meta-analysis may further increase the heterogeneity. We therefore conducted this comprehensive network meta-analysis of 57 RCTs involving 24,956 patients to illustrate this issue. In our analysis, VEGFR-TKIs were associated with a significantly increased risk of all-grade and high-grade HFSR.

We additionally explored the potential risk factors for VEGFR-TKI–associated HFSR and found that the incidence of HFSR associated with VEGFR-TKIs varies significantly according to tumor type. This finding could be because different malignancies have different pathogeneses and different spectra of patient comorbidities. We find that the treatment of VEGFR-TKIs in patients with thyroid cancer does prominently increase the risk of HFSR compared with controls (RR, 12.62; 95% CI, 3.57-44.60). One possible explanation of the results is the number of analyzed trials was limited (only 2 RCTs were included). Another important possible explanation of the results is the pooled analysis might have been affected by single large RCT. Indeed, HFSR is the most common adverse events in the DECISION (stuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine refractory thyrOid caNcer) trial, occurring in 76.3% (158 of 207) of patients with cancer.[41]

Our results also revealed a significantly high incidence of VEGFR-TKIs–induced HFSR in patients with renal cell or hepatocellular carcinoma. The reason is that a significant proportion of patients with renal cell carcinoma have a decreased renal function because of prior nephrectomy, which could impair the clearance of drugs, and that VEGFR-TKIs is primarily metabolized by liver, thus decreased liver function from hepatocellular carcinoma might affect the drug clearance significantly.

The incidence of HFSR associated with VEGFR-TKIs varied significantly among patients receiving different kinds of VEGFR-TKI, which was inconsistent with the previous study,[68] a finding that may be due to differences in the spectrum and specificity of target receptors. We also found that VEGFR-TKIs are associated with HFSR in addition to axitinib ($P > .1$). The main adverse effect of vandetanib is that it can slightly affect the blood supply of the heart, and the resulting discomforts, such as mild dizziness, tiredness, and high blood pressure, and the risk of HFSR are relatively low. Another potential risk factor for HFSR may be concurrent treatment with VEGFR-TKIs. Our results demonstrate that VEGFR-TKI monotherapy and combination therapy both lead to a significant increase in the risk of developing all-grade and high-grade HFSR, whereas VEGFR-TKIs monotherapy is associated with a higher risk. This may be because a placebo is often used as a control in monotherapy trials. Similarly, this may also be the reason why the risk of HFSR with placebo in the control therapy is significantly higher than that of nonplacebo.

The VEGF pathway plays an important role in mucosal integrity and neuronal functioning.[69] The detailed mechanisms by which VEGFR-TKIs induce HFSR remain undetermined. Evidence suggests the effects may be related directly to antireceptor effect. First, anti-VEGF treatment might decrease the renewal capacity of the endothelial cell in response to trauma, which in turn causes endothelial dysfunction.[70]

Second, platelet-derived growth factor and c-Kit are both presented in the ductal epithelium of the eccrine sweat glands,[71,72] and inhibition of 1 of these 2 receptors is sufficient to evoke the reaction.

Third, c-Kit ligand is also presented on human keratinocytes,[73] and inhibition of c-Kit might have direct toxic effect on the keratinocytes.

Fourth, the oncogene receptors *RET* (rearranged during transfection) and *Flt-3* may play an important role in the development of HFSR.[67]

All of the factors mentioned above may increase the risk of HFSR. However, as yet, there are limited data on the possible mechanisms underlying VEGFR-TKI–associated HFSR. More studies focusing on this issue are required.

Despite our efforts to minimize the effects of confounding variables, our analysis has several limitations. First, this meta-analysis was based on clinical trial levels rather than on individual patient data. Many factors, such as age, functional status, stage, and histology of the malignant tumor, cannot be assessed and incorporated into the analysis.

Second, the studies included in our analysis were conducted at academic centers and major research

institutions, and most of the patients had adequate vital organ function, which may not reflect the general patient population in a community or patients with organ dysfunctions.

Third, most of the RCTs included in our analysis had an arbitrary cutoff threshold (ie, reported in >10% of patients in either arm) for reporting HFSR. Some RCTs were excluded because safety data for the incidence of HFSR below these thresholds were not reported. Therefore, our results might underestimate the incidence of HFSR associated with VEGFR-TKIs.

CONCLUSIONS

Our meta-analysis suggests that the use of VEGFR-TKIs does significantly increase the risk of HFSR. Also, the risk of HFSR varies according to tumor type, the type of VEGFR-TKI used, phase of trials, and concomitant usage of anticancer agents. These findings will help physicians to recognize the risk of HFSR associated with VEGFR-TKIs and will help to tailor both dose and schedule to suit individual patients.

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