Dermatol Ther (Heidelb) (2015) 5:77–86
DOI 10.1007/s13555-014-0067-9

CASE REPORT

Sorafenib-Associated Facial Acneiform Eruption

Philip R. Cohen

To view enhanced content go to www.dermtherapy-open.com
Received: November 3, 2014 / Published online: December 25, 2014

ABSTRACT

Introduction: Sorafenib is an oral multikinase inhibitor that targets tumor cell angiogenesis and proliferation. Drug-associated cutaneous adverse events, such as alopecia and hand–foot skin reaction, occur frequently. Sorafenib-related side effects affecting hair, nails, and skin are summarized and the characteristics of sorafenib-treated patients who developed acneiform facial lesions are reviewed to present the clinical features of these individuals.

Case Report: A man with sorafenib-associated facial acneiform lesions mimicking those of chloracne is described.

Discussion: PubMed was used to search the following terms, separately and in combination: acne, acneiform eruption, chloracne, cutaneous adverse events, hepatocellular carcinoma, renal cell carcinoma, skin side effects, and sorafenib. Inclusion criteria for selecting papers to be reviewed included case reports and studies that described cutaneous and mucosal adverse side effects associated with sorafenib. All papers fulfilling inclusion criteria were reviewed and relevant manuscripts, along with their reference citations, were evaluated. Five patients—a woman with liver epithelioid hemangioendothelioma, three men with metastatic renal cell carcinoma, and a man with hepatocellular carcinoma—have developed sorafenib-associated facial acneiform eruption. The eruption typically occurred after 4 weeks of treatment at a dose of 400 mg twice daily. The lesions presented as either papules and pustules (2 patients) or, similar in appearance and distribution to chloracne, only open and closed comedones (3 patients). The sorafenib-associated facial acneiform eruption partially improved after initiating topical antibiotics, keratolytics, and/or retinoids; however, progressive improvement or resolution occurred after lowering the daily dose or discontinuation of sorafenib.

Conclusions: Sorafenib-associated facial acneiform eruption is a rarely occurring cutaneous adverse event that has only been

Electronic supplementary material The online version of this article (doi:10.1007/s13555-014-0067-9) contains supplementary material, which is available to authorized users.

P. R. Cohen (✉)
Division of Dermatology, University of California San Diego, 10991 Twinleaf Court, Twinleaf Court, California 92131-3643, USA
e-mail: mitehead@gmail.com

observed in five individuals. The skin lesions usually presented after 4 weeks of sorafenib (at a dose of 400 mg twice daily) treatment. The morphology and distribution of the lesions mimicked those of chloracne in three of the patients. Two of the patients also had other drug-related skin side effects. Topical acne-directed therapy was only partially effective in clearing the lesions; lowering the dose or discontinuation of sorafenib resulted in progressive improvement or resolution of the facial acneiform eruption.

Keywords: Acne; Acneiform eruption; Chloracne; Cutaneous adverse events; Hepatocellular carcinoma; Renal cell carcinoma; Skin side effects; Sorafenib

INTRODUCTION

Sorafenib is an oral multikinase inhibitor that is currently approved for the treatment of hepatocellular carcinoma, renal cell carcinoma, and thyroid cancer. In addition to frequently occurring alopecia and hand–foot skin reactions, other common adverse skin effects related to sorafenib include desquamative 'rash' and erythematous eruption, seborrheic dermatitis-like facial erythema, stomatitis, subungual splinter hemorrhages, and xerosis [1–4]. A unique cutaneous reaction after initiating treatment with sorafenib—a facial acneiform eruption—is described in a man with hepatocellular carcinoma and the characteristics of other patients with this rare sorafenib-induced cutaneous adverse event are reviewed to present the clinical features of these individuals.

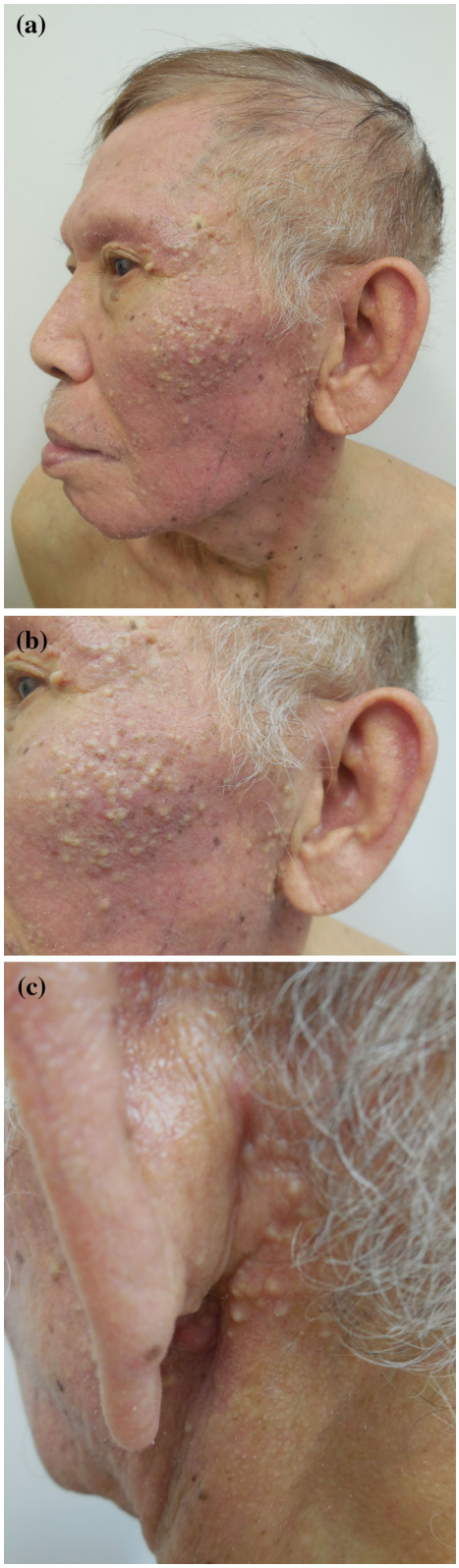
Case Report

A 79-year-old Asian man presented for evaluation of facial acneiform lesions of 2½ months duration. He also had experienced scalp and eyebrow hair loss, an itchy facial rash, peeling of his fingertips and painful lesions on feet, and dry skin. His medical history was significant for hepatitis B (genotype B) and he had been receiving entecavir 0.5 mg daily for the past 9 months, since December 2013; his most recent polymerase chain reaction quantitative hepatitis B viral load in August 2014 was <20 (undetectable). He had no exposure to aromatic hydrocarbons.

Four months earlier, in May 2014, his alpha fetoprotein level was elevated (20.8 ng/mL, normal <15 ng/ml). A magnetic resonance imaging exam of his abdomen revealed several hepatic lesions consistent with hepatocellular carcinoma. On June 26, 2014 he was started on sorafenib 400 mg twice daily. Within 6 weeks after initiating treatment with sorafenib, his alpha fetoprotein had decreased to 15 ng/ml.

Within 9 days after starting sorafenib, he noted new lesions on his face and behind his ears. Subsequently, he developed a red facial rash and began to lose hair on his scalp and eyebrows. Shortly thereafter, within a month after initiating treatment, he developed generalized xerosis with hand and foot lesions.

Cutaneous examination of his face showed a chloracne-like eruption consisting predominantly closed comedones not only on his malar cheeks, but also on his ears, preauricular area and postauricular skin. In addition, there were several non-inflammatory small cystic lesions and occasional open comedones. There were no inflammatory papules (Fig. 1).



◀**Fig. 1** Distant (**a**) and closer (**b**) views of left side of the face of a 79-year-old Asian man show numerous closed comedones and non-inflammatory small cystic lesions on the malar cheeks, the preauricular area and the ears; occasional open comedones are also noted, but are not inflammatory papules. A closer view of the left postauricular area (**c**) also shows several closed comedones. The lesions appeared 9 days after he started sorafenib (400 mg twice daily) for the treatment of his hepatocellular carcinoma. The morphology and distribution of the facial acneiform lesions mimic those of chloracne

The forehead, glabella region, and paranasal malar area also showed a pruritic seborrheic dermatitis-like eruption consisting of erythema with superficial scaling on the supraorbital ridges. There was loss of the eyebrows and partial alopecia of the scalp. There was also inflammation of the seborrheic keratoses on his chest and back and xerosis was diffusely present.

Hand–foot skin reaction was also present. Asymptomatic peeling of the distal fingertips was observed. Also, painful hyperkeratotic plaques were present on the plantar pressure areas of both feet.

Topical therapy for the acneiform eruption included topical clindamycin 1% solution twice daily, followed by tretinoin 0.025% cream in the evenings. Desonide 0.05% cream twice daily was initiated for the seborrheic dermatitis-like eruption. Betamethasone dipropionate 0.05% cream (under plastic occlusion in the evening) was applied to the hands and feet twice daily. A moisturizing cream was applied to the body once daily.

The patient returned after 1 month; 10 days earlier his family had decided to discontinue the sorafenib because he was tolerating it poorly. His seborrheic dermatitis-like eruption and facial pruritus had completely cleared and his hand–foot skin reaction was nearly resolved.

The chloracne-like facial eruption had partially improved; however, since multiple closed comedones still persisted, his topical therapy with clindamycin solution and tretinoin cream was continued. His oncologist is restaging him and considering other therapeutic options or possibly restarting sorafenib at a lower dose.

DISCUSSION

Sorafenib targets tumor cell angiogenesis and proliferation by inhibiting multiple kinases including c-Kit protein, FMS-like tyrosine kinase 3, platelet-derived growth factor beta, Raf kinase, RET receptor tyrosine kinase, and vascular endothelial growth factor receptors 2 and 3 [2, 5]. The hair, nails, and skin of patients treated with sorafenib are potentially also affected by the drug (Table 1) [2–4, 6–53]. In contrast to a significant percentage—ranging from a reported 24–91%—of patients receiving epidermal growth factor receptor inhibitors (such as cetuximab, erlotinib, and gefitinib) who develop a diffuse papulopustular acneiform eruption, sorafenib-associated acneiform facial eruption has seldom been observed [37–39].

PubMed was used to search the following terms, separately and in combination: acne, acneiform eruption, chloracne, cutaneous adverse events, hepatocellular carcinoma, renal cell carcinoma, skin side effects, and sorafenib. Inclusion criteria for selecting papers to be reviewed included case reports and studies that described cutaneous and mucosal adverse side effects associated with sorafenib. All papers fulfilling inclusion criteria were reviewed and relevant manuscripts, along with their reference citations, were evaluated.

Several reports discuss acneiform eruptions in patients who have received sorafenib.

Table 1 Cutaneous adverse events associated with sorafenib

Frequently occurring events
Alopecia [2, 4, 6–9]
Hand-foot skin reaction [2–4, 6, 8–16]
Common occurring events
Erythematous eruption on trunk [2, 15, 17]
'Rash'/desquamation [3, 4, 6, 9]
Seborrheic dermatitis-like facial erythema [2, 8, 9, 15, 16, 18, 19]
Stomatitis [2, 7]
Subungual splinter hemorrhage [2, 8, 9, 16, 20]
Xerosis [2, 7, 9, 21]
Uncommon occurring events
Actinic keratoses [22]
Erythema multiforme [23–28]
Follicular-based erythematous papules [15, 21]
Inflammation of actinic keratoses [29]
Inflammation of seborrheic keratoses [30]
Keratoacanthoma and squamous cell carcinoma [22, 31, 32]
Keratosis pilaris-like lesions [30]
Plaques: dyskeratotic or keratotic [22, 33]
Pruritus [9, 34, 35]
Psoriasiform eruption [36]
Warts, warty papules and nodules [10, 22]
Rarely occurring events
Acneiform eruption [37–43]
Angioedema [21]
Cheilitis [15, 44]
Epidermal cyst on face [2, 16, 19, 30]
Erythema marginatum hemorrhagicum [45]
Genital (labial and scrotal) eczema [2, 15]
Eruptive melanocytic nevi [30, 46, 47]
Leukocytoclastic vasculitis [30, 48]
Nonpigmented fixed drug eruption [49]
Perforating folliculitis [21, 50]
Spiny follicular hyperkeratosis eruption [39, 51]
Ultraviolet radiation recall (dermatitis) [52]
Yellow skin [53]

However, three of the patients had developed epidermal cysts on their face [2, 9, 16]. In addition, a critical review of other studies

showed that the observed lesions were either secondary to another drug [42] or may not have actually been acne [40, 41] or were not distinguished from other cutaneous adverse events [43].

To the best of my knowledge, including the patient in this report, a drug-related acneiform facial eruption has only been described in five individuals who were treated with sorafenib (Table 2) [37–39]. The patients include a 42-year-old woman with liver epithelioid hemangioendothelioma and 4 men, ranging from 51 to 79 years of age (median, 58 years old), with either metastatic renal cell carcinoma (3 patients) or hepatocellular carcinoma (1 patient). The dose of sorafenib ranged from 600 mg daily (1 patient) to 800 mg (1 patient for 1 day) twice daily; the other 3 patients were receiving 400 mg twice daily.

Three of the patients had symptoms associated with their acneiform lesions: pain or a burning sensation, pruritus, and an increase in facial oiliness. Three of the patients also had acneiform lesions located on other areas of the body: scalp, neck, axillae and arms, genital area, and the upper back, chest and/or trunk. The facial lesions appeared within 9 days to 8 weeks (median, 4 weeks) after starting treatment with sorafenib; indeed, the patient in this report developed his acneiform eruption within the first 2 weeks after starting sorafenib.

The acneiform lesions appeared as papules and pustules for two of the patients. However, the lesions of the currently reported patient were predominantly monomorphic closed comedones. In addition, similar to two of the other patients whose acneiform eruption consisted of open and closed comedones, his facial lesions also had features in common with those observed in chloracne—particularly the development of lesions behind the ears, the absence of inflammatory papules, and the occurrence of non-inflammatory small cystic lesions [54].

The current patient also had several other drug-related cutaneous reactions: alopecia, hand–foot skin reactions, inflammation of seborrheic keratoses, seborrheic dermatitis-like facial eruption, and generalized xerosis. The 52-year-old man with metastatic renal cell carcinoma sorafenib-related facial acneiform eruption also developed other adverse cutaneous events from the drug including another rarely reported eruption: sandpaper-like skin texture associated with spiny filiform follicular hyperkeratosis [39]. Analogous to patients who have developed papulopustular eruptions after receiving epidermal growth factor receptor inhibitors [55], investigators have suggested that the development of skin eruptions (such as 'rash' and hand–foot skin reaction) to sorafenib is associated with successful antitumor activity of the drug [3, 17, 35, 45, 56]. Indeed, similar to other sorafenib-treated patients who developed therapy-associated cutaneous adverse events, the development of drug-induced skin effects in the current patient was associated with a favorable response of his hepatocellular carcinoma to sorafenib: a decrease of his alpha fetoprotein tumor marker.

Four of the patients received topical therapy for their acneiform facial eruption; these included benzoyl peroxide, clindamycin, erythromycin, fluocinonide, isotretinoin, and metronidazole. One patient also received oral tetracycline. Although there was a variable degree of improvement following these interventions, either lowering the sorafenib daily dose or discontinuing the drug was consistently associated with partial or complete resolution of the facial eruption. Indeed, one patient's lesions cleared when his sorafenib was discontinued for a surgical

Table 2 Characteristics of patients with sorafenib-associated facial acneiform facial eruptions

Case [ref]	1 [37]	2 [38] C1	3 [39]	4 [38] C2	5 CR
Age (years) Race Sex	42 NS Female	51 White Male	52 White Male	65 White Male	79 Asian Male
Ca	LEH	mRCC	mRC	mRCC	HCC
FAL	+	+[a]	+	+ [c]	+[e]
OSAL	Trunk (upper)	Arms, axillae, back (upper), chest (upper)	Genital area, neck, scalp	-	-
Symptoms	-	Burning sensation, oiliness (increased), pruritus	Pain	oiliness (increased)	-
Lesion morph	Papules, pustules	Open comedones = closed comedones (Ca-L)	Papules, pustules	Open comedones = closed comedones (Ca-L)	Open comedones> closed comedones (Ca-L)
Soraf dose	400 mg BID x4wk, then 800 mg BID	400 mg BID	600 mg QD	400 mg BID	400 mg BID
Onset*	4.1	6	4	8	1.3
OSCAE	NS	NS	Alopecia, HFSR, SFFH, Sp-l	NS	Alopecia, HFSR, ISK, SD-LE, xerosis
Treatment	Cleared 2 weeks after Soraf dose lowered to 400 mg BID	70% improvement after BP x 2 months	Improvement after oral tetracycline and topical: BP, EES, Flu, and Met	Tret 0.05%	Clin, Tret 0.025%
Comment	Pt died 2 months after lowering dose of Soraf from cancer prog	[b]	Soraf stopped for surgery and ACE resolved; ACE reappeared when restarted soraf	Exposure to Agent Orange in Vietnam [d]	Lesions slowly resolving with topical therapy after stop Soraf

ACE acneiform eruption, *BID* twice daily, *BP* benzoyl peroxide, *Ca* cancer, *Ca-L* chloracne-like, *C* case, *Clin* clindamycin 1% solution twice daily, *CR* current report, *EES* erythromycin, *FAL* facial acneiform lesions, *Flu* fluocinonide cream, *HCC* hepatocellular carcinoma, *HFSR* hand–foot skin reaction, *ISK* inflamed seborrheic keratosis, *LEH* liver epithelioid hemangioendothelioma, *Met* metronidazole, *mRC* metastatic renal carcinoma, *mRCC* metastatic renal cell carcinoma, *NS* not stated, *OSAL* other sites of acneiform lesions, *OSCAE* other sorafenib-associated cutaneous adverse events, *prog* progression, *Pt* patient, *QD* daily, *SD-LE* seborrheic dermatitis-like eruption, *SFFH* spiny filiform follicular hyperkeratosis, *soraf* sorafenib, *Sp-l* sandpaper-like skin texture, *Tret 0.025*% tretinoin 0.025% cream each evening, *Tret 0.05*% tretinoin 0.05% cream each evening, + present, − absent

[a] The facial acneiform lesions were located on bilateral malar cheeks and postauricular areas

[b] The facial acneiform lesions were located on the nose and bilateral malar cheeks, temples, and postauricular areas

[c] The facial acneiform lesions were located on bilateral malar cheeks, preauricular areas, ears, and postauricular areas

[d] Number of weeks on sorafenib prior to appearance of acneiform eruption

[e] A skin biopsy of an acneiform lesion showed milia-like cyst with a sparse lymphocytic inflammatory dermal infiltrate

[f] The patient did not return for follow-up examination

procedure and subsequently recurred when the drug was restarted.

CONCLUSION

Sorafenib is an oral multikinase inhibitor associated with the potential development of several cutaneous adverse events in patients treated with the drug. Alopecia and hand–foot reaction were frequently occurring events; indeed, appearance of the latter has been associated with a successful antitumor activity of the drug. In contrast, the development of a facial acneiform eruption was a rarely observed sorafenib-associated side effect that has only been described in five patients—a woman with liver epithelioid hemangioendothelioma, three men with metastatic renal cell carcinoma, and a man with hepatocellular carcinoma. The sorafenib dose ranged from 600 mg daily to 800 mg twice daily; most of the patients were receiving 400 mg twice daily. The eruption typically appeared about 4 weeks after starting sorafenib treatment; however, it was noted as early as 9 days or as late as 2 months after therapy had been initiated. Whereas two of the patients presented with papules and pustules, the other three individuals only had open and closed comedones, the appearance and distribution of which were similar to those observed in persons with chloracne. Topical antibiotics, keratolytics, and retinoids resulted in partial improvement; however, lowering the daily dose or discontinuation of sorafenib promoted progressive improvement or resolution of the facial acneiform eruption.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. The author meets the ICMJE criteria for authorship for this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

Conflict of interest. Dr. Philip R. Cohen declares no conflict of interest.

Compliance with ethical guide lines. Informed consent was obtained from the patient for being included in the study and for the publication of photographs. This article does not contain any studies with human subjects performed by the author.

REFERENCES

1. Scandurra G, Aiello RA, Ali M, Taibi E, Sano MV, Todaro FM, La Rocca R, Licciardello P, Caruso M. Appropriate management of cutaneous adverse events maximizes compliance with sorafenib treatment: a single center experience. Future Oncol. 2012;8:609–15 (PMID = 22646774).

2. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, Moon KC, Koh JK. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol. 2009;161:1045–51 (PMID = 19558553).

3. Vincenzi B, Santini D, Russo A, Addeo R, Guiliani F, Montella L, Rizzo S, Venditti O, Frezza AM, Caraglia M, Colucci G, Del Prete S, Tonini G. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist. 2010;15:85–92 (PMID = 20051477).

4. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006;24:2505–12 (PMID = 16636341).

5. Wozel G, Sticherling M, Schon MP: Cutaneous side effects of inhibition of VEGF signal transduction. J DutschDermatolGes 2010;8:243-9 (PMID = 19832927).

6. Pragasam V, Verma R, Vasudevan B. Sorafenib and sunitinib: a dermatologist's perspective. Indian Dermatol Online J. 2014;5(1):1–3 (PMID = 24616845).

7. Ishak RS, Aad SA, kyel A, Farhat FS. Cutaneous manifestations of anti-angiogenic therapy in oncology: review with focus on VEGF inhibitors. Crit Rev Oncol Hematol. 2014;90:152–64 (PMID = 24355408).

8. Robert C, Soria JC, Spatz A, Le Cesne A, Malka D, Pautier P, Wechsler J, Lhomme C, Escudier B, Boige V, Armand JP, Le Chevalier T. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet Oncol. 2005;6:491–500. (PMID = 15992698).

9. Robert C, Mateus C, Spatz A, Wechsler J, Escudier B. Dermatologic symptoms associated with the multikinase inhibitor sorafenib. J Am Acad Dermatol. 2009;60:299–305 (PMID = 19028406).

10. Curry JL, Torres-Cabala CA, Kim KB, Tetzlaff MT, Duvic M, Tsai KY, Hong DS, Prieto VG. Dermatologic toxicities to targeted cancer therapy: shared clinical and histologic adverse skin reactions. Int J Dermatol. 2014;53:376–84 (PMID = 2387947).

11. McLellan B, Kerr H. Cutaneous toxicities of the multikinase inhibitors sorafenib and sunitinib. Dermatol Ther. 2011;24:396–400 (PMID = 21910797).

12. Scandurra G, Aiello RA, Ali M, Taibi E, Sano MV, Todaro FM, LaRocca R, Licciardello P, Caruso M. Appropriate management of cutaneous adverse events maximizes compliance with sorafenib treatment: a single-center experience. Future Oncol. 2012;8:609–15 (PMID = 22646774).

13. Lipworth AD, Robert C, Zhu AX. Hand–foot syndrome (hand–foot skin reaction, palmar–plantar erythrodysesthesia): focus on sorafenib and sunitinib. Oncology. 2009;77:257–271 (PMID = 19923864).

14. Yang CH, Lin WC, Chuang CK, Chang YC, Pang ST, Lin YC, Kuo TT, Hsieh JJ, Chang JWC. Hand–foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. Br J Dermatol. 2008;158:592–596 (PMID = 18070211).

15. Maddox JS, Kung EF, Petronic-Rosic V, Sethi A. Cutaneous drug eruptions induced by sorafenib: a case series. J Drugs Dermatol. 2008;7:891–893 (PMID = 19112807).

16. Autier J, Mateus C, Wechsler J, Spatz A, Robert C. Cutaneous side effects of sorafenib and sunitinib. Ann Dermatol Venereol. 2008;135(7):148–53 [quiz 7, 154 (PMID = 18342102)].

17. Galan Brotons A, Borras-Biasco J, Rosique-Robles JD, Vicent Verge JM, Castera MDE. Generalized erythematous skin eruptions induced by sorafenib: cutaneous toxicity and treatment outcome. Clin Transl Oncol. 2008;10:844–6 (PMID = 19068457).

18. Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: an update. J Am Acad Dermatol. 2008;58:545–70 (PMID = 18342708).

19. Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol. 2008;144:886–92 (PMID = 18645140).

20. Robert C, Faivre S, Raymond E, Armand JP, Escudier B. Subungual splinter hemorrhages: a clinical window to inhibition of vascular endothelial growth factor receptors? [letter] Ann Intern Med. 2005;143:313–4 (PMID = 16103482).

21. Wolber C, Udvardi A, Tatzreiter G, Schneeberger A, Volc-Platzer B. Perforating folliculitis, angioedema, hand–foot syndrome—multiple cutaneous side effects in a patient treated with sorafenib. J Dtsch Dermatol Ges. 2009;7:449–52 (PMID = 19178612).

22. Williams VL, Cohen PR, Stewart DJ. Sorafenib-induced premalignant and malignant skin lesions. Int J Dermatol. 2011;50:396–402 (PMID = 21413947).

23. MacGregor JL, Silvers DN, Grossman ME, Sherman WH: Sorafenib-induced erythema multiforme. [letter] J Am Acad Dermatol. 2007;56:527–28 (PMID = 17241689).

24. Lewin J, Farley-Loftus R, Pomeranz MK. Erythema multiforme-like drug reaction to sorafenib. J Drug Dermatol 2011;10:1462–3 (PMID = 22134572).

25. Bilac C, Muezzinoglu T, Ermertcan AT, Kayhan TC, Temeltas G, Ozturkcan S, Temiz P. Sorafenib-induced erythema multiforme in metastatic renal carcinoma. Cutan Ocul Toxicol. 2009;28:90–2 (PMID = 19514932).

26. Bilac C, Muezzinoglu T, Ermertcan AT, Kayhan TC, Temeltas G, Ozturkcan S, Temiz P. Sorafenib = induced erythema multiforme in metastatic renal cell carcinoma. Cutan Ocul Toxicol. 2009;28:90–92 (PMID = 19514932).

27. Ikeda M, Fujita T, Mii S, Tanabae K-I, Tabata K-I, Matsumoto K, Satoh T, Iwamura M. Erythema

multiforme induced by sorafenib for metastatic renal cell carcinoma. Jpn J Clin Oncol. 2012;42:820–4 (PMID = 22782962).

28. Ikeda M, Fujita T, Amoh Y, Mii S, Matsumoto K, Iwamura M. Stevens-Johnson syndrome induced by sorafenib for metastatic renal cell carcinoma. Urol Int. 2013;91:482–3 (PMID = 239649404).

29. Lacouture ME, Desai A, Soltani K, Petronic-Rosic V, Laumann AE, Ratain MJ, Stadlert WM. Inflammation of actinic keratoses subsequent to therapy with sorafenib, a multitargeted tyrosine-kinase inhibitor. Clin Exp Dermatol. 2006;31:783–5 (PMID = 16824050).

30. Kong HH, Turner ML. Array of cutaneous adverse effects associated with sorafenib. J Am Acad Dermatol. 2009;61:360–1 (PMID = 19615549).

31. Cohen PR: Development of cutaneous premalignant lesions and malignant tumors in patients receiving sorafenib [comment on invasive squamous cell carcinoma and sorafenib in a black patient]. JAMA Dermatol. http://archderm.jamanetwork.com/article.aspx?articleid=426443. Posted Feb 13, 2011. Accessed Nov 30, 2014.

32. Hong DS, Reddy SB, Prieto VG, Wright JJ, Tannir NM, Cohen PR, Diwan AH, Evans HL, Kurzrock R. Multiple squamous cell carcinomas of the skin after therapy with sorafenib combined with tipifarnib. Arch Dermatol. 2008;144:779–82 (PMID = 18559769).

33. Chappell JA, Burkemper NM, Semchyshyn N. Localized dyskeratotic plaque with milia associated with sorafenib. J Drug Dermatol. 2009;8:573–6 (PMID = 19537383).

34. Ensslin CJ, Rosen AC, Wu S, Lacouture ME. Pruritus in patients treated with targeted cancer therapies: systematic review and meta-analysis. J Am Acad Dermatol. 2013;69:708–20 (PMID = 23981682).

35. Bauer C, Przybilla B, Rueff F. Severe cutaneous reaction to sorafenib: induction of tolerance. Acta Derm Venereol. 2008;88:627–8 (PMID = 19002355).

36. Diamantis ML, Chon SY. Sorafenib-induced psoriasiform eruption in a patient with metastatic thyroid carcinoma. J Drugs Dermatol. 2010;9:169–71 (PMID = 20214183).

37. Fleta-Asin B, Vano-Galvan S, Ledo-Rodriguez A, Truchuelo-Diez M, Jaen-Olasolo P. Facial acneiform rash associated with sorafenib. Dermatol Online J 2009;15(4):7 (PMID = 19450400).

38. Pickert A, Hughes M, Wells M. Chloracne-like drug eruption associated with sorafenib. J Drug Dermatol. 2011;10:1331–4 (PMID = 22052319).

39. Joncas V, Sammour R, Krasny M, Bouffard D, Provost N. A distinctive cutaneous reaction to sorafenib and a multikinase inhibitor. Int J Dermatol. 2008;47:767–9 (PMID = 18613894).

40. Porta C, Paglino C, Imarisio I, Bonomi L. Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitnib. Clin Exp Med. 2007;7:127–34 (PMID = 18188524).

41. Alexandrescu DT, Vaillant JG, Dasanu CA. Effect of treatment with a colloidal oatmeal lotion on the acneform eruption induced by epidermal growth factor receptor and multiple tyrosine-kinase inhibitors. Clin Exp Dermatol. 2007;32:71–4 (PMID = 17034418).

42. Duran I, Hotte SJ, HirteH, Chen EX, MacLean M, Turner S, Duan L, Pond GR, Lathia C, Walsh S, Wright JJ, Dancey J, Siu LL. Phase I targeted combination trial of sorafenib and erlotinib in patients with advanced solid tumors. Clin Cancer Res. 2007;13:4849-57 (PMID = 17699864).

43. Ji YX, Zhang ZF, Lan KT, Nie KK, Geng CX, Liu SC, Zhang L, Zhuang XJ, Zou X, Sun L, Zhang ZC. Sorafenib in liver function impaired advanced hepatocellular carcinoma. Chin Med Sci J. 2014;29:7–14 (PMID = 24698672).

44. Hotte SJ, Hirte HW: BAY 43-9006. early clinical data inpatients with advanced solid malignancies. Cur Pharm Des. 2002;8:2249–53 (PMID = 12369852).

45. Rubsam K, Flaig MJ, Ruzicka T, Prinz JC: Erythema marginatum hemorrhagicum: a unique side effect of sorafenib. [letter] J Am AcadDermatol 2011;64:1194-1196 (PMID = 21571189).

46. Kong HH, Sibaud V, Chanco Turner ML, et al. Sorafenib-induced eruptive melanocytic lesions. Arch Dermatol. 2008;144:820–2 (PMID = 18559790).

47. Bennani-Lahlou M, Mateus C Escudier B, Massard C, Soria JC, Spatz A, Robert C. Eruptive nevi associated with sorafenib treatment. Ann Dermatol Venereol. 2008;135:672–4 (PMID = 18929917).

48. Chung NM, Gutierrez M, Turner ML. Leukocytoclastic vasculitis masquerading as hand–foot syndrome in a patient treated with sorafenib. Arch Dermatol. 2006;142:1510–11 (PMID = 17116852).

49. Tanabe K, Amoh Y, Mii S, Eto H, Iwamura M, Kasuoka K. Non-pigmented fixed drug eruption induced by sorafenib. Acta Derm Venereol 2010;90:307 (PMID = 20526556).

50. Pichler M, Carriere C, Mazzoleni G, Kluge R, Eisendle K. Acne inversa-like lesions associated

with the multi-kinase inhibitor sorafenib. Clin Exp Dermatol. 2014;39:232–3 (PMID = 24330088).

51. Franck N, Barete S, Moguelet P, Blanchet B, Carlotti A, Ropert S, Avril MF, Frances C, Billemont B, Goldwasser F. Spiny follicular hyperkeratosis eruption: a new cutaneous adverse effect of sorafenib. [letter] J Clin Oncol. 2010;28:e640–2 (PMID = 20855839).

52. Magne N, Chargari C, Auberdiac P, Moncharmont C, Merrouche Y, Spano J-P. Ultraviolet recall dermatitis reaction with sorafenib. Invest New Drugs. 2011;29:1111–3 (PMID = 20567994).

53. Dasanu C, Cutcher J, Alexandrescu D. Yellow skin discoloration associated with sorafenib use for treatment of metastatic renal cell carcinoma. South Med J. 2007;100:328–30 (PMID = 17396743).

54. Panteleyev AA, Bickers DR. Dioxin-induced chloracne—reconstructing the cellular and molecular mechanisms of a classic environmental disease. Exp Dermatol. 2006;15:705–30 (PMID = 16881967).

55. Perez-Soler R. Rash as a surrogate marker for efficacy of epidermal growth factor receptor inhibitors in lung cancer. Clin Lung Cancer. 2006;8 Suppl 1:S7–14 (PMID = 17239291).

56. Shomura M, Kagawa T, Shiraishi K, Hirose S, Arase Y, Koizumi J, Mine T. Skin toxicity predicts efficacy to sorafenib in patients with advanced hepatocellular carcinoma. World J Hepatol. 2014;6:670–6 (PMID = 25276283).