Hand-Foot Skin Reaction Increases with Cumulative Sorafenib Dose and with Combination Anti-Vascular Endothelial Growth Factor Therapy

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Abstract

Purpose: Sorafenib, a vascular endothelial growth factor (VEGF) receptor-2 and RAF kinase inhibitor, commonly causes skin toxicity. We retrospectively analyzed dermatologic toxicity in patients receiving combined antiangiogenic therapy involving sorafenib and bevacizumab.

Experimental Design: Castration-resistant prostate cancer and metastatic non-small cell lung cancer patients were accrued to phase II studies, receiving sorafenib 400 mg twice daily. A phase I study explored sorafenib 200 to 400 mg twice daily with bevacizumab 5 to 10 mg/kg every 2 weeks in patients with advanced solid tumors. The probability of development of maximum grade of dermatologic toxicity as a function of the cumulative dose of sorafenib was determined. Additional analyses compared extent of toxicity, pharmacokinetics, and patient risk factors.

Results: Ninety-six patients were enrolled: 54 received sorafenib and 42 received bevacizumab/sorafenib. Hand-foot skin reaction (HFSR) was observed in 50 of 96 (52%) patients. Grade 2 to 3 HFSR developed in 16 of 54 (30%) sorafenib patients and 24 of 42 (57%) bevacizumab/sorafenib patients ($P = 0.012$) and was associated with cumulative sorafenib exposure ($P = 0.0008$). Twenty-four of 42 phase I patients randomized to start with bevacizumab had increased risk of grade 2 to 3 HFSR than those starting with sorafenib ($P = 0.013$) after adjusting for association between HFSR risk and hypertension ($P = 0.01$), which was the only toxicity associated with HFSR. There was no association between HFSR and baseline history of neuropathy, prior taxane/platinum treatment, or systemic sorafenib levels.

Conclusions: Sorafenib-related HFSR is associated with increasing cumulative sorafenib dose. HFSR is increased in patients treated with bevacizumab/sorafenib combination anti-VEGF therapy, and this finding is not explained by pharmacokinetic interaction between the two agents. Our results suggest that the pathophysiology of HFSR may be related to VEGF inhibition.

Antiangiogenesis therapy is an increasingly important category in the anticancer armamentarium. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, and sorafenib, a multikinase inhibitor that targets RAF kinase, VEGF receptors (VEGFR) 1 to 3, platelet-derived growth factor-α and -β, c-KIT, and RET, have been approved for use in various malignancies.[5,6] Cutaneous side effects are recognized adverse effects of many molecularly targeted therapies, including epidermal growth factor receptor inhibitors, and some cytotoxic agents (e.g., 5-fluorouracil and liposomal doxorubicin; ref. 1).

The development of cutaneous signs may also have clinical implications, as in the case of cetuximab, where presence of rash is predictive of response (2).

Hand-foot skin reaction (HFSR; palmar-plantar dysesthesia; acral erythema) and rash have been described with the use of sorafenib but have not been shown to be predictive of response to therapy (3, 4). Sorafenib-related non-HFSR skin eruptions include facial/scalp erythema and dysesthesias, alopecia, splinter hemorrhages, keratoacanthomas (5), leukocytoclastic vasculitis (6), and epidermal inclusion cysts. A single pooled analysis of four phase I trials showed an increased incidence of HFSR with higher starting doses of single-agent sorafenib (7). However, HFSR incidence in relation to cumulative sorafenib dose has not been studied, nor has there been an exploration of dermatologic adverse events when sorafenib is combined with other targeted therapies. We report a significantly increased incidence of HFSR with combination sorafenib-based anti-VEGF/VEGFR treatment and a relationship between cumulative sorafenib dose and the development of HFSR. In addition, we

[5] http://www.cancer.gov/cancertopics/druginfo/fda-sorafenib-tosylate
[6] http://www.cancer.gov/cancertopics/druginfo/fda-bevacizumab

Translational Relevance

Sorafenib inhibits multiple kinases including vascular endothelial growth factor (VEGF) receptor-2. Hand-foot skin reaction (HFSR) is currently emerging as a major toxicity of sorafenib treatment requiring clinical management and dose modifications, although the mechanism underlying HFSR is not clearly understood. The dose level of sorafenib as a single agent has been associated with the development of HFSR, but the relationship between cumulative dose of sorafenib and development of HFSR has not been explored. We report the first correlation between cumulative sorafenib dose and HFSR for both single-agent sorafenib and combined anti-VEGF therapy. In addition, this is the first study to examine dermatologic toxicities of combination anti-VEGF therapies involving sorafenib and bevacizumab. We find that the frequency of adverse events is greater with combination anti-VEGF therapy than with sorafenib alone. This study supports the hypothesis that the anti-VEGF properties of sorafenib may cause HFSR. This finding has important clinical relevance regarding monitoring and treatment of patients on sorafenib and other anti-VEGF therapy.

analyzed multiple patient and treatment-associated risk factors for development of various cutaneous toxicities in sorafenib-treated patients.

Patients and Methods

Patient eligibility. Three trials done at the National Cancer Institute were included in this retrospective analysis. Two were phase II sorafenib monotherapy trials in metastatic castration-resistant prostate cancer (8) and non-small cell lung cancer. A phase I trial of the combination of sorafenib and bevacizumab in advanced solid tumors was also analyzed (9). All participants were required to have well-controlled blood pressure or cardiac disease, good end-organ function, measurable disease, an Eastern Cooperative Oncology Group performance status of 0 to 2 (the combination study required an Eastern Cooperative Oncology Group performance status of 0-1) at the time of enrollment, and no active intracranial disease. Patients had not previously received the experimental agent(s). All trials were approved by the Institutional Review Board of the National Cancer Institute and written informed consent was obtained before enrollment.

Treatment plan and dose modifications. Each cycle was 28 days. Sorafenib was administered at 400 mg twice daily in both sorafenib monotherapy studies. In the combination bevacizumab/sorafenib

phase I study, patients were treated with intravenous bevacizumab 5 to 10 mg/kg every 2 weeks and sorafenib 200 to 400 mg twice daily or days 1 to 5 according to dose level (Table 1) that consisted of a dose escalation cohort and a second group of patients. The latter was randomized to receive 1 month of bevacizumab or sorafenib monotherapy followed by combination therapy for all subsequent cycles; doses administered to this group were dose level 1.

Toxicities were graded according to Common Terminology Criteria for Adverse Events (version 3); HFSR definition based on grade is listed in Table 2. Clinically significant HFSR was categorized as grade 2 and 3 for all analyses, as this level of toxicity required modifications in patient management. Each study had a distinct algorithm for drug holiday and reductions (Table 3). The Dermatology Service was consulted for most grade 2 and all grade 3 cases of HFSR as needed.

Patient monitoring and response assessment. Pretreatment assessments were made within 1 to 2 weeks of therapy initiation and included history and physical examination, laboratory studies, electrocardiogram, chest radiograph, and noninvasive imaging to determine tumor burden. Patients were examined at least every 4 weeks. Reassessment imaging was done every two cycles and evaluated by a reference radiologist without knowledge of the patient's clinical status. Results were characterized using Response Evaluation Criteria in Solid Tumors (10). Prostate-specific antigen responses were recorded according to the Prostate-Specific Antigen Working Group definition (11). Prostate-specific antigen was used for determination of disease response in patients with prostate cancer for the first 22 patients (8); monthly CA125 levels were measured but not used for clinical decision-making for patients with ovarian cancer (9, 12).

Pharmacokinetics. Samples for pharmacokinetic analysis were drawn and evaluated as described previously (13) at baseline, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 h after administration of initial doses of sorafenib in all three trials (8, 9). The pharmacokinetic variables AUC_{0-12}, C_{max} and t_{max} were calculated using the WinNonlin professional software version 5.0. AUC_{0-12} was calculated for each patient as the area under the curve from time 0 to 12 using the linear trapezoidal method.

Statistical analysis. The data for the single-agent sorafenib studies were pooled, as the same dose and general modification scheme was used in both studies. Comparisons were made to combination anti-VEGF/VEGFR therapy. Cumulative sorafenib dose for each cycle was used for the analyses to minimize the variations in sorafenib dosing strategies (dose reductions and dose levels) between the studies and among patients. The analyses comparing toxicity grades or treatment characteristics among or between the trials or to patient risk factors were done using categorical or nonparametric tests, including Fisher's exact test, Mehta's modification to Fisher's exact test for generalized $r \times c$ tables (14), a Cochran-Armitage test for trend (15), Jonckeere-Terpstra test for trend (16), a Kruskal-Wallis test, or a Wilcoxon rank-sum test. The probability of development of the maximum grade of toxicity as a function of the cumulative dose of drug administered was determined by the Kaplan-Meier method, with the statistical significance of the difference between curves determined by the log-rank test. Logistic regression analysis for ordered categories was used to assess the relationship between increasing grade of HFSR toxicity and prognostic factors when considered jointly after verifying that there were

Table 1. Dose levels for combination sorafenib + bevacizumab trial

Dose level	No. patients	Sorafenib	Bevacizumab
1	30	200 mg twice daily	5 mg/kg every other week
2	6	200 mg twice daily	10 mg/kg every other week
3	Not accrued	400 twice daily	10 mg/kg every other week
4	4	200 mg twice daily 5 d/wk	5 mg/kg every other week
5A	1	200 mg twice daily 5 d/wk	10 mg/kg every other week
5B	1	400 twice daily 5 d/wk	5 mg/kg every other week

Table 2. HFSR grading

Grading for HFSR*

Grade 1	Minimal skin changes or dermatitis (e.g., erythema) without pain
Grade 2	Skin changes (e.g., peeling, blisters, bleeding, and edema) or pain not interfering with function
Grade 3	Ulcerative dermatitis or skin changes with pain interfering with function
Grade 4	None

*Based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

proportional odds. All *P* values are two-tailed and presented without adjustment for multiple comparisons.

Results

Patient accrual. Ninety-six patients were accrued to the three studies between September 2004 and August 2007. Forty-one patients were treated on the prostate cancer study, 13 patients on the non-small cell lung cancer study, and 42 patients on the two-drug combination phase I study. Tumor types and demographics are included in Table 4.

Dermatologic toxicity. Grade 1 to 3 HFSR was observed in 50 of 96 (52%) patients in the three trials. Thirty-one percent (17 of 54) of patients on the single-agent sorafenib studies had grade 1 to 3 HFSR, whereas 79% (33 of 42) of patients who received combination bevacizumab and sorafenib had HFSR. Clinically important HFSR was defined as grades 2 and 3 (Fig. 1) and was noted in 16 of 54 (30%) sorafenib alone patients and 24 of 42 (57%) sorafenib/bevacizumab patients (*P* = 0.012). Once initial diagnosis of HFSR was made, patients had a cyclical waxing/waning course of recurrent grade 2 toxicity for the duration of the treatment (range, 1-30+ cycles). Four of 41 (10%) and 4 of 13 (31%) of patients on the prostate cancer and lung cancer studies were dose reduced for HFSR toxicity, respectively; 9 of 42 (21%) patients on the combination study were dose reduced for HFSR. Holds in sorafenib for grade 2 HFSR at a median of once every two cycles were required in patients after maximal dose reduction to sorafenib 200 mg/d in patients on the combination therapy trial. Management interventions included emollients, cushioning, pyridoxine therapy (maximum dose 800 mg/d), and paring of calluses with varying degrees of benefit. Combination therapy

resulted in higher-grade HFSR (*P* = 0.0006) as well as a lower cumulative sorafenib dose at which the highest grade toxicity was noted (21,117 mg in the combination trial versus not reached in the single agent trial; *P* = 0.0008; Fig. 2A).

Skin lesions other than HFSR were observed in 52% of patients. Several types of rash were observed including diffuse maculopapular eruptions, facial and scalp erythema, keratoacanthomas, and epidermal inclusion cysts. The variety and grade distributions of these skin findings were similar in all three studies, affecting 30 of 54 (56%) patients on sorafenib alone treatment and 20 of 42 (48%) patients treated with a combination of bevacizumab and sorafenib. The dose of sorafenib at which the rashes were noted did not differ between the two groups (Fig. 2B). The frequency of grade 2 to 3 non-HFSR skin reactions did not differ between single-agent therapy (10 of 54; 19%) and combination therapy (6 of 42; 14%).

Risk factors for HFSR. Patient data were analyzed from the prostate cancer single-agent sorafenib study (41 patients) and the sorafenib/bevacizumab study (42 patients) to identify possible risk factors for HFSR. There was no association between HFSR and prior taxane exposure, age, baseline neuropathy, or development of rash while on study drugs in either study (Table 4). No association of HFSR and prior platinum or liposomal doxorubicin treatment was seen in the combination sorafenib/bevacizumab trial. Analysis of the association between HFSR and the other most common sorafenib toxicities (fatigue, diarrhea, and hypertension) on the combination study revealed that only hypertension was associated with the development of HFSR, with 7 of 13 (54%) patients without hypertension developing HFSR compared with 26 of 29 (90%) who developed or worsened preexisting hypertension (*P* = 0.02). Both cumulative sorafenib and bevacizumab dose were associated with increasing grade of HFSR toxicity (*P* = 0.009 and *P* < 0.0001, respectively) in the cohort of patients randomized to one cycle of single-drug therapy. In the same cohort of patients, those who received bevacizumab first had a greater risk of being associated with increasing grade of HFSR compared with those who received sorafenib first (*P* = 0.013; odds ratio, 5.85; 95% confidence interval, 1.44-23.8) after adjusting for development of hypertension on study, which also was associated with an increased risk of HFSR (*P* = 0.01; odds ratio, 6.13; 95% confidence interval, 1.54-24.31). There were inadequate data to assess the relationship between clinical response and HFSR due to the paucity of responses (10 partial responses overall by Response Evaluation Criteria in Solid Tumors: 7 in the combination therapy group, 1 in the single-agent prostate group, and 2 in the single-agent non-small cell lung cancer group).

Table 3. Variables for dose modifications of sorafenib

Toxicity	Sorafenib (prostate cancer)	Sorafenib (lung cancer)	Sorafenib plus bevacizumab
First grade 2 adverse event	No change*	200 mg reduction	Hold; no reduction
Recurrent grade 2 adverse event	No change*	200 mg reduction	50% reduction
Grade 3 adverse event	200 mg reduction	50% reduction	50% reduction
Grade 4 adverse event	Discontinue	Discontinue †	Discontinue

NOTE: All reductions and holds require temporarily halting sorafenib until adverse event resolves to grade ≤1 then restarting.
*Dosing continued as long as patient tolerated treatment.
† Grade 4 nonhematologic toxicity.

Table 4. Demographics

|	Sorafenib alone in prostate cancer	Sorafenib alone in lung cancer	Combination sorafenib and bevacizumab
Age			
Range (median)	48-88 (66)	35-84 (64)	30-76 (58)
Sex			
Male	41	8	14
Female	0	5	28
Patients treated with prior			
Taxanes	31	11	26
Liposomal doxorubicin	0	0	12
No. prior treatments	1-8 (4)	1-7 (1)	1-15 (6)
Tumor type	Prostate 41	Non-small cell lung cancer 13	Epithelial ovarian cancer 15
			Melanoma 7
			Sarcoma 5
			Breast 3
			Renal 3
			Colorectal 2
			Others 7*
Cycles administered [†]			
Range (median)	1-10 (2)	1-7 (3)	1-26+ (median, 4)
Cumulative sorafenib dose (mg) [‡]			
Range (median)	4,800-200,000 (44,000)	16,800-95,600 (44,800)	4,600-174,200 (32,900)

*Uterine adenocarcinoma (1), endometrial carcinoma (1), thyroid (1), testicular (1), adrenal (1), basal cell carcinoma (1), and cervix (1).
[†] $P = 0.0002$.
[‡] $P = 0.19$.

Fig. 1. *A,* grade 2 HFSR showing early tender erythematous plaques at pressure points. *B,* grade 2 HFSR showing large sheets of desquamating skin overlying a tender erythematous plaque on the heel. *C,* histology of an early HFSR lesion from *A* shows epidermal thickening, reactive epithelial changes in the basal layer of the epidermis and in eccrine sweat ducts, mild perivascular infiltrate, and mild vascular dilatation (×40). *D,* higher magnification of HFSR histology from *A* (×100).
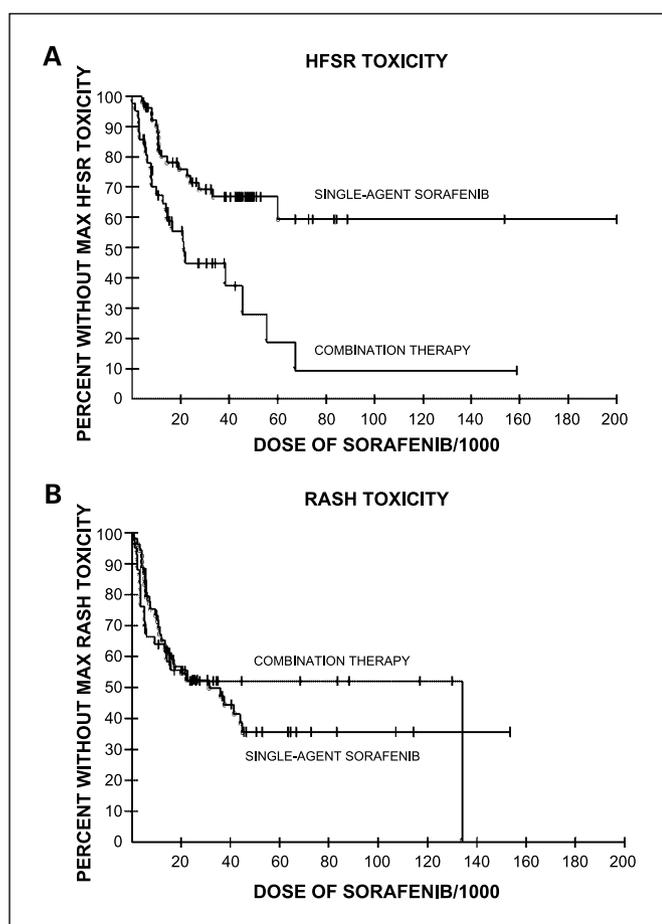
Fig. 2. *A,* Kaplan-Meier curves for the development of HFSR toxicity with single-agent sorafenib (°) versus combination therapy (*). *P* = 0.0008. Median dose of sorafenib to noted HFSR toxicity for combination therapy was 21,117 mg versus not reached for single agent. *B,* Kaplan-Meier curves for the development of rash with single-agent sorafenib (°) versus combination therapy (*). *P* = 0.99. Median dose of sorafenib to noted rash for combination therapy was 26,870 versus 31,000 mg for single agent.

Pharmacokinetics. The dose-normalized AUC_{0-12} and C_{max} were highly correlated (r = 0.94) and AUC_{0-12} was used for subsequent analyses. There was no statistically significant association between HFSR or dry skin and sorafenib exposure as measured by AUC_{0-12} in the pooled analysis of the three studies. However, an association was found between increasing rash grade and increasing AUC_{0-12} (P = 0.02). We have reported previously that there was no significant change in pharmacokinetic measurements with combination sorafenib and bevacizumab therapy compared with single-agent sorafenib (9).

Discussion

Single-agent sorafenib therapy at standard doses of 400 mg twice daily has been shown to be well tolerated, with a total incidence of HFSR in ∼25% to 30% of patients (7, 17); the use of bevacizumab alone has not been associated with development of HFSR. The approval of sorafenib for renal cell carcinoma and hepatocellular carcinoma and its use in combination therapies for other cancers make it important to

identify the mechanisms and predictors of the development of sorafenib-associated HFSR. We hypothesized that combination therapy targeting the VEGF pathway might result in augmentation of sorafenib HFSR. Comparison of patients receiving single-agent sorafenib versus reduced dose sorafenib in combination with bevacizumab confirmed that hypothesis. Expected potential risk factors such as prior taxane exposure, preexisting peripheral neuropathy, or development of rash were not associated with HFSR. However, an increase in the incidence and severity of HFSR was shown with combination sorafenib/bevacizumab therapy compared with single-agent sorafenib at any given cumulative dose of sorafenib (Fig. 2), suggesting that the anti-VEGF effects of bevacizumab potentiates sorafenib-related HFSR symptoms.

Sorafenib is associated with a variety of different dermatologic side effects, including facial/scalp erythema and dysesthesias, alopecia, splinter hemorrhages, keratoacanthomas (5), leukocytoclastic vasculitis (6), and epidermal inclusion cysts. HFSR is the sorafenib dermatologic toxicity with the greatest frequency and the greatest morbidity. HFSR associated with sorafenib therapy affects friction and weight-bearing acral surfaces more focally than the classic hand-foot syndrome, which has been reported with traditional chemotherapeutic agents such as cytarabine, 5-fluorouracil, and methotrexate (Table 2; refs. 18, 19).

Previous studies have reported a dose-dependent relationship between the starting dose of sorafenib and the incidence of HFSR. Our study adds to these data by showing the increased incidence of HFSR with increasing cumulative sorafenib dose. This was observed both in our single-agent sorafenib studies and in the combination sorafenib/bevacizumab study. The association with cumulative dose cautions providers to maintain a high index of suspicion for HFSR the longer patients receive sorafenib. The effect of dose on the development of HFSR is not well delineated, but based on clinical experience, dose reduction and discontinuation of sorafenib reduce the severity of HFSR. Although no other association was found between risk of HFSR and number and type of prior therapies including exposure to pegylated liposomal doxorubicin, previous toxicities, baseline neuropathy, or dermatologic toxicity from prior treatment, an additional confounder that was not evaluated may have contributed to our findings. Development of HFSR was not shown to be a harbinger of clinical benefit as suggested by rash in response to epidermal growth factor receptor inhibitors (2).

There are no data to date addressing the role of the VEGF pathway in the pathophysiology of HFSR. However, several findings in this study suggest that the VEGF pathway is important in the causation of HFSR: (*a*) the frequency and severity of HFSR was increased when sorafenib is paired with bevacizumab, (*b*) the predilection of HFSR for traumatic foci suggests that VEGF inhibition may retard tissue repair from minor trauma, (*c*) the increased incidence of HFSR in patients randomized to initiate treatment with one cycle of single-agent bevacizumab before combination therapy illustrates the potentiating effects of bevacizumab on sorafenib-related HFSR, (*d*) the association of HFSR and the development of or worsened preexisting hypertension suggests a vascular effect, and (*e*) the cumulative bevacizumab dose was also directly associated with incidence of HFSR (P < 0.0001), further illustrating the effect of the anti-VEGF property of bevacizumab on this

sorafenib-associated toxicity. Apart from this study, it is known that bevacizumab treatment results in poor wound healing (20).

Sorafenib causes an array of non-HFSR dermatologic toxicities (21, 22). Approximately half of the patients in the three studies developed skin rash, with no variance between the studies. Why this incidence was higher than previously reported (18-40%) is unclear; our patients had a high frequency of dermatologic consultations and thus had a higher number of recognized rashes (7, 17). Several of the dermatologic findings (*de novo* keratosis pilaris, epidermal inclusion cysts, and keratoacanthomas) are characterized by keratinocyte proliferation and focal apoptosis histologically. The mitogen-activated protein kinase, MSK1, and VEGF pathways play important role in normal keratinocyte function and inhibition of these pathways by sorafenib may result in the toxicity observed (23). This hypothesis should be explored in future studies.

Development of non-HFSR skin toxicities was associated with circulating sorafenib concentration. This suggests that rash may herald higher circulating concentration and thus higher sorafenib concentration in skin. Preclinical sorafenib organ distribution studies showed that the half-life of sorafenib in skin is longer (72.8 h) than in other organs (20-36 h).[7] Other hypotheses regarding the etiology of sorafenib-associated HFSR have been posited. These include (*a*) accumulation of potentially toxic local concentrations in eccrine sweat glands that present in greatest number or density in the palms and soles, (*b*) damaged vascular integrity due to the dual VEGFR-2 and platelet-derived growth factor-β inhibition by sorafenib, and (*c*) keratinocyte injury from sorafenib inhibition of c-kit or RAF kinase (24–26). The histology of skin biopsies of early sorafenib-related HFSR lesions showed focal epithelial damage with dyskeratotic keratinocytes, reactive epithelial changes in the basal layer of the epidermis and in eccrine sweat ducts, and lack of obvious vascular damage (Fig. 1C).

In summary, sorafenib-related dermatologic manifestations are varied. HFSR and rash are the most common dermatologic toxicities associated with sorafenib, and their etiology remains uncertain. We report a direct association between cumulative sorafenib and bevacizumab doses and incidence of HFSR as well as increased HFSR in patients treated with combination anti-VEGF/VEGFR therapy. Our results suggest that the inhibition of the VEGF pathway by sorafenib may be an important factor in HFSR pathogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

[7] http://emea.europa.eu/humandocs/PDFs/EPAR/nexavar/H-690-en6.pdf

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