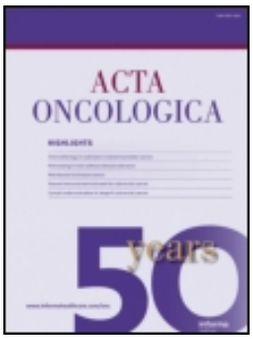

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**REVIEW ARTICLE**

# Risk of hand-foot skin reaction with sorafenib: A systematic review and meta-analysis

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**Abstract**

*Background.* Hand-foot skin reaction (HFSR) is a dose-limiting toxicity associated with sorafenib, an oral multi-kinase inhibitor with clinical activity against solid tumors. This study was conducted to determine the risk of developing HFSR among patients receiving sorafenib. *Patients and Methods*. Databases from Pubmed, Web of Science, and abstracts presented at the American Society of Clinical Oncology annual meetings from 2004 through July, 2007 were searched to identify relevant studies. Eligible studies were prospective clinical trials using single agent sorafenib. The summary incidence rate and the relative risk (RR) were calculated using random-effects model. *Results.* A total of 4 883 patients in 11 trials with metastatic tumors were included for analysis. Among patients receiving sorafenib, the summary incidence of all-grade HFSR was 33.8% (95% CI: 24.5–44.7%) with significant difference between patients with RCC and non-RCC malignancy (RR 1.52, 95% CI: 1.32–1.75%, $p < 0.001$). The incidence of high-grade HFSR was 8.9% (95% CI: 7.3–10.7%). In addition, sorafenib was associated with a significant increased risk of HFSR with RR of 6.6 (95% CI: 3.7 to 11.7, $p < 0.001$) in comparison with controls. *Conclusion.* There is a significant risk of HFSR associated with sorafenib. Proper management and further study are recommended to reduce the risk.

Sorafenib is an orally active multi-kinase inhibitor with effects on tumor cell proliferation and tumor angiogenesis. It was initially developed as an inhibitor of Raf kinase, but has been found to have broad spectrum activity against multiple tyrosine kinases including vascular endothelial growth factor receptor family (VEGFR 1, 2, 3), platelet-derived growth factor receptor family (PDGFR-β), stem-cell growth factor receptor (c-KIT), Fms-like tyrosine kinase 3 (Flt-3), and the receptor encoded by the ret proto-oncogen (RET) [1]. It has an anti-angiogeneic property mediated by its inhibitory effect on VEGFR and PDGFR. Initial clinical trials suggested that sorafenib acted as a cytostatic rather than a cytotoxic agent, allowing stabilization of rather than regression of disease [2].

Sorafenib first came to attention in early clinical trials for refractory solid tumors. Additional interest in its anti-tumor activity surfaced after a phase II randomized discontinuation trial evaluating its effect on patients with metastatic renal carcinoma [3]. It is the first drug approved for the treatment of advanced renal cell cancer since the approval of interleukin-2 in 1992, and appeared to be a more appealing alternative due to its more tolerable side effect profile. More recently, sorafenib has been found to have significant clinical activity against hepatocellular cancer in phase II and phase III studies [4,5]. Sorafenib is also being investigated in combination with other chemotherapeutic agents in advanced solid tumors [6,7].

As with other antineoplastic agents, sorafenib is associated with many side effects including diarrhea, nausea, fatigue, hypertension and dermatological toxicities. In a phase II placebo controlled randomized discontinuation trial using sorafenib in patients with metastatic renal cell cancer, dermatologic changes including hand-foot skin reaction (HFSR), alopecia, stomatitis, facial and scalp erythema, and subungual splinter hemorrhages were reported in greater than 90% of patients, with HFSR among the more frequent adverse manifestations [3].

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HFSR is similar to conventional hand-foot syndrome (HFS), but has distinct features. HFS is a distinct localized cutaneous reaction characterized by erythema, numbness, tingling, and either dysesthesia or paresthesia, particularly on the palms and/or soles. It rarely affects the trunk, neck, chest, scalp and extremities. Swelling of the skin, desquamation, ulceration or blistering may occur in advanced cases. It was first described in the literature in1974 in patients receiving mitotane therapy for hypernephroma [8]. In 1984, Lokich and Moore reported on HFS associated with continuous infusion of various chemotherapeutic agents. Since they believed that HFS may be confused with the childhood viral illness of a similar name, "palmar-plantar erythrodysesthesia" was suggested as an alternate name for this chemotherapy-induced cutaneous manifestation [9]. HFS has been associated with several systemic chemotherapeutic agents including 5-FU, capecitabine, doxorubicin, cyclophosphamide, vinorelbine, and docetaxel. The frequency and severity of HFS is dose-related, as it is affected by duration, dosage and accumulation of these chemotherapeutic agents [10]. The skin toxicity HFSR associated with sorafenib shares some similarities to the conventional HFS (i.e. palmplantar distribution, dose dependency, tenderness, and impact on consistent antineoplastic therapy), but differs in clinical and histological characteristics (HFSR is characterized by thick, well defined hyperkeratotic lesions frequently affecting digit flexural locations), for which the distinguishing term HFSR has been introduced.

Although sorafenib-induced HFSR is usually not a life-threatening side effect, it affects the quality of life in a significant manner and can be complicated by infection, pain, and limitation of activities of daily living (ADL). In addition, it is a dose-limiting toxicity, and may lead to compromised efficacy because of dose reduction. It is a common side effect as observed by many clinical trials. In a randomized placebo-controlled phase III trial called TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial), it was reported that HFS occurred in approximately 26.0% of patients [11]. In this trial, dermatological toxicities were the most frequent cause for dose reduction (13%), interruption (21%), and discontinuation (10%). However, the reported incidence of HFSR varies significantly among different clinical trials, ranging between 9.1% and 61.9%. To better determine the risk of HFSR in patients receiving sorafenib, we have conducted a systematic review and meta-analysis of the published data derived from prospective clinical studies using sorafenib as a single agent.

## Methods

### *Data source*

PUBMED database was searched from January 1996 to July 2007 using key words including "sorafenib" and "BAY 43-9006". The search was conducted using these key words alone and in combination with "hand-foot syndrome" or "hand-foot skin reaction" and "palmar-plantar erythrodysesthesia". In addition, we manually searched all of the abstracts that contained "sorafenib" presented at recent 2004-2007 American Society of Clinical Oncology (ASCO) annual meetings and the ASCO Prostate Cancer Symposium. An independent search using the Web of Science database (a product developed by the Institute for Scientific Information, a citation database) was also conducted to ensure that there were no additional studies. From these studies we were able to obtain patient number and characteristics, treatment strategy, study results including toxicities and follow-up.

### *Study selection*

Sorafenib has been approved for the use in patients with advanced renal cell cancer as a single agent starting at 400 mg twice daily. Thus it has practical implications to determine the risk of HFSR associated with sorafenib at this dose level. Phase I trials were excluded from analysis due to the variations in dose. We analyzed prospective clinical trials including expanded access programs using sorafenib as a single agent. Trials that met the following criteria were included: 1) prospective clinical trials in cancer patients; 2) assignment of participants to the treatment with sorafenib as a single agent at a starting dose of 400 mg twice a day; 3) data available for HFSR.

### *Clinical end points*

The clinical end points were extracted from the safety profile in each trial. HFSR was recorded according to the National Cancer Institute Common Toxicity Criteria version II or III [12]. These two versions are the same regarding the grading of HFSR. Those patients suffering from HFSR ranged from grade I, minimal skin changes or dermatitis (e.g., erythema) without pain; grade II, skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function; and grade III, ulcerative dermatitis or skin changes with pain interfering with function. We included the incidence of all patients with HFSR grade I and above.

*Statistical analysis*

All statistical analysis was performed using version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ). The number of patients with HFSR and the number of those patients receiving sorafenib were extracted from the selected clinical trials. For each study, the proportion of patients with HFSR was calculated and the 95% exact confidence interval was derived. For studies with a control arm, the relative risk of HFSR among patients assigned to sorafenib was also calculated and compared only with those assigned to control treatment in the same trial.

For meta-analysis, both fixed-effects model (weighted with inverse variance) and random-effects model were considered [13]. For each meta-analysis, the Cochran's Q statistic was first calculated to assess the heterogeneity among the proportions of the included trials. For p-value for Cochran's Q statistic was less than 0.1, the assumption of homogeneity was deemed invalid [14], and random-effects model was reported. Otherwise, both the fixed-effects model and the random-effects model results were reported. A two-tailed p-value of less than 0.05 was judged as statistically significant.

## Results

*Search results*

Our search yielded a total of 223 articles on sorafenib in the literature. After reviewing each publication, we identified original studies including randomized controlled trials and single arm phase II studies. From these studies, four clinical trials fulfilled our inclusion criteria [3,5,11,15]. From the abstracts published during recent ASCO annual meetings from 2004–2007 and ASCO Prostate Cancer Symposium, we identified 68 abstracts that included sorafenib. After reviewing each abstract, we included seven additional trials to our meta-analysis.[4,16–22] Among the eleven trials included, four were blinded [3,5,11,16] and the other three trials were open-labeled. Three trials were sponsored by Bayer Pharmaceuticals and Onyx Pharmaceuticals [3,11,16], and one trial was sponsored solely by Bayer Pharmaceuticals [5]. One trial in prostate cancer was supported by the National Cancer Institute [17]. The support for the other trials was not described.

*Patients*

A total of 4 883 patients from 11 clinical studies were available for analysis, with 4 020 patients treated with sorafenib as a single agent. The baseline characteristics of patients in the eleven studies are listed in Table I. HFSR was not listed as a baseline characteristic in any of the patients. The baseline ECOG status for most of the patients was between 0 and 1. Underlying malignancies for the eleven studies included renal cell cancer, melanoma, non-small cell lung cancer, prostate cancer, hepatocellular cancer, non-GIST sarcoma, and neuroendocrine tumor. Treatment was randomly assigned in five clinical studies including three randomized controlled trials and two randomized discontinuation trials [3,11,15,16,20].

Table I. Characteristics of studies included in the meta-analysis.

| Trial | Latest Publication | Trial Design | No. Enrolled | Age median (years) | Underlying Malignancy |
|---|---|---|---|---|---|
| Escudier et al. [16] | NEJM | Randomized phase III (Placebo vs Sorafenib) | 903 | 58 | RCC |
| Eisen et al. [49] | BJC | Randomized discontinuation phase II (Placebo vs Sorafenib) | 37 | 53 | Melanoma |
| Ratain et al. [3] | JCO | Randomized discontinuation phase II (Placebo vs Sorafenib) | 202 | 58 | RCC |
| Szczylik et al. [18] | 2007 ASCO meeting | Randomized phase II (IFN vs Sorafenib) | 189 | 62 | RCC |
| Gatzemeier et al. [4] | 2006 ASCO meeting | Single arm phase II | 52 | 62 | NSCLC |
| Wu et al. [17] | 2006 Prostate Cancer symposium | Single arm phase II | 22 | 64 | Prostate |
| Ghassan et al. [5] | JCO | Single arm phase II | 147 | 69 | HCC |
| Figlin et al. [21] | 2007 ASCO meeting | Expanded access program | 2502 | 63 | RCC |
| D'Adamo et al. [19] | 2007 ASCO meeting | Single arm phase II | 134 | 55 | Non-GIST Sarcoma |
| Hobday et al. [22] | 2007 ASCO meeting | Single arm phase II | 93 | 59 | Neuroendocrine tumors |
| Liovet et al. [20] | 2007 ASCO meeting | Randomized phase III (Placebo vs Sorafenib) | 602 | 66 | HCC |

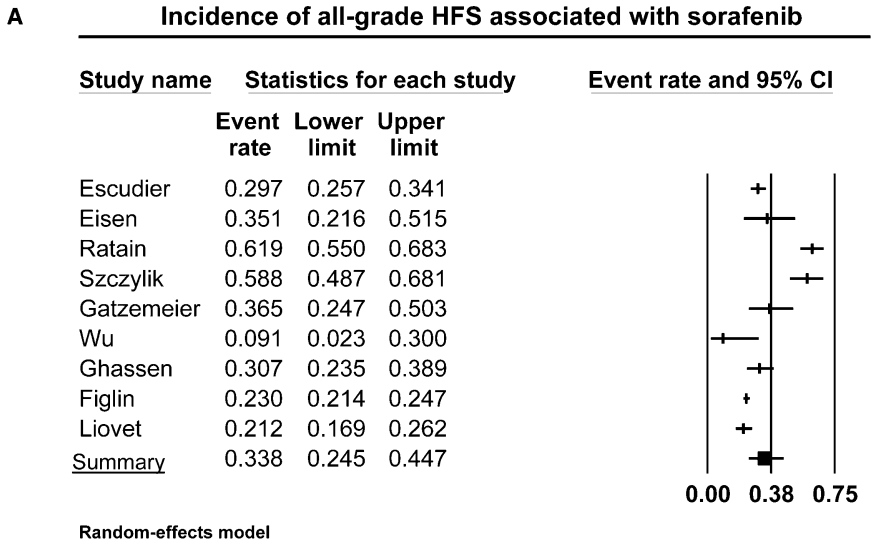
Abbreviations: RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; HCC, hepatic cellular carcinoma; NEJM, New England Journal of Medicine; BJC, British Journal of Cancer. ASCO meeting, American Society of Clinical Oncology annual meeting.

*Incidence of HFSR*

A total of 3 797 patients with various advanced solid tumors were identified who were treated with sorafenib as a single agent with data of all-grade HFSR available for analysis. The initial dose for sorafenib was 400 mg twice daily for patients in all of these trials. The incidence of all-grade HFSR in these studies ranges between 9.1 to 61.9%, with the highest being in the phase II placebo controlled randomized discontinuation trial in patients with metastatic renal cell cancer [3], and the lowest incidence observed in patients with prostate cancer [17]. Using random-effects model, meta-analysis revealed that the summary incidence of all-grade HFSR in all these patients was 33.8% (95% CI: 24.5–44.7%) (Figure 1A).

*Incidence of high-grade HFSR*

High-grade (grade III) HFSR is associated with significant morbidity and results in dose-reduction



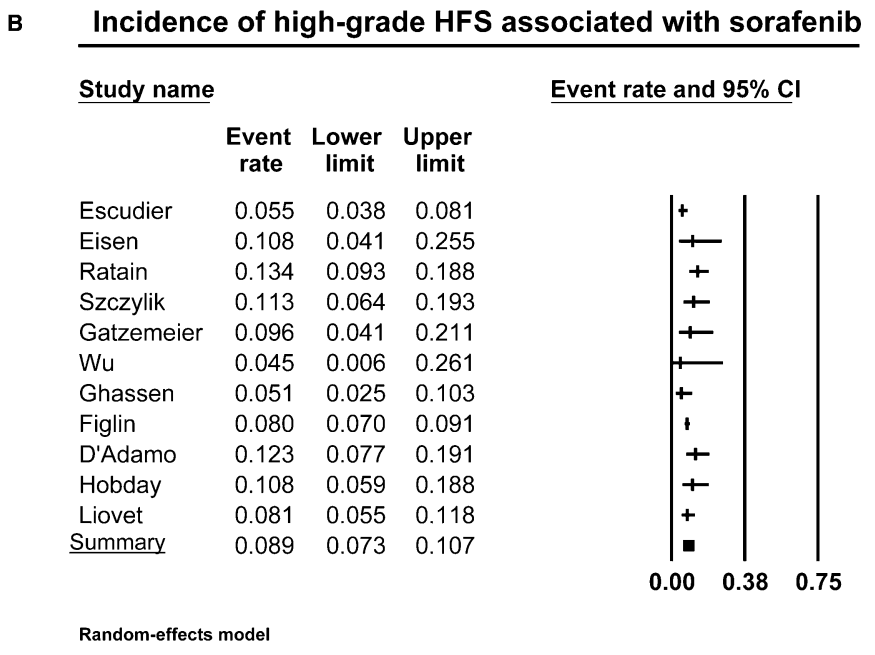




Figure 1. Annotated forest plot for meta-analysis of the incidence of hand-foot skin reaction (HFSR) in cancer patients who received sorafenib.
The summary incidences of all-grade (A) and high-grade (B) HFSR are calculated using a random-effects model. The incidences and 95% confidence intervals for each study and the final combined result are displayed numerically on the left and graphically as a forest plot on the right. Under study name, the first author's name was used to represent each trial.

of sorafenib. A total of 4 020 patients with various advanced solid tumors were identified who were treated with sorafenib as a single agent with data of high-grade HFSR available for analysis. The incidence of grade III HFSR in these studies ranged between 4.5 to 13.4% with the highest again being in the phase II placebo controlled randomized discontinuation trial in patients with metastatic renal cell cancer [3], and the lowest incidence again seen in patients with prostate cancer [17]. Using the random-effects model, the calculated summary incidence of grade III HFSR was 8.9% (95% CI: 7.3–10.7%) (Figure 1B).

### *Incidence of HFSR in patients with RCC versus non-RCC solid tumors*

In order to identify predisposing factors for HFSR, we further explore the relationship between sorafenib-associated HFSR and tumor type, and analyzed the incidence of HFSR in patients with RCC and non-RCC cancers. Among 3 252 patients with RCC, the incidence of all-grade HFSR is 42.0% (95% CI: 24.9–61.3%) (Figure 2A), and the incidence of high-grade HFSR is 8.9% (95% CI: 6.3–12.3%) (Figure 2B); while for 545 patients with non-RCC malignancies, the incidence of all-grade HFSR is 27.6% (95% CI: 20.2–36.4%) (Figure 3A), and the incidence of high-grade HFSR is 9.1% (95% CI: 7.2–11.3%) (Figure 3B).

Interestingly, there is significant difference detected between patients with RCC and non-RCC cancer in terms of the incidence of sorafenib-associated all-grade HFSR (RR 1.52, 95% CI: 1.32–1.75%, $p < 0.001$). However, there is no significant difference between RCC and non-RCC in terms of the incidence of high-grade HFSR (RR 0.98, 95% CI: 0.76–1.26%, $p = 0.86$).

### *Relative risk of hand-foot skin reaction*

Relative risk (RR) can be used to determine the particular contribution of sorafenib to the development of HFSR in these patients with various

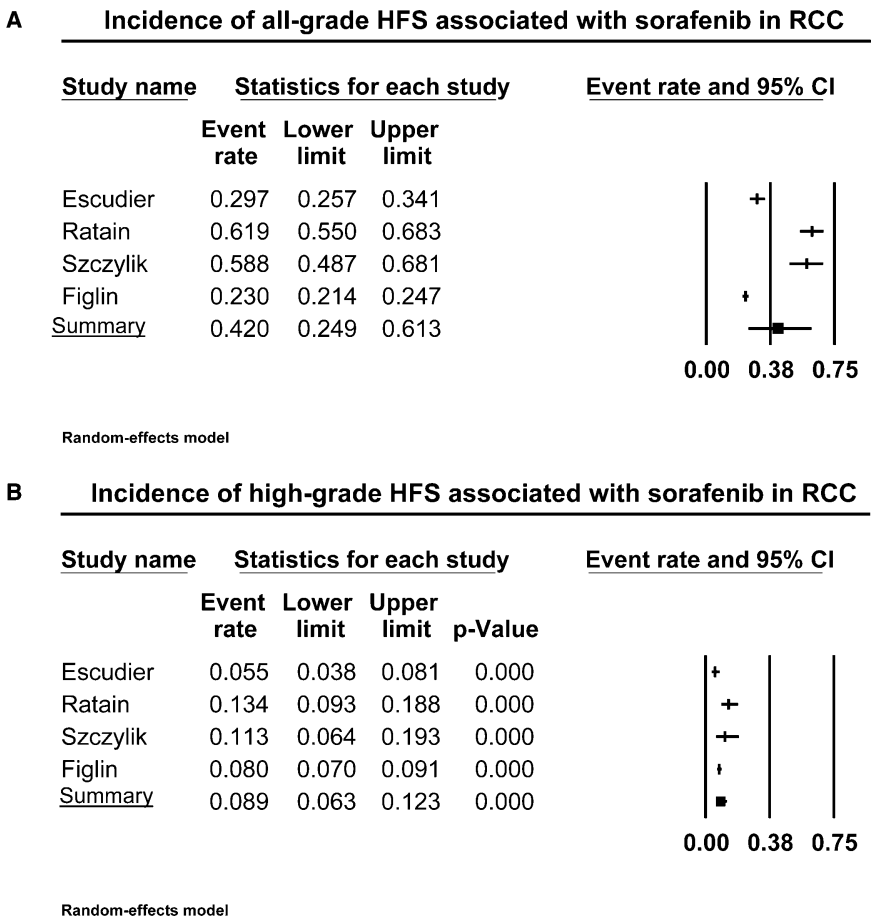



Figure 2. Annotated forest plot for meta-analysis of the incidence of hand-foot skin reaction (HFSR) associated with sorafenib in patients with renal cell cancer.
The summary incidences of all-grade (A) and high-grade (B) HFSR associated with sorafenib for patients with RCC are calculated using a random-effects model. The incidences and 95% confidence intervals for each study and the final combined result are displayed numerically on the left and graphically as a forest plot on the right. Under study name, the first author's name was used to represent each trial.

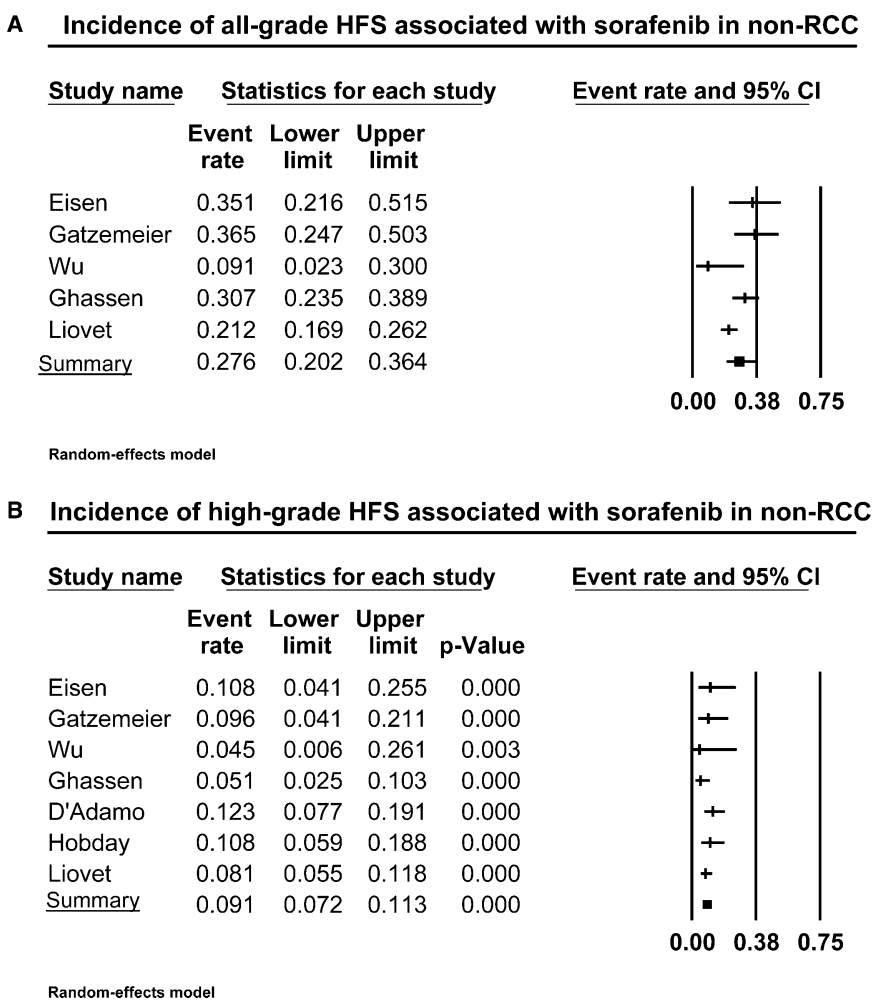



Figure 3. Annotated forest plot for meta-analysis of the incidence of hand-foot skin reaction (HFSR) associated with sorafenib in patients with non-renal cell cancer.
The summary incidence of all-grade (A) and high-grade (B) HFSR is calculated using a random-effects model. The incidences and 95% confidence intervals for each study and the final combined result are displayed numerically on the left and graphically as a forest plot on the right. Under study name, the first author's name was used to represent each trial.

underlying malignancy and history of other therapeutic interventions, which may be confounding factors. A meta-analysis of relative risk (RR) for HFSR associated with sorafenib compared with controls was performed on the three randomized clinical trials for patients with metastatic renal cell cancer and hepatocellular carcinoma [11,16,20]. One trial utilized interferon as a control [16], whereas the other two trials used placebo as control [11,20]. The incidences of HFSR were low in controls for these studies ranging from 3.0 to 6.7%. Using a random-effects model, meta-analysis showed that the summary RR of all-grade HFSR for sorafenib versus controls was 6.6 ( 95% CI: 3.7–11.7, $p < 0.001$) (Figure 4). Sorafenib was therefore found to be associated with a significantly greater risk for developing HFSR.

## Discussion

Our meta-analysis has demonstrated that sorafenib is associated with a significantly increased risk of HFSR in patients being treated for renal cell cancer and other solid tumors. The overall incidence of all-grade HFSR was 33.8% (95% CI: 24.5–44.7%) with the majority of those affected by HFSR being grades I and II with a significant proportion of those being grade III (8.9% by our analysis). As sorafenib will be used more frequently in cancer patients either alone or in combination with other agents, it is important for physicians to recognize this risk and treat the side effect properly as it may develop into a serious and devastating toxicity.

Our study also revealed the significant disparity in the incidence of sorafenib-associated HFSR in patients with RCC versus non-RCC malignancies.

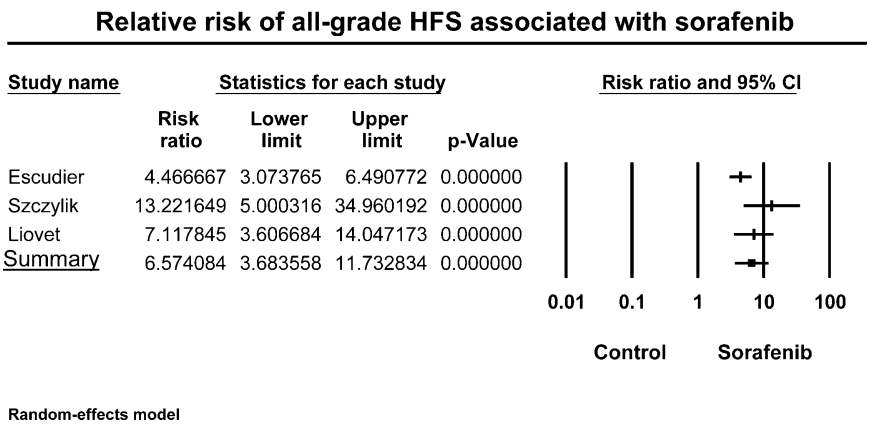



Figure 4. Relative risk (RR) of hand-foot skin reaction associated with sorafenib versus control in patients with metastatic renal cell carcinoma and hepatocellular carcinoma.
The summary RR was calculated using a random-effects model. RR and 95% confidence intervals for each study and the final combined result are displayed numerically on the left and graphically as a forest plot on the right. Under study name, the first author's name was used to represent each trial.

The source of this disparity is not clear. A large portion of RCC patients being treated with sorafenib have undergone nephrectomy for primary treatment of their disease, and in turn may have a resultant decreased glomerular filtration rate. The consequence may be a greater accumulation of sorafenib in RCC patients and a higher incidence of toxicity, in particular HFSR. Alternatively, RCC patients may have a unique biology and prior treatment that predisposes them to HFSR

Our study showed that the risk of HFSR increased about 6.6-fold with sorafenib starting at the standard dose in patients with metastatic renal cell carcinoma and hepatocellular carcinoma (Figure 4). The pathogenesis of sorafenib-associated HFSR is uncertain. Cutaneous toxic effects including HFSR are among the more common adverse manifestations of the many emerging VEGF blocking agents including sorafenib and sunitinib. The dose-dependent nature of HFSR with sorafenib suggests a direct toxic effect of the offending agents [23]. It has been hypothesized that cytotoxic drugs may be excreted in sweat, making palms and soles more prone to HFSR due to the increased number of eccrine sweat glands in the extremities, as areas with apocrine sweat glands are not affected [24]. Studies have demonstrated increased detection of cytotoxic drugs notorious for HFSR in the uppermost part of the skin on the palmar-plantar surfaces, deep in sweat ducts, and around their openings in the upper skin layers which suggests delivery of the drug via sweat to the skin [25]. Interestingly, it has been reported that a patient stricken with an above the knee amputation being treated for metastatic renal cell carcinoma with sorafenib developed hand-foot-stump syndrome [26]. This case supports the notion that there is a direct toxic effect of sorafenib in the areas affected relating this to the high concentration of eccrine glands in the patient's palms and single sole as well the hyperhidrosis of the encased stump [26].

As VEGF plays a physiological role in mucosal integrity and neuronal functioning, it is possible that blocking VEGF activity may result in a combined effect which may manifest as HFSR [27]. However, current studies do not support this hypothesis. Histologic examination of the skin with HFSR shows epidermal changes that suggests alterations in keratinocyte maturation. While sorafenib inhibits VEGFR and FLT 3, these receptors are not expressed on keratinocytes [28]. However, this does not exclude the possibility that VEGF may be involved in the development of HFSR by its inhibition on vascular endothelium. Indeed, bevacizumab, a humanized antibody against VEGF, appears to enhance the incidence and severity of HFSR associated with sorafenib in phase I trials [29].

Others propose a more mechanical effect of direct pressure to the areas affected. Studies have demonstrated that combined suppression of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms [30]. As sorafenib is a tyrosine kinase inhibitor affecting both VEGF and PDGF, the capillary endothelium may be first damaged by sorafenib. Subsequently while the hand and foot surfaces are under direct pressure from walking, hand washing or other daily use, the affected vessels under the pressure areas are open to mechanical damage and present as HFSR with inflammation and blisters [31]. Regional temperature gradients, effect of gravity, and vascular make-up of the distal extremities may also contribute to the localization to the palms and soles [32].

The molecular mechanism underlying the development of sorafenib-induced HFSR is not clear. Histological analysis of affected skin in patients with HFSR treated with sorafenib revealed a marked thickening of the stratum corneum, along with eccrine disarray and a mild perivascular infiltrate (M. Lacouture, unpublished data). Thus HFSR may be due to a direct effect of sorafenib on receptors located on the eccrine glands themselves. It is known that both PDGF and c-Kit are expressed in sweat duct epithelium [33,34]. It is conceivable that alterations in the pathophysiology of eccrine ducts of patients treated with inhibitors against one of these two receptors may cause this cutaneous manifestation. Another hypothesis is the alteration of keratinocytes by inhibition of the c-Kit receptor. It has been shown that the c-Kit ligand is expressed on human keratinocytes [35], and it is reasonable that the direct inhibiting effect of sorafenib on C-Kit may be toxic to the keratinocytes. Among the molecularly targeted agents used for cancer treatment, sorafenib and sunitinib have the highest association with HFSR (Table II). This implies that these two agents share unique properties which when administered to patients results in HFSR. Indeed, both sorafenib and sunitinib target receptors that are not common to other agents such as imatinib and bevacizumab, as shown in Table II. In particular, the oncogene receptors RET and Flt-3 are targeted by these two agents but not by other molecular targeting agents, suggesting that these two targets may play important role in the development of HFSR. Currently RET and Flt-3 expression in human keratinocytes or sweat duct epithelium has not been described in the literature, but further investigation into this area may be valuable in understanding the pathogenesis of HFSR associated with sorafenib.

It has been noted in the literature a rare association between imatinib and palmoplantar hyperkeratosis in patients being treated long term for chronic myeloid leukemia [36]. Imatinib, sorafenib and sutent all target PDGFR and C-Kit (Table II); however, the incidence of HFSR associated with imatinib is quite rare. Therefore it is less likely that inhibition of PDGFR and C-Kit receptors alone would result in cutaneous manifestations of HFSR. Thus, both the inhibition of sweat duct epithelium through PDGFR/c-Kit and the reduction of angiogenesis through VEGF pathway may be important for the development of HFSR. The dual antiproliferative and antiangiogenic properties of sorafenib and sunitinib would trigger a change in sweat duct epithelium and vasculature which in turn lead to the cutaneous manifestations seen in patients with HFSR, while anti-proliferative property of imatinib or anti-angiogenic effect of bevacizumab alone is not sufficient to induce significant HFSR. However, the inhibition of PDGFR/c-Kit and VEGFR may not be sufficient to induce HFSR. Indeed, a phase II study in 48 patients with renal cell carcinoma combining bevacizumab, imatinib and erlotinib did not report any cases of HFSR [37]. Thus, additional pathways blocked by sorafenib or sunitinib, e.g. Flt-3 and RET, may also contribute to the development of HFSR.

Table II. Association of hand-foot skin reaction with molecular targets.

| Agent | Molecular Target | Incidence of HFSR |
|---|---|---|
| Bevacizumab | VEGF-A (interacting with VEGFR-1, 2) [49] | Minimal |
| Imatinib | Bcr-abl, *C-Kit, PDGFRα*, β tyrosine kinase [50] | rare |
| Sunitinib | VEGFR-1,-2; *PDGFR, C-Kit,* ***Flt-3, RET*** [51] | 14 – 20% [52,53] |
| Sorafenib | VEGFR-2,-3, Raf, PDGFR, C-Kit, **Flt-3, RET** | 33.8% |

Abbreviations: PDGFR, platelet derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; HFSR, Hand-Foot Skin Reaction. Targets shared by sunitinib and sorafenib but not imatinib and bevacizumab are bolded.

Because of the high incidence of HFSR associated with sorafenib use, early detection and timely treatment will be a vital component in managing patients during their treatment course to allow for continued treatment. Initial consideration is the decision to reduce dose, interrupt treatment, or if severe enough to ultimately discontinue the treatment. It is suggested by the manufacture package insert that for those experiencing grade I toxicity to consider topical therapy. Grade II lesions are suggested to be remedied with treatment interruption with or without subsequent dose reduction if not improved with topical treatment or for multiple recurrences. Grade III toxicity (as shown Figure 5) is managed by treatment interruption with or without subsequent dose reduction unless it recurs greater than two times, for which discontinuation is recommended. As with most other side effects found with kinase inhibitors, resumption of treatment is not always accompanied by the same side effect [28].

HFSR has been an ongoing problem since its discovery in the mid-70's and various treatment strategies have been employed. At the first sign of HFSR, all patients should undertake supportive measures including wearing cotton socks, gel inserts, and soft shoes to avoid pressure points. Furthermore, patients should avoid extremes of temperature, pressure and friction on the skin [38]. Indeed, prophylactic pedicures to resolve calluses can prevent initial and future episodes of HFSR [28].

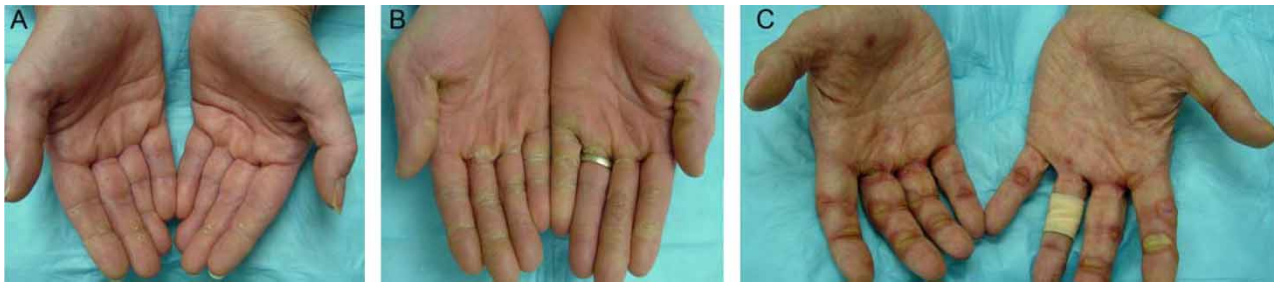



Figure 5. Example of grades I (A), II (B), III (C) hand-foot skin reaction (HFSR) in patients receiving sorafenib.

Cooling of the affected areas may be effective for immediate relief and may also alleviate future toxicity as vasoconstriction to the distal extremities may reduce drug exposure to these areas.

Non-pharmacologic treatments are recommended prior to and during the development of symptoms. Topical agents including moisturizing creams, Epsom salt (magnesium sulfate) mixed with warm water [39], aloe vera lotion and emollients are among the several products accessible for patients initiating therapy. Moisturizing creams such as urea-containing creams and topical petroleum-lanolin based ointment with antiseptic hydroxyquinoline have been effective by helping to maintain skin integrity [32].

Pharmacologic agents have also played an integral role in the treatment of HFS associated with cancer chemotherapies. Dimethyl sulfoxide(DMSO) has been effective in treating doxorubicin associated HFS thought to be stemming from its ability to scavenge free radicals [40]. Oral pyridoxine has been shown to prevent or delay the onset of HFS in patients being treated with a number of chemotherapeutic agents including 5-FU continuous infusion, docetaxel, and pegylated liposomal doxorubicin(PLD) [41–43]. It is an inexpensive vitamin, and a feasible adjunct to chemotherapies associated with HFS. Systemic steroids have also been evaluated and have been effective in the prevention of HFS most notably in patients receiving PLD [44]. The role of steroids in the treatment of HFS is not clear. A recent case report revealed that dramatic improvement of persistent severe HFS resistant to topical DMSO and oral pyridoxine with the use of prednisone in a patient treated for metastatic breast cancer with PLD. It is possible that the inflammatory nature of HFS can be treated with the anti-inflammatory properties of systematic steroid [45]. Interestingly, other agents that have been investigated for the treatment and prevention of HFS associated with chemotherapy are vitamin E, nicotine patch, and celecoxib [46–48]. As one of the proposed mechanisms of HFSR is the direct toxic effect of the agents via delivery by sweat, it is conceivable that inhibition of hyperhidrosis in these areas may delay or prevent this side effect. Studies in the future evaluating reduction of hidrosis in the palms and soles may be valuable. It is important to note that past studies have not been performed in patients treated with sorafenib. Furthermore, there have not been any large randomized trials exclusively for selecting the most effective treatment of HFS, and most of these studies are observational.

Our study has the following limitations. First, the results described here are affected by the limitations of individual clinical trials that were included in the meta-analysis. The detection of HFSR may vary significantly among academic centers and institutions where these studies were performed. Second, there is significant heterogenicity among the included clinical trials, including a wide range of variation in tumor type and sample size. Calculation using random-effects model in this study may improve the accuracy of incidence estimation. In addition, the patients in this study were mostly a selected group of patients involved in clinical trials with metastatic cancers. These results were observed in academic centers and major research institutions, and may not apply to patients treated in the community. However, this study does include many patients from expanded access program who are mostly from community setting. The incidence of HFSR in these patients is not significantly different from other studies which were performed in major academic institutions.

In conclusion, this study has demonstrated that sorafenib is associated with a significant risk of developing HFSR in patients being treated for advanced solid tumors, particularly renal cell carcinoma. Early detection and management of HFSR is imperative to allow patients to continue life-prolonging therapy with minimal morbidity. Cautions must be taken to monitor HFSR along with other side effects when sorafenib is combined with other agents in clinical trials due to unclear underlying mechanism. The significant incidence and risk demonstrated in this study suggests the necessity for additional basic and clinical studies to investigate the pathogenesis and treatment of sorafenib-associated HFSR.

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