

Prospective Study of the Cutaneous Adverse Effects of Sorafenib, a Novel Multikinase Inhibitor

Julien Autier, MD; Bernard Escudier, MD; Janine Wechsler, MD; Alain Spatz, MD; Caroline Robert, MD, PhD

Objectives: To provide an accurate description and to evaluate the incidence and severity of cutaneous reactions induced by sorafenib tosylate, a new oral multikinase inhibitor.

Design: Double-blind, prospective dermatologic sub-study performed on all consecutive patients included in our center in a large phase 3 trial.

Setting: Institutional practice at the Gustave Roussy Institute.

Patients: Eighty-five patients with renal cell cancer treated between November 1, 2003, and February 28, 2005.

Interventions: Patients were randomized to receive either sorafenib (n=43) or placebo (n=42). Dermatologic examination was performed before treatment, every 3 weeks during the first 4 cycles, and every 4 weeks thereafter.

Main Outcome Measures: Incidence and severity of cutaneous reactions to sorafenib.

Results: Thirty-nine patients (91%) experienced at least 1 cutaneous reaction in the sorafenib group vs 3 (7%) in the placebo group. A hand-foot skin reaction that appeared to be clinically distinct from the well-known chemotherapy-induced hand-foot syndrome was observed in 26 patients receiving sorafenib (60%). Reversible grade 3 hand-foot skin reaction was documented in 2 patients receiving sorafenib and led to a dose reduction. Other cutaneous reactions were facial erythema, scalp dysesthesia, alopecia, and subungual splinter hemorrhages.

Conclusions: Sorafenib induces frequent cutaneous adverse events, some of which may lead to a dose reduction. Close collaboration between oncologists and dermatologists is needed to improve both the characterization and the management of these side effects. Appropriate patient education before the initiation of therapy and the introduction of early symptomatic measures may improve management.

Arch Dermatol. 2008;144(7):886-892

NEW ANTICANCER targeted agents are associated with frequent cutaneous adverse events that are important to consider because they can sometimes lead to treatment discontinuation.¹ Indeed, visible cutaneous symptoms can be very difficult for patients to accept, even when the treatment is effective in combating the cancer, as with the use of anti-epidermal growth factor receptor molecules. Therefore, cutaneous side effects should be carefully reported and analyzed during the development of new drugs and not reported under the vague and global category of "cutaneous rash."

Sorafenib tosylate is a novel, orally active, small-molecule, multikinase inhibitor that inhibits wild-type RAF gene products, V599-E mutant BRAF, and several tyrosine kinase receptors involved in tumor angiogenesis and tumor progres-

sion, including vascular endothelial growth factor receptors (VEGFRs) 2 and 3, platelet-derived growth factor receptor β , fms-like tyrosine kinase 3, and c-KIT.^{2,3} Several preclinical studies showed a large spectrum of antitumor activity in human xenograft models of various cancers.⁴

Phase 1 studies of sorafenib monotherapy showed promising efficacy in renal cell carcinoma (RCC).^{2,3,5-7} These results were confirmed in phase 2 and 3 studies in RCC.⁸⁻¹⁰ Preliminary results of a randomized phase 3, placebo-controlled trial in patients with advanced RCC showed that the median duration of progression-free survival (PFS) was 24 weeks in patients treated with sorafenib compared with 12 weeks in patients receiving placebo. The majority (78%) of patients had stable disease, with 2% of patients having a partial response.⁸⁻¹⁰ Sorafenib was recently approved for the treatment of advanced RCC⁸ and hepatocarci-

Author Affiliations: Dermatology Unit (Drs Autier and Robert) and Immunotherapy Unit (Dr Escudier), Department of Medicine, and Pathology Department (Dr Spatz), Gustave Roussy Institute, Villejuif, France; and Pathology Department, Henri-Mondor Hospital, Creteil, France (Dr Wechsler).

noma.¹¹ Studies are ongoing in several tumor types, including melanoma and non-small-cell lung cancer, as a monotherapy or in combination with additional anti-tumor agents. Sorafenib is usually well tolerated; however, several side effects, including fatigue, diarrhea, and hypertension, have been reported. Cutaneous effects have been frequently reported and are described as hand-foot skin reaction (HFSR), noncharacterized skin eruption, alopecia, pruritus, dry skin, and flushing.^{5,6,9,10,12} Since skin toxic reactions may have a significant effect on patient quality of life and may affect adherence to treatment, especially for potentially long-term treatments such as sorafenib, description and comprehensive understanding of the management of potential cutaneous effects associated with this new agent, which is now available to large numbers of patients, are urgently needed.

To obtain an accurate description of the cutaneous effects observed with sorafenib, we performed a prospective dermatologic substudy in patients with advanced RCC receiving either sorafenib or placebo in a randomized, double-blind, placebo-controlled phase 3 clinical trial.⁸ The primary objective of this study was to determine the incidence rate and the types of cutaneous reactions to sorafenib.

METHODS

STUDY DESIGN

Patients with histologically confirmed metastatic clear-cell renal carcinoma, whose disease had progressed after 1 previous systemic treatment within the past 8 months, were eligible. Eligibility criteria included the following: age 18 years or older; good performance status (0 or 1); life expectancy at least 12 weeks; and adequate bone marrow, liver, pancreatic, and renal function. Patients with brain metastases or previous exposure to drugs targeting the vascular endothelial growth factor pathway were excluded.

The phase 3 study on which our study is based was conducted in 117 centers across 19 countries. Patients were stratified according to country and prognostic factors and were randomized 1:1 to receive continuous oral sorafenib tosylate, 400 mg twice daily, or placebo in a double-blind fashion. Doses were delayed or reduced if clinically significant hematologic or other toxic reactions considered related to sorafenib occurred. Doses were reduced to 400 mg once daily and then 400 mg every other day. If further dose reductions were required, treatment was discontinued.

Our study was a dermatologic monocentric substudy of this phase 3 trial. It was conducted on 85 consecutive patients included in our center during a 16-month period, between November 1, 2003, and February 28, 2005.

All patients participating in this substudy provided written informed consent in addition to the informed consent for the clinical trial. This study was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines and in accordance with applicable local laws and regulations.

CUTANEOUS EVENT ASSESSMENT

Detailed descriptions of clinical and histopathological features as well as characterization of the severity and evolution of these cutaneous effects were assessed.

Data were collected at each clinic visit during this double-blind study. Patients were queried about skin symptoms and

Table 1. Patient Characteristics

Characteristic	Sorafenib Tosylate (n=43)	Placebo (n=42)
Age, median, y (range)	59 (38-75)	61 (37-78)
Sex, No. (%)		
Male	26 (60)	36 (86)
Female	17 (40)	6 (14)
Motzer score category, No. (%) ^a		
Low	32 (74)	25 (59)
Intermediate	11 (26)	17 (41)

^aThe Motzer prognostic score predicts survival for patients with metastatic renal cell carcinoma. It includes 3 variables: Karnofsky performance status, hemoglobin level, and corrected serum calcium value.¹⁴

skin events. Dermatologic examination was performed by a single dermatologist (C.R.) or a single oncologist (B.E.) familiar with sorafenib and its potential adverse effects, at baseline and every 3 weeks during the first 4 cycles and every 4 weeks thereafter. Photographs were obtained at baseline from patients with preexisting skin lesions. Cutaneous lesions occurring during therapy were photographed and biopsied for pathological examination in willing patients. Cutaneous reactions were classified according to the National Cancer Institute's common toxicity criteria,¹³ as follows:

Alopecia:

Grade 1—Thinning or patchy

Grade 2—Complete

Skin eruption and desquamation:

Grade 1—Macular or papular eruption or erythema without associated symptoms

Grade 2—Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering less than 50% of body surface area

Grade 3—Severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering 50% or more of body surface area

Grade 4—Generalized exfoliative, ulcerative, or bullous disease

HFSR:

Grade 1—Minimal skin changes or dermatitis (eg, erythema) without pain

Grade 2—Skin changes (eg, peeling, blisters, bleeding, edema) or pain, not interfering with function

Grade 3—Ulcerative dermatitis or skin changes with pain interfering with function

Other:

Grade 1—Mild

Grade 2—Moderate

Grade 3—Severe

Grade 4—Life threatening; disabling

RESULTS

PATIENT CHARACTERISTICS

Ninety-six patients were screened in our center for this phase 3 trial. Eighty-five patients were eligible for treatment and randomized in the sorafenib (n=43) or placebo (n=42) arm.

Baseline patient and disease characteristics are given in **Table 1**. All 85 patients had evaluable data for PFS

Table 2. Cutaneous Reactions

Reaction	No. (%)	
	Sorafenib Tosylate (n=43)	Placebo (n=42)
Hand-foot skin reaction	26 (60)	0
Grade 1	16 (37)	0
Grade 2	8 (19)	0
Grade 3	2 (5)	0
Facial and scalp eruption	27 (63)	1 (2)
Scalp dysesthesia	21 (49)	1 (2)
Subungual splinter hemorrhages	30 (70)	2 (5)
Alopecia	19 (44)	0
Body hair loss	8 (19)	0
Stomatitis	8 (19)	0
Nipple hyperkeratosis or pain	7 (16)	0
Eruptive facial cysts	2 (5)	0

and for evaluation of cutaneous events. No patient was discontinued from the study because of a cutaneous adverse event.

CUTANEOUS EVENTS

At least 1 cutaneous adverse event was experienced by 39 patients (91%) in the sorafenib group and 3 patients (7%) in the placebo group (**Table 2**).

Hand-Foot Skin Reaction

An HFSR was reported in 26 patients in the sorafenib group, for an overall incidence of 60%, and in no patient in the placebo group. This cutaneous event generally occurred after 2 or 3 weeks of treatment. The symptoms began before the fifth week in 18 patients (69%) and before the third month of treatment in all patients in whom an HFSR occurred. Palms were involved in 14 patients and soles in 18 patients.

Symptoms were described by the patients as paresthesia, tingling, burning, or painful sensations on the palms and soles, as well as decreased tolerance to contact with hot objects.

These subjective signs usually preceded cutaneous lesions and rarely occurred without later development of cutaneous lesions. In 9 of the 26 patients (35%), these symptoms negatively affected walking capacity.

Physical signs included symmetric acral erythematous and edematous lesions that were present in several patients with associated desquamation and fissures. These lesions were largely observed on the palms and soles, but involvement of the lateral sides of fingers and the peri-ungual zones with some extension to the dorsal surfaces of hands and feet was noted.

Hyperkeratosis was frequent, occurring in 14 patients (54% of patients with HFSR), and was in some cases the only manifestation of HFSR (**Figure 1**). The hyperkeratosis typically presented as yellowish, painful, hyperkeratotic plaques localized in the pressure sole areas (heels and metatarsals). In some cases, hyperkeratosis was surrounded by an erythematous and/or



Figure 1. Hyperkeratotic hand-foot skin reaction.

edematous halo (**Figure 2**). Bullous lesions occurred in 1 patient.

Histologic examination was performed on 3 patients with HFSR. The epidermis showed parakeratosis and dyskeratosis. The dermis contained a dense, superficial, perivascular lymphocytic infiltrate with some degree of non-leukocytoclastic vasculitis (**Figure 3**).

For the analysis of severity, only the most severe episode of HFSR occurring in each patient was considered.



Figure 2. Hand-foot skin reaction with keratotic lesion surrounded by an erythematous halo.

The grade distribution of the worst symptoms or signs in the 26 patients who experienced HFSR is shown in Table 2. Eight patients had grade 2 HFSR and 2 patients had grade 3 HFSR. The presence of HFSR led to dose reductions at 200 mg twice daily in 2 patients (grade 3). The HFSR resolved in 3 to 4 weeks in these patients without evidence of sequelae. After restoration of full-dose treatment, 1 patient had a new episode of HFSR and treatment was maintained at half dose, and 1 patient had no relapse.

Median PFS was 279 days in patients with grade 1 to 3 HFSR at week 6 vs 167 days in the patients without HFSR among the 43 patients treated with sorafenib. However, we could not demonstrate any positive correlation between the incidence or the severity of the HFSR after 6 weeks of treatment and PFS (hazard ratio, 0.653; $P = .31$). It is possible that this lack of statistical correlation could be owing to the limited number of patients included in this substudy.

Facial and Scalp Erythematous Eruption

A facial eruption was observed in 27 patients (63%) in the sorafenib group and in 1 patient (2%) in the placebo group. It usually occurred after 1 to 3 weeks of treatment and spontaneously disappeared in less than 2 months. No facial erythema was noticed after 24 weeks of treatment.

Facial drug reaction appeared as a homogeneous, slightly erythematous facial eruption associated with a superficial desquamation. Lesions usually involved the mediofacial area and spared the periorbital area (**Figure 4**). The erythema was sometimes exacerbated

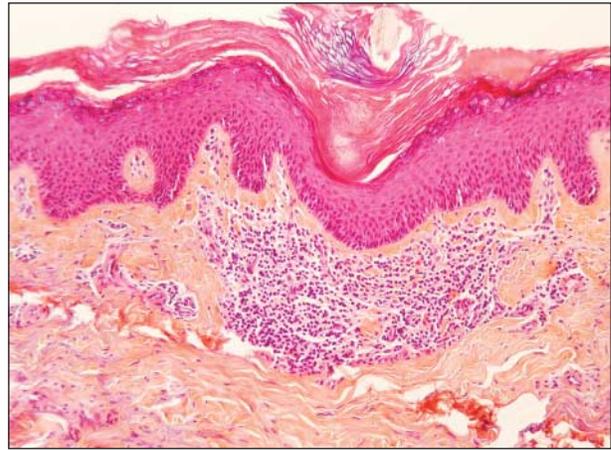


Figure 3. Histologic section of a hand-foot skin reaction showing focal parakeratosis and a dense superficial perivascular lymphocytic infiltrate with moderate nonleukocytoclastic vasculitis (hematoxylin-eosin, original magnification $\times 200$).

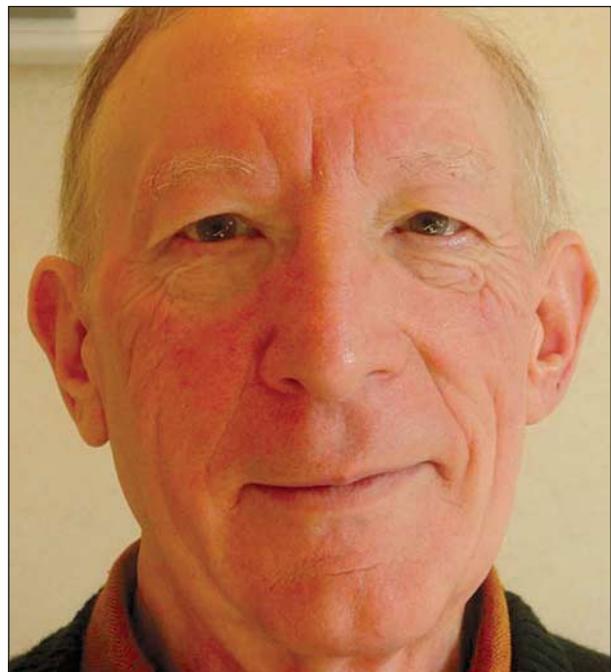


Figure 4. Characteristic facial eruption sparing the periocular areas.

by hot temperatures. Pathological analysis of the scalp or facial eruption was performed in 2 patients and showed a nonspecific lymphocytic infiltrate without eosinophils or vasculitis (not shown).

Facial and scalp eruption related to sorafenib is very similar to classic seborrheic dermatitis and usually did not require any treatment. No correlation was found between the occurrence of the facial eruption and response to treatment.

Scalp Dysesthesia

Scalp dysesthesia was frequently reported in the sorafenib group (21 patients [49%]) but not in the placebo group (1 patient [2%]). In 13 patients, scalp dysesthesia was the sole skin manifestation associated with treat-

ment. Scalp dysesthesia was an early symptom, typically observed between the first and third weeks of treatment and spontaneously resolving within several days to several weeks. No patient reported scalp dysesthesia after 21 weeks of treatment.

Subungual Splinter Hemorrhages

These spontaneous, painless hemorrhages were noticed in 30 patients (70%) in the sorafenib group and in 2 patients (5%) in the placebo group. These subungual splinter hemorrhages were characterized by straight black or red lines under the nails. The hemorrhages were almost exclusively present under the fingernails and very rarely under the toenails, and they generally had a distal distribution. Splinter hemorrhages commonly occurred during the first 2 months of treatment. In most patients they resolved spontaneously.

Alopecia and Body Hair Loss

Alopecia developed in 19 patients (44%) in the sorafenib group and in none in the placebo group. Only 1 patient had grade 2 alopecia. Alopecia did not lead to a dose reduction in any patient. This symptom generally appeared between the 3rd and 15th weeks of treatment. The alopecia spontaneously resolved in some patients despite continued treatment.

Body hair loss was noted in 8 patients (19%), and this sign was not always associated with alopecia. Several male patients indicated that facial hair growth was slowed during treatment.

Other Cutaneous Signs

Some other cutaneous symptoms were noted less frequently in patients in the sorafenib group. These included stomatitis or cheilitis (in 8 patients, with 1 patient having grade 2 cheilitis), painful sensation or hyperkeratosis of the nipples (7 patients), diffuse xerosis (8 patients), and exanthema (1 patient).

In 2 patients in the sorafenib group, facial cutaneous lesions were noticed after 6 and 15 weeks of treatment. These lesions consisted of different clinical forms of epidermoid cysts, including microcysts, milia, and larger epidermoid cysts. Patients reported a sensation of "granular" skin.

One of these patients also presented with diffuse keratotic lesions after 21 weeks of treatment. These lesions extended progressively with no sign of spontaneous regression after 35 weeks of treatment. Histopathological examinations showed aspects of focal hyperkeratosis, epidermal cysts, and acquired perforating dermatosis. The same patient also had 3 keratoacanthomas located on the dorsum of the left hand, the presternal area, and the cervical area. This patient did not have any predisposing factor for skin tumors, such as immunosuppression or significant sun exposure.

COMMENT

This prospective study shows that cutaneous side effects are frequently observed in patients treated with sor-

afenib. Because sorafenib is now available to treat advanced RCC and hepatocarcinoma, many physicians and patients will have to face such side effects, and educating them about early identification and management of these cutaneous effects is critical.

More than 90% of the patients receiving the active treatment in this substudy experienced at least 1 cutaneous symptom. Hand-foot skin reaction occurred in more than 60% of the treated patients and appears to be the most likely cutaneous event that may influence tolerability of sorafenib. Sorafenib-induced HFSR appears different from classic hand-foot syndrome (HFS). Classic HFS, also termed *acral erythema* or *palmar-plantar erythrodysesthesia*, occurs with various chemotherapeutic agents including cytarabine, capecitabine, doxorubicin hydrochloride, and fluorouracil. The incidence of HFS ranges from 6% to 68% depending on the nature of the chemotherapeutic agent.^{15,16} Sorafenib-induced HFSR shares several clinical and pathological nonspecific aspects with classic HFS, such as initial paresthesia or painful sensations, erythema, fissures, and nonspecific pathological inflammatory infiltrates. However, sorafenib-induced HFSR, more frequently than classic HFS, is associated with palmar and/or plantar hyperkeratosis. Indeed, our findings noted that hyperkeratosis is an early, and sometimes the only, manifestation of sorafenib-induced HFSR, whereas it is less frequently reported in classic HFS, where it occurs mostly during the chronic phase of the disease.¹⁷ Moreover, hyperkeratosis associated with sorafenib-induced HFSR is more often a patchy keratoderma, located on the pressure areas, whereas it is more diffuse in classic HFS.

The HFSR was more frequent in our study than in the previous phase 1 and 2 studies^{2,5,6,10,17} and was observed with a higher frequency than in the overall phase 3 clinical trial population (30%).⁸ It is possible that mild HFSR may have been missed by non-skin-oriented clinicians as opposed to clinicians specifically sensitized to the assessment of cutaneous side effects in this substudy. These differences also may be explained by the use of different doses of sorafenib; our patients received 400 mg twice daily, whereas earlier phase 1 and 2 studies were dose-escalation trials with fewer patients receiving sorafenib twice daily. These observations support a dose-dependent mechanism of HFSR as noted in earlier phase 1 trials and as described in classic HFS.¹⁸ In 2 patients, dose reduction to 400 mg once daily allowed gradual clearing of the symptoms with normal reepithelialization over a 4-week period.

The pathogenesis of HFSR associated with sorafenib has not yet been established. The dose dependence in many cases suggests a direct toxic effect on the skin. The continuous regimen might increase and prolong the circulating drug levels and lead to accumulation in the skin. The histopathological findings of sorafenib-induced HFSR were rather nonspecific. Two biopsy specimens showed a nonleukocytoclastic vasculitis that might be linked to a direct effect of VEGFR inhibition in the skin. Sunitinib malate also has been associated with HFS similar to sorafenib-associated HFSR and subungual hemorrhages.^{1,18} Both sorafenib and sunitinib target VEGFR and platelet-derived growth factor receptor, suggesting that

blockade of these receptors might be responsible for these side effects.^{1,18} It is possible that alterations of specific small vessels that are commonly traumatized by frequent impact (nails) or pressure (contact areas of soles and palms), and therefore require continuous endothelial repair involving VEGFR or platelet-derived growth factor receptor, might be involved in the pathophysiologic mechanism of these manifestations.

A positive correlation between cutaneous side effects and treatment outcome has been described in patients treated with epidermal growth factor receptor inhibitors.¹⁹ In a pooled analysis from 4 phase 1 dose-escalation trials, patients receiving sorafenib tosylate doses of 400 mg twice daily who experienced skin toxic reactions or diarrhea had a significantly increased time to progression compared with patients without such toxic effects.¹⁷ In our substudy, among 43 patients treated with sorafenib, although median PFS was 279 days in patients with grade 1 to 3 HFSR at week 6 vs 167 days in the patients without HFSR, we could not demonstrate any positive correlation between the incidence or severity of the HFSR after 6 weeks of treatment and PFS, nor did we find any correlation between treatment outcome and facial skin eruption, which might be owing to the limited number of patients.

An HFSR can significantly affect a patient's quality of life, and early identification of cutaneous side effects and institution of symptomatic therapy are critical. Before treatment is initiated, patients should be clearly educated regarding the risk of occurrence of these potential cutaneous side effects and be told that HFSR is not per se a sign of treatment intolerance.

In our experience, preventive measures such as treating preexisting plantar hyperkeratosis and avoiding tight-fitting shoes can be useful to limit the intensity of the HFSR.

When mild HFSR develops, emollient creams and shock absorbers can be used to relieve painful pressure points. When hyperkeratosis is the only manifestation of HFSR, keratolytic topical treatment containing urea or salicylic acid and regular pedicure care can be sufficient. In the case of more severe inflammation with painful erythema, topical corticosteroids applied twice daily are usually effective. Most often, grade 2 HFSR can be treated symptomatically as described with no need for sorafenib decrease or discontinuation. For grade 3 HFSR, decreasing the sorafenib dose by 50% or temporarily stopping treatment combined with symptomatic treatment usually relieves symptoms quickly. In this study, treatment was not discontinued because of HFSR, but the dose was decreased by 50% in 2 patients. In our further experience, we found that, when sorafenib was discontinued for severe HFSR, sorafenib could often be reinitiated at the same dose without systematic recurrence of severe HFSR.

Other skin events were frequent but had less effect on patients' quality of life, such as the seborrhealike dermatitis or subungual splinter hemorrhages noted in more than 60% of the patients. Both signs did not require treatment and usually resolved spontaneously in a few weeks.

An intriguing although less frequent cutaneous side effect observed in our series was the occurrence of mul-

tle facial cystic lesions observed after 6 to 11 weeks of treatment. Although such cystic lesions were seen in only 2 patients in this prospective substudy, similar lesions in additional patients who were seen in our center and treated with sorafenib suggest that this effect is related to sorafenib treatment. One patient with cystic lesions also developed keratotic papules and nodules, pathological examination of which showed features of acquired perforating dermatosis and multiple keratoacanthomas and suggested that they could be various manifestations of keratinocyte differentiation and/or proliferation dysfunctions with excessive keratin production. An effect of sorafenib on keratinocyte differentiation or proliferation was further suggested by recent publications reporting inflammation of actinic keratoses associated with the occurrence of squamous carcinomas in one report and multiple keratoacanthomas in another.^{20,21} Further studies are ongoing to better characterize these peculiar skin manifestations.

CONCLUSIONS

Skin adverse events are very frequent during sorafenib treatment. Some of these cutaneous events, such as facial erythematous eruption or subungual hemorrhages, go unnoticed by patients, but others, such as severe HFSR, may have a significant effect on patients' quality of life and may lead to treatment discontinuation. Physicians should be aware of these potential side effects and educate patients before sorafenib is prescribed.

The pathophysiologic mechanism of sorafenib-induced HFSR is unknown, and its clinical presentation seems different from that of HFS seen with more classic chemotherapies.

Simple symptomatic treatment as well as preventive measures directed at preexisting sole keratoderma may result in significant improvement in HFSR. Efforts should be made to establish effective curative or preventive therapies for these frequent side effects.

In summary, it is critical to carefully describe and evaluate cutaneous symptoms seen with newer targeted agents such as sorafenib because an accurate description is necessary before studies are conducted to investigate and assess the pathophysiologic mechanism of the observed symptoms. Early identification of these symptoms may allow optimal preventive and curative symptomatic treatment when necessary. Further studies of these effects may lead to improved understanding of mechanisms underlying cutaneous events and skin physiology in general.

Accepted for Publication: December 28, 2007.

Correspondence: Caroline Robert, MD, PhD, Dermatology Unit, Gustave Roussy Institute, 39 rue Camille Desmoulins, 94805 Villejuif CEDEX, France (crobert@igr.fr).

Author Contributions: Dr Robert had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Escudier, Spatz, and Robert. *Acquisition of data:* Autier, Escudier, Wechsler, Spatz, and Robert. *Analysis and interpretation of data:* Autier, Escudier,

Wechsler, Spatz, and Robert. *Drafting of the manuscript*: Autier and Robert. *Critical revision of the manuscript for important intellectual content*: Autier, Escudier, Wechsler, Spatz, and Robert. *Statistical analysis*: Autier. *Obtained funding*: Escudier and Robert. *Administrative, technical, and material support*: Autier. *Study supervision*: Robert. **Financial Disclosure**: Drs Robert and Escudier received consulting fees from Bayer. The investigators did not receive monetary support for enrolling subjects. **Funding/Support**: This study was supported in part by Bayer Onyx, which sponsored the TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) study (see Escudier et al⁸).

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We are indebted to Laury Verzele, who helped in preparing the tables, and to Dominique Rodary, who took the photographs.

REFERENCES

1. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol*. 2005;6(7):491-500.
2. Strumberg D. Preclinical and clinical development of the oral multikinase inhibitor sorafenib in cancer treatment. *Drugs Today (Barc)*. 2005;41(12):773-784.
3. Zakarija A, Soff G. Update on angiogenesis inhibitors. *Curr Opin Oncol*. 2005;17(6):578-583.
4. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*. 2004;64(19):7099-7109.
5. Awada A, Hendlisz A, Gil T, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. *Br J Cancer*. 2005;92(10):1855-1861.
6. Clark JW, Eder JP, Ryan D, Lathia C, Lenz HJ. Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. *Clin Cancer Res*. 2005;11(15):5472-5480.
7. Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J Clin Oncol*. 2005;23(5):965-972.
8. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma [published correction appears in *N Engl J Med*. 2007;357(2):203]. *N Engl J Med*. 2007;356(2):125-134.
9. Escudier BSC, Eisen T. Randomized phase III trial of the Raf kinase and VEGF inhibitor sorafenib (BAY 439006) in patients with advanced renal cell carcinoma [ASCO meeting abstract 4510]. *J Clin Oncol*. 2005;23:3805.
10. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24(16):2505-2512.
11. ASCO 2007: plenary top 5. *Oncology (Williston Park)*. 2007;21(7):896.
12. Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann Oncol*. 2005;16(10):1688-1694.
13. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0: an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47(1):13-47.
14. Baack BR, Burgdorf WH. Chemotherapy-induced acral erythema. *J Am Acad Dermatol*. 1991;24(3):457-461.
15. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol*. 1999;40(3):367-398.
16. Strumberg D, Awada A, Hirte H, et al. Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? *Eur J Cancer*. 2006;42(4):548-556.
17. Robert C, Faivre S, Raymond E, Armand JP, Escudier B. Subungual splinter hemorrhages: a clinical window to inhibition of vascular endothelial growth factor receptors? *Ann Intern Med*. 2005;143(4):313-314.
18. Pérez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol*. 2005;23(22):5235-5246.
19. Kong HH, Cowen EW, Azad NS, Dahut W, Gutierrez M, Turner ML. Keratoacanthomas associated with sorafenib therapy. *J Am Acad Dermatol*. 2007;56(1):171-172.
20. Lacouture ME, Desai A, Soltani K, et al. Inflammation of actinic keratoses subsequent to therapy with sorafenib, a multitargeted tyrosine-kinase inhibitor. *Clin Exp Dermatol*. 2006;31(6):783-785.
21. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2004;22(3):454-463.