

CASE REPORT

Sorafenib (Nexavar[®], BAY 43-9006)-induced Hand-foot Skin Reaction with Facial Erythema

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Sorafenib (Nexavar[®], BAY 43-9006) is a novel, orally administered multi-kinase inhibitor that has recently been approved for the treatment of metastatic renal cell carcinoma. It is also used to delay disease progression in patients with advanced solid organ malignancies and metastatic melanoma. Sorafenib is associated with a relatively high incidence of dermatologic adverse events. The commonly occurring dermatologic adverse events associated with sorafenib include hand-foot skin reaction, facial erythema, splinter subungual hemorrhages, alopecia, pruritus and xerosis. We report here on a case of a 50-year-old man who was diagnosed with metastatic hepatocellular carcinoma. He developed both facial erythema and hand-foot skin reaction after the administration of sorafenib. (*Ann Dermatol* 23(1) 119~122, 2011)

-Keywords-

Facial erythema, Hand-foot skin reaction, Sorafenib

INTRODUCTION

The U.S. Food and Drug Administration (FDA) has approved the use of sorafenib (Nexavar[®], BAY43-9006). Sorafenib is a new, orally administered, small-molecule, multi-kinase inhibitor that is used for the treatment of patients with advanced renal cell carcinoma (RCC)¹. It has also been recently approved for the treatment of hepatocellular carcinoma (HCC)². The use of sorafenib is

associated with a relatively high incidence of dermatologic adverse events. The commonly occurring dermatologic adverse events associated with sorafenib include hand-foot skin reaction (HFSR), facial erythema (rash and desquamation), splinter subungual hemorrhages, alopecia, pruritus and xerosis³. The development of rash and hand-foot syndrome (HFS) has been reported in the majority of patients and appears to represent a toxic, dose-dependent reaction⁴. We report here on a case of a 50-year-old man who was diagnosed with metastatic HCC. He developed both facial erythema and HFSR after the administration of sorafenib (800 mg/day for 10 days).

CASE REPORT

A 50-year-old male presented to our department for the evaluation of patches on his fingers and the soles of his feet. In addition, papules had been noted on his face one week earlier. The patient had HCC. Clinical examination revealed hyperkeratotic patches on the plantar pressure areas of his feet (Fig. 1A). There were erythematous patches with central yellow-colored blisters on the lateral sides and tips of his fingers (Fig. 1B). There were also small erythematous papules on his face (Fig. 2). The symptoms reported by the patient included paresthesias, tingling, burning and painful sensations on the palms and soles, as well as decreased tolerance for contacting hot objects. The skin lesions had developed 10 days after he began oral treatment with sorafenib, 800 mg/day. The histopathology of a skin biopsy taken from the hyperkeratotic patch of his sole showed parakeratosis, dyskeratosis and vacuolar degeneration of the keratinocytes in the epidermis (Fig. 3). As a result of the clinical and pathologic findings, the diagnosis was HFSR with facial erythema to sorafenib. The sorafenib was discontinued. Treatment with topical glucocorticoids and oral antihistamines was

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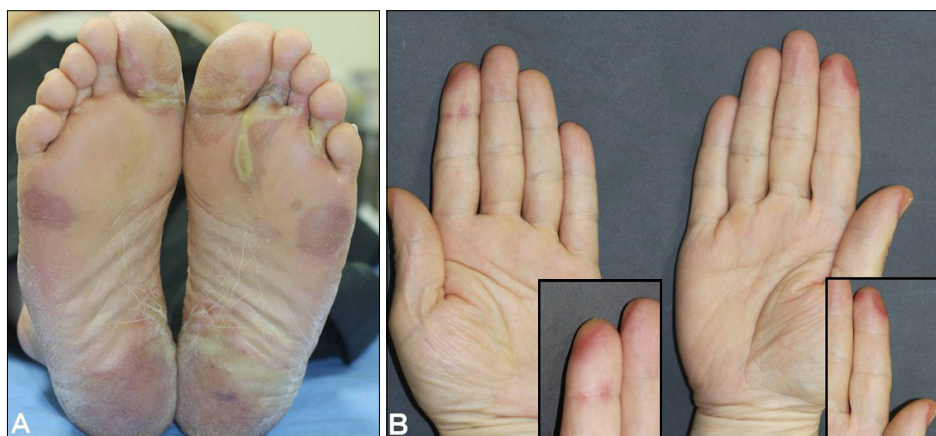


Fig. 1. (A) Yellow discoloration hyperkeratotic patches on the plantar pressure areas (B) Erythematous patches with central yellow-colored blisters on lateral sides and tips of fingers.



Fig. 2. Discrete erythematous tiny papules on the face. The lesions mostly involved the mediotfacial area and spared the periorbital area.

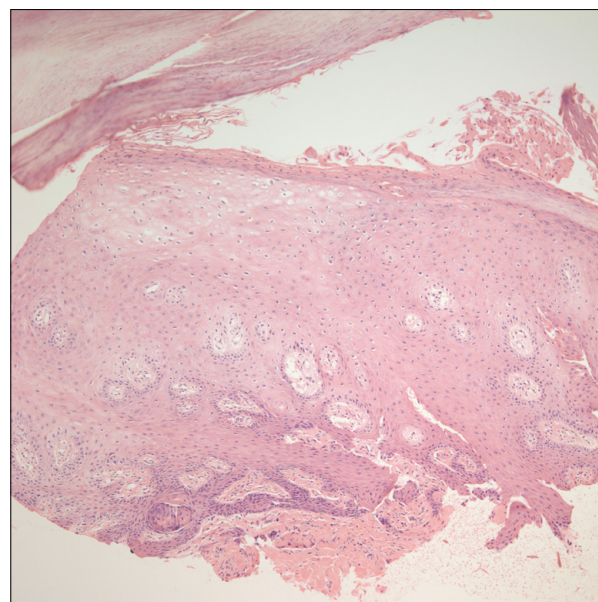


Fig. 3. The histopathological findings of the hyperkeratotic patch showed parakeratosis, dyskeratosis and vacuolar degeneration of keratinocytes in the epidermis (H&E stain, ×100).

initiated, and the skin lesions cleared within two weeks.

DISCUSSION

Sorafenib (BAY43-9006) is a multi-kinase inhibitor that inhibits the molecular components of the Raf-MEK-ERK signaling pathway. The drug limits tumor growth and VEGFR-1, VEGFR-2, VEGFR-3 and PDGFR- β expressions, and so it inhibits neoangiogenesis. Sorafenib delays disease progression by targeting two key pathways that are known to be important in the pathogenesis of HCC^{5,6}. Sorafenib is generally safe and well-tolerated in patients who have advanced, progressive solid tumors, including RCC, melanoma, HCC and colorectal cancer. There is little evidence of any clinically relevant drug-drug interactions.

The most frequently reported toxicities attributed to sorafenib include rash, hypertension, fatigue, anorexia and diarrhea. Up to 93% of the patients who receive sorafenib as monotherapy experience cutaneous effects, including rash (18~66%), HFS (25~62%), alopecia (18~53%), stomatitis (12~35%), xerosis (11~23%) and flushing (16%)^{3,4}.

The rash on the patient's face appeared as a homogeneous, slightly erythematous eruption that was associated with superficial desquamation. The lesions mostly involved the mediotfacial area and they spared the periorbital area. The erythema was sometimes exacerbated by hot temperatures⁷. The facial eruptions related to sorafenib use are very similar to classic seborrheic dermatitis and

these facial eruptions typically do not require active treatment. No correlation was found between the occurrence of the facial eruptions and the response to treatment. Symptomatic relief can be achieved with a topical emollient, topical imidazole derivatives and/or topical steroids.

HFSR manifests as palmoplantar lesions, and especially in areas exposed to trauma or friction. These lesions can have a significant effect on a patient's quality of life. HFSR induced by sorafenib use has a different presentation than classic HFS. Classic HFS is also known as acral erythema or palmar-plantar erythrodysesthesia, and this occurs during the use of various chemotherapeutic agents, including cytarabine, capecitabine, doxorubicin hydrochloride and fluorouracil. The incidence of HFS ranges from 6% to 68%, depending on the particular chemotherapeutic agent being used^{4,8}. HFSR induced by sorafenib shares several of the non-specific clinical and pathological features of classic HFS. These include initial paresthesias or painful sensations, erythema, fissures and non-specific pathological inflammatory infiltrates. However, sorafenib-induced HFSR is more frequently associated with palmar and/or plantar hyperkeratosis, as compared to that of classic HFS. Our findings revealed that hyperkeratosis is an early manifestation, and sometimes the only manifestation, of sorafenib-induced HFSR. Hyperkeratosis is less frequently reported in cases of classic HFS, where it occurs mostly during the chronic phase of the disease⁷. In addition, hyperkeratosis that is associated with sorafenib-induced HFSR more commonly presents as a patchy keratoderma located on the pressure areas and this patchy keratoderma is typically more diffuse in cases of classic HFS.

The recommended treatments for HFSR include the use of moisturizers, cooling, absorbers, corticosteroids and keratolytics such as urea and salicylic acid⁹. It is recommended that patients who have grade 2 or 3 HFSR have their sorafenib dose reduced, with or without subsequent treatment interruption, if the topical treatment is not successful¹⁰. HFSR is a relatively early cutaneous symptom seen during sorafenib therapy. Consequently, prevention is critical in order to minimize the development of HFSR during the first four weeks of therapy. In order to help prevent HFSR, patients should avoid traumatic activity, excessive friction and the use of constrictive footwear. As seen in the case reported here, severe symptoms of HFSR can develop soon after sorafenib therapy is initiated. The patients who develop HFSR within two to four weeks after initiating sorafenib therapy are particularly in need of proper medical management to relieve symptoms and to prevent progression to high-grade HFSR¹¹.

Two cases of sorafenib-induced cutaneous adverse events

have currently been reported in the Korean medical literature^{12,13}. However, neither of these patients experienced facial erythema or HFSR. Multi-targeted tyrosine kinase inhibitors, including sorafenib, can induce a variety of dermatologic adverse events. These events require early recognition and effective management in order to ensure that lifesaving anti-neoplastic therapy can be continued. Observations, such as the case described here, can contribute to a better understanding of this problem and aid physicians in the early management of these patients.

REFERENCES

1. Kane RC, Farrell AT, Saber H, Tang S, Williams G, Jee JM, et al. Sorafenib for the treatment of advanced renal cell carcinoma. *Clin Cancer Res* 2006;12:7271-7278.
2. Llovet J, Ricci S, Mazzaferro V, Hilgard P, Raoul J, Zeuzem S, et al. Randomized phase III trial of sorafenib versus placebo in patients with advanced hepatocellular carcinoma (HCC) [abstract]. *J Clin Oncol* 2007;25:LBA1.
3. 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;24:2505-2512.
4. Strumberg D, Awada A, Hirte H, Clark JW, Seeber S, Piccart P, 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;42:548-556.
5. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43-9006 exhibits broad spectrum oral anti-tumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;64:7099-7109.
6. Ito Y, Sasaki Y, Horimoto M, Wada S, Tanaka Y, Kasahara A, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. *Hepatology* 1998;27:951-958.
7. 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;144:886-892.
8. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol* 1999;40:367-398.
9. Lacouture ME, Wu S, Robert C, Atkins MB, Kong HH, Guitart J, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist* 2008; 13:1001-1011.
10. Chu D, Lacouture ME, Fillos T, Wu S. Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis. *Acta Oncol* 2008;47:176-186.
11. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Br J*

- Dermatol 2009;161:1045-1051.
12. Park JH, Kim S, Choi SC, Lee ES, Yang JM. Cutaneous adverse effects associated with sorafenib therapy (Nexavar[®], BAY 43-9006). Korean J Dermatol 2008;46:141-143.
 13. Kim HJ, Kim JH, Kim JB, Kim HK, Ko YS, Joh OJ, et al. A case of leukocytoclastic vasculitis after use of sorafenib (Nexavar[®]). Korean J Dermatol 2008;46:648-651.
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