Dermatologic symptoms associated with the multikinase inhibitor sorafenib

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Background: The multikinase inhibitor sorafenib (Nexavar) is associated with a relatively high incidence of dermatologic symptoms.

Objective: We sought to evaluate and provide guidance on the diagnosis and clinical management of dermatologic symptoms associated with sorafenib in patients with advanced solid tumors.

Methods: English-language studies representative of a patient population with a variety of tumor types, who received single-agent sorafenib, were selected. Particular emphasis was placed on the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs).

Results: Frequently observed dermatologic side effects (any grade in TARGETs) of sorafenib include rash/desquamation (40%), hand–foot skin reaction (30%), alopecia (27%), and pruritus (19%). Generally, dermatologic symptoms resolve with appropriate management, including topical treatments, dose interruptions, dose reductions, or a combination of these.

Limitations: The results presented here are based on a limited number of studies.

Conclusion: Although sorafenib is associated with dermatologic symptoms, these are usually resolved with appropriate intervention, patient-led practical treatment, and preventative measures. (J Am Acad Dermatol 2009;60:299-305.)

Sorafenib inhibits Raf serine/threonine kinases (Raf-1, wild-type B-Raf, and *b-raf* V600E),[1] which regulate the ubiquitous Raf/MEK/ERK pathway.[2] Dysregulated overactivation of this pathway is associated with tumorigenesis.[3-5] Sorafenib also inhibits receptor tyrosine kinases that promote tumor angiogenesis (eg, vascular endothelial growth factor receptor [VEGFR]-1,[6] VEGFR-2, VEGFR-3; platelet-derived growth factor receptor-β) and tumor progression (eg, Flt-3, RET).[1,7] Preclinical studies have shown that sorafenib acts on the tumor (inhibition of proliferation; induction of apoptosis) and tumor vasculature (inhibition of angiogenesis).[1]

Abbreviations used:

bid:	twice daily
CK:	cytokeratin
HFSR:	hand–foot skin reaction
TARGETs:	Treatment Approaches in Renal cancer Global Evaluation Trial
VEGFR:	vascular endothelial growth factor receptor

Sorafenib (400 mg twice daily [bid]) was well tolerated, and had encouraging preliminary antitumor activity, in phase I/II trials involving patients with advanced solid tumors.[8-12] In a phase II trial, 93% of patients with renal cell carcinoma receiving sorafenib (400 mg bid) had dermatologic symptoms, including rash/desquamation (66%) and hand–foot skin reaction (HFSR) (62%), and dermatologic-related symptoms, such as alopecia (53%). Most symptoms were grade 1/2 in severity; only 17% were grade 3/4 in severity.[12]

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Table I. Incidence of overall and individual cutaneous reactions occurring in 10% or more of patients in pooled phase I,[8-11] phase II,[12] and phase III (Treatment Approaches in Renal cancer Global Evaluation)[13] trials of patients with advanced cancer

	Pooled phase I* (n = 173) No. (%)		Phase II† (n = 202) No. (%)		Phase III†‡			
					Sorafenib (n = 451) No. (%)		Placebo (n = 451) No. (%)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any	49 (47)§	11 (11)§	153 (76)	34 (17)	288 (64)	37 (8)	152 (34)	1 (<1)
Hand–foot skin reaction	31 (18)	13 (8)	98 (49)	27 (13)	109 (24)	25 (6)	30 (7)	0
Rash/desquamation	42 (24)	4 (2)	129 (64)	5 (2)	176 (39)	4 (1)	69 (15)	1 (<1)
Pruritus	30 (17)	1 (<1)	0	0	84 (19)	1 (<1)	29 (6)	0
Alopecia	29 (17)	N/A	107 (53)	N/A	121 (27)	N/A	15 (3)	N/A
Dry skin	17 (10)	0	47 (23)	0	50 (11)	0	18 (4)	0
Nail changes	4 (2)	0	0	0	3 (<1)	0	7 (2)	0
Flushing	0	0	32 (16)	0	32 (7)	1 (<1)	13 (3)	0
Other	12 (7)	0	87 (43)	0	68 (15)	0	20 (4)	0

N/A, Not applicable.
*Reported events are drug-related, treatment emergent.
†Reported events are treatment emergent.
‡Incidences taken from published data and data on file.
§Based on 104 patients (data unavailable for Strumberg et al.[11] [n = 69]).

The efficacy and tolerability of sorafenib were confirmed in the phase III Treatment Approaches in Renal cancer Global Evaluation Trial (TARGETs), involving 903 patients with metastatic clear-cell renal cell carcinoma, leading to its approval in this indication.[13] It has also been recently approved for hepatocellular carcinoma, based on a significant improvement in overall survival versus placebo,[14,15] and is currently being evaluated in phase II/III trials in other cancers, including melanoma, breast cancer, and nonsmall-cell lung cancer.[16-19]

This review will summarize dermatologic symptoms associated with sorafenib, emphasizing those reported in the TARGETs. With appropriate intervention, many dermatologic symptoms are manageable. Guidance on the clinical management, including diagnosis and symptomatic alleviation, and modifications to treatment regimens will be provided.

METHODS

Data were sourced from sorafenib publications, authors' own data, observations from experts, and PubMed searches. English-language studies involving sorafenib were selected, including 4 phase I monotherapy trials, a randomized discontinuation phase II trial, and the phase III TARGETs. These 6 studies are representative of a patient population with a diverse variety of tumor types who received single-agent sorafenib. The authors independently extracted and assessed data and discussed implications of these to present quantitative and observational findings in this review.

DERMATOLOGIC SIDE EFFECTS OF SORAFENIB

Frequently occurring dermatologic side effects of sorafenib include HFSR, facial erythema (rash/desquamation), splinter subungual hemorrhages, alopecia, pruritus, and xerosis (Table I).[9,12,13]

In TARGETs, dermatologic symptoms generally arose within the first 6 weeks of treatment. Symptoms were mainly grade 1/2 in severity and resolved with appropriate management. No grade 4 dermatologic toxicities were reported.[13]

Symptoms frequently attributed to sorafenib

Hand–foot skin reaction. HFSR typically presents as painful symmetric red areas on the palms and soles (Fig 1). The lateral sides of fingers or the periungual zones can also be affected. A tingling sensation and intolerance to contact with hot objects often precede or accompany HFSR, and patients may experience difficulty walking and holding objects. A comprehensive system for classifying HFSR severity is provided by the National Cancer Institute Common

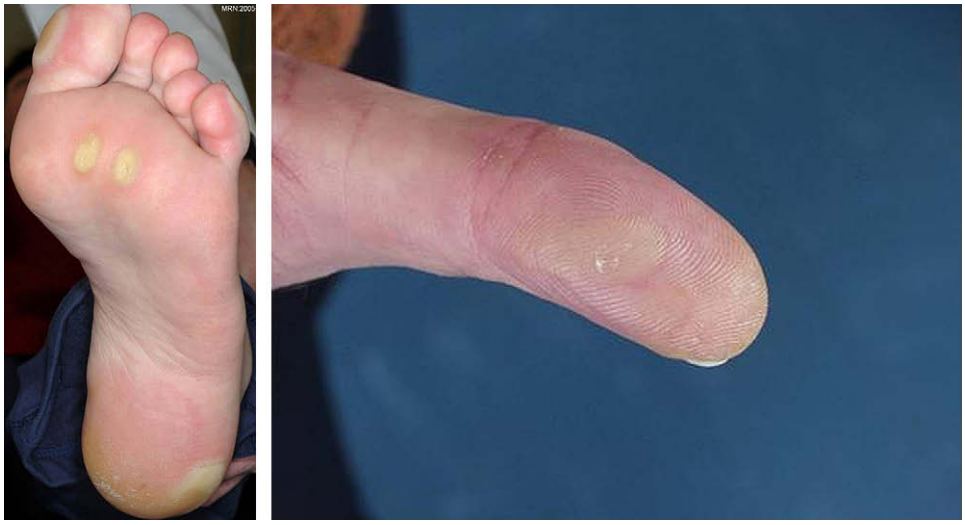

Fig 1. Hand–foot skin reaction in patients given sorafenib; note patchy hyperkeratosis on plantar pressure areas. Photograph courtesy of C. Robert.

Terminology Criteria for Adverse Events version 3.0 (Table II).

HFSR was the second most frequent (30%) adverse event associated with sorafenib in TARGETs, usually occurring after 2 to 3 weeks.[13] HFSR is likely to be drug-related, because it was reported in only 7% of patients receiving placebo. Most cases of HFSR were reported at grade 1/2 severity, and permanent discontinuation of sorafenib as a result of HFSR occurred in only 3 of 451 patients. In a recent meta-analysis of HFSR in patients receiving sorafenib, the overall incidence of this dermatologic event (at any grade) was 33.8% (8.9% of patients had high-grade HFSR).[20]

Although sorafenib-induced HFSR may sometimes be indistinguishable from classic hand–foot syndrome, also referred to as acral erythema or palmar plantar erythrodysesthesia, which is associated with chemotherapies such as capecitabine,[21] it is typically less severe and more localized with sorafenib. Furthermore, sorafenib-associated HFSR presents more frequently with hyperkeratosis than does classic hand–foot syndrome. Some patients exhibit only patchy keratodermia restricted to pressure areas, whereas classic hand–foot syndrome lesions are often diffuse and less restricted to pressure areas.

Histologic analysis of HFSR shows a thickened epidermis with hyperkeratosis, nonspecific inflammatory dermal cell infiltrates, and dilated dermal vessels.[22] Modifications in cytokeratin (CK) expression (ie, loss of CK10 expression and increased CK14 expression) were observed after immunostaining with anti-CK antibodies, suggesting that sorafenib may affect keratinocyte differentiation (unpublished data from author). The dose-dependency of HFSR symptoms suggests that sorafenib exerts a direct toxic effect on the skin.[23]

Patients and physicians should be aware of practical measures to prevent and manage HFSR symptoms (Table III). Treatment remains symptomatic for grade 1 HFSR, and patients should receive appropriate topical intervention. In grade 2 HFSR resisting symptomatic treatment, a decrease of sorafenib dose to 400 mg daily for a minimum of 7 days and up to 28 days should be considered. If toxicity does not resolve to grade 0 or 1 despite dose reduction, the treatment should be interrupted for a minimum of 7 days and until toxicity has resolved to grade 0 or 1. When resuming treatment after dose interruption, the dose should be reduced to 400 mg daily. If toxicity is maintained at grade 0 or 1 for a minimum of 7 days, the dose can be increased back to full dose (ie, 400 mg bid). In the event that HFSR reaches grade 3, a treatment interruption for a minimum of 7 days, combined with symptomatic treatment, is recommended until symptoms return to grade 0 or 1.[24] When treatment is resumed, the dose should be decreased by one dose level (ie, to 400 mg daily). If symptoms remain at grade 0 or 1 for a minimum of 7 days, the treatment can be increased by one dose level. On the third occurrence of grade 3 symptoms, sorafenib should be discontinued.[25] This protocol was found to lead to rapid symptom relief. In rare instances where treatment was discontinued for severe HFSR, subsequent reinitiation at the same dose was often possible, without recurrence of severe HFSR.[23]

Table II. Classification of hand–foot skin reaction severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)*

Grade	Grade description
1	Minimal skin changes or dermatitis (eg, erythema) without pain
2	Skin changes (eg, peeling, blisters, bleeding, edema) or pain, not interfering with function
3	Ulcerative dermatitis or skin changes with pain interfering with function

*This considers both objective symptoms severity and quality of life.

Table III. Prevention and management of hand–foot skin reaction (courtesy of C. Robert)

Treatment type	Recommendations
Patient-led practical prevention	Reduce exposure of hands and feet to hot water (washing dishes, long showers, hot baths)
	Avoid constrictive clothing (eg, tight-fitting garments, shoes, belts, or elastic bands)
	Avoid excessive rubbing (applying lotion, massaging)
	Avoid vigorous exercise or activities that place undue stress on the hands and feet (jogging, aerobics, jumping)
	Sparingly apply an alcohol-free moisturizer immediately after bathing if the skin gets dry
	Moisturizing cream can be applied sparingly on the hands and feet
	Moisturizing cream can be worn at night under cotton gloves and socks
	Wear open shoes with padded soles during treatment
	A pedicure before treatment may be effective for patients with plantar hyperkeratosis
Patient-led practical management	Soak hands in very cool water for 10 to 15 minutes 3 times a day if this is found to provide relief
	Dry well
	Apply petroleum jelly to the hands and feet while the skin is still moist
	Apply moisturizers sparingly
	Use a foot bath and pumice stone to exfoliate feet (or regular pedicures) in case of hyperkeratotic lesion and apply moisturizing cream immediately afterward
	Use shock-absorbing soles to relieve painful pressure points
Chemical	Urea- or salicylic acid–containing topical treatments for chemical exfoliation of skin (available over the counter)
	Topical corticosteroids applied twice daily (for more severe inflammation with painful erythema) under medical supervision
Other	Analgesics to relieve pain

Facial erythema. Facial erythema occurs particularly frequently and was observed in 27 of 43 patients treated with sorafenib in a trial at our center (Fig 2).[22] Very similar in appearance to seborrheic dermatitis, facial erythema usually occurs 1 to 2 weeks after treatment and is often preceded by scalp dysesthesia. High atmospheric temperatures appear to aggravate symptoms; however, the biologic mechanism of this effect is unknown. Facial erythema was not associated with sunitinib or imatinib, suggesting that inhibition of RAF, rather than VEGFR or platelet-derived growth factor receptor, may have a role.[24] Pathologic analysis of scalp skin of two patients receiving sorafenib showed a compact hyperkeratosis and loss of the usual basket-weave configuration of the eosinophilic stratum corneum. The condition usually fades or disappears after several weeks of sorafenib and usually does not require any treatment. Symptomatic relief can be achieved with topical emollient, topical imidazole derivatives, or topical steroids.

Splinter subungual hemorrhages. Painless distal subungual hemorrhages under the fingernails (sometimes toenails) were reported in more than 60% of patients receiving sorafenib in a dermatologic substudy of TARGETs.[22] Presenting as straight black or red lines (Fig 3), the hemorrhages comprise blood confined within the nail bed epidermis. They typically occur spontaneously after 1 to 2 weeks of sorafenib and are carried forward with the growth of the nail, disappearing over time. Such lesions were reported historically in patients presenting with thrombotic or embolic events (endocarditis or circulating anticardiolipin antibody). Subungual hemorrhages are also observed in healthy people, usually resulting from minimal trauma, and are usually confined to one digit.[26] Multiple splinter subungal hemorrhages can be observed in several digits of

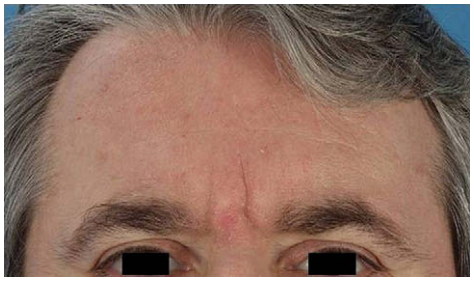

Fig 2. Facial erythematosquamous rash mimicking seborrheic dermatitis in patient given sorafenib. Photograph courtesy of C. Robert.

patients receiving sorafenib (Fig 3) and sunitinib, and may reflect the antiangiogenic effect of the drugs.[27,28] Splinter subungual hemorrhages are asymptomatic and do not require any treatment.[22]

Alopecia. Alopecia was reported in 27% of patients receiving sorafenib versus 3% of those given placebo in TARGETs.[13]

Sorafenib-induced alopecia is characterized by thinning/patchy hair and slow beard growth. Symptoms generally appear during weeks 3 to 15 of treatment.[22] Although alopecia is sometimes reported with epidermal growth factor receptor inhibitors, such as erlotinib and gefitinib, this event is much less frequent with VEGFR and platelet-derived growth factor receptor inhibitors sunitinib and imatinib.[24]

Although there is no treatment for alopecia at present, it is temporary and hair typically regrows after treatment cessation or, in some patients, while still on sorafenib therapy. Hair that grows during sorafenib therapy tends to be brittle and curly (Fig 4). Some patients report that their new hair is more pigmented than it was before treatment.

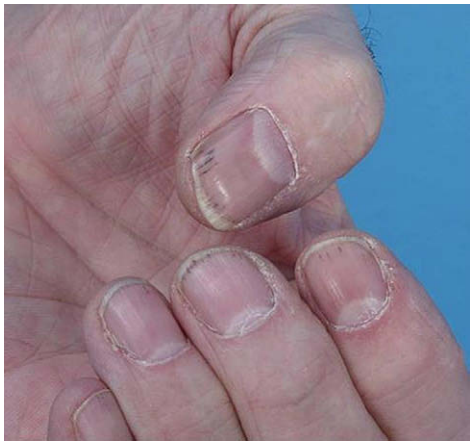

Fig 3. Subungual splinter hemorrhages in patient given sorafenib. Photograph courtesy of C. Robert.

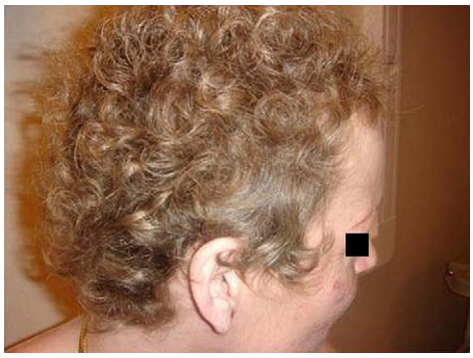

Fig 4. Severe alopecia in patient treated with sorafenib. Patient did not have curly hair before sorafenib treatment; she presented with severe diffuse alopecia after 6 weeks of therapy. Although sorafenib was not interrupted, her hair regrew but with curly appearance. Photograph courtesy of C. Robert.

Other, less frequent skin side effects occurring with sorafenib

Xerosis is reported in 10% to 20% of patients, predominantly on the inferior limbs, and can be alleviated by emollient cream or oil, applied on moist skin. Other skin rashes can also occur with sorafenib. Several cases of disseminated exanthematous rash were observed (Fig 5), resembling more classic skin hypersensitivity to drugs. In some rare cases, lesions were observed resembling erythema multiforme. These exanthematous rashes occurred within the first days or weeks of treatment.

Eruptive benign nevi was also observed in 5 patients treated with sorafenib for a mean duration of 9 months, which appeared unrelated to intense sun exposure or additional medication.[29] Studies are under way to evaluate the potential mechanism of this skin manifestation.

Papular, pustular, cystic, and keratotic lesions (Fig 6) can also occur with sorafenib, although the frequency of these skin lesions is unknown. These lesions, located on the face or disseminated on the body, usually present after several weeks or months of treatment. Some patients presented with keratoacanthomas,[30] and one presented with inflammation of multiple actinic keratoses and a squamous cell carcinoma.[31]

A recent report describes the development of a deep yellow skin discoloration in a patient receiving sorafenib.[32] In addition, a significant hand–foot syndrome, featuring acral skin desquamation and tender erythema at pressure points, was also present in this patient. Thorough clinical and laboratory investigations did not reveal any evidence of jaundice, vitamin-B12 deficiency, anemia, carotenemia, or hypothyroidism.

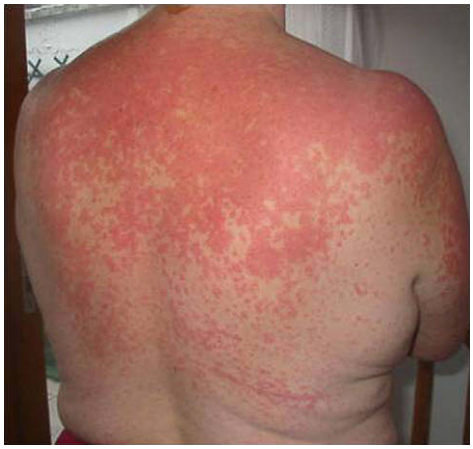

Fig 5. Exanthematous rash. Photograph courtesy of C. Robert.

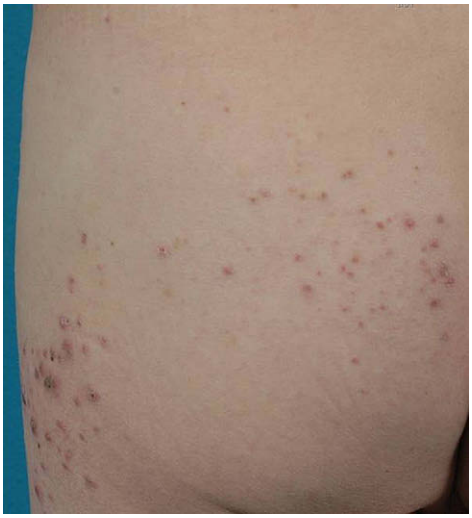

Fig 6. Eruptive hyperkeratotic folliculitis on the buttocks of a patient given sorafenib. Photograph courtesy of C. Robert.

Management of these rashes varies according to clinical presentation. In the case of moderate exanthematous rashes (grade 1/2), treatment can be continued and symptomatic antihistaminic treatment prescribed. In the rare cases of erythema multiforme or grade 3 rashes, suggesting hypersensitivity, treatment should be interrupted. Grade 1/2 papular, cystic, and keratotic lesions can be symptomatically treated with topical antibiotics and cleaned using a sterile needle. Keratoacanthomas should be excised surgically to allow pathologic examination, because differential diagnosis with differentiated squamous cell carcinoma usually requires pathologic examination of the entire lesion.

CONCLUSION

Sorafenib is associated with a relatively high incidence of dermatologic symptoms, mainly grade 1/2 in severity, which can be resolved with appropriate topical treatments, dose interruptions, dose reductions, or a combination of these. HFSR represents one of the most problematic dermatologic symptoms associated with sorafenib. A relationship between the onset of skin toxicities and clinical outcome has been suggested for sorafenib.[33] In a pooled analysis of phase I trials, time to disease progression was significantly longer for patients receiving sorafenib at or close to 400 mg bid who experienced grade 2 HFSR/rash or diarrhea.[33] However, no link between skin toxicity and response to treatment was found in the large phase III TARGETs.

Understanding the biologic mechanisms by which sorafenib induces dermatologic reactions requires further investigation and is likely to lead to more suitable management strategies of skin side effects, and to increased knowledge of skin pathophysiology.

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