Sorafenib and sunitinib: A dermatologist's perspective

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ABSTRACT

Sorafenib and sunitinib are inhibitors of tumor angiogenesis have recently generated curiosity regarding its role in cutaneous toxicities, which has severely affected the daily activities resulting in interruption or dose modification of therapy in renal cell carcinoma and hepatocellular carcinomas. We discuss the pathophysiology, adverse cutaneous effects and their grading, potential high risk factors, role of gene polymorphism, critical period of hand-foot skin reaction development and their management.

Key words: Burgdorf reaction, hand-foot skin reaction, palmar-plantar erythrodysesthesia

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INTRODUCTION

The multikinase inhibitors (MKI) sorafenib and sunitinib are important inhibitors of tumor angiogenesis that target vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3, platelet-derived growth factor receptor-beta (PDGFR)-β, protein-serine/threonine kinases family designated rapidly accelerated fibrosarcoma (RAF) Fms-like Tyrosine Kinase-3 and proto-oncogene or tyrosine-proteinkinase (c-KIT) They have been approved for use in malignancies such as renal cell carcinoma, hepatocellular carcinoma and gastrointestinal stromal tumor.[1] These anti-cancer drugs are part of the standard management protocol for maintaining remission of these malignancies. However, they can cause a variety of cutaneous toxicities such as hand-foot skin reaction (HFSR) and non-HFSR. Although, HFSR does not appear to directly affect survival, it can impact quality of life and lead to MKI dose modification or interruption.

PATHOPHYSIOLOGY

The hypotheses put forward in the causation of HFSR and non-HFSR by sorafenib and sunitinib includes (a) inhibition of mitogen-activated protein kinase, stress-activated protein kinase, and VEGF pathways. This results in keratinocyte proliferation and focal apoptosis leading to non-HFSR adverse effects such as keratosis pilaris, epidermal inclusion cysts, and keratoacanthomas. (b) sorafenib inhibits c-kit or RAF kinase that results in keratinocyte injury and is seen histopathologically as focal epithelial damage with dyskeratotic keratinocytes and reactive epithelial changes in the basal layer of the epidermis and in eccrine sweat ducts.[2-4] (c) sunitinib induces endothelial-cell apoptosis in animal-tumor models, and pathologic changes observed suggest that dermal-vessel alteration and apoptosis might be due to direct anti-VEGFR or anti-PDGFR effects on dermal endothelial cells.

Causes for cutaneous toxicity and acral predilection

Potential high risk factors associated with cutaneous toxicities caused by sorafenib and sunitinib may be due to (a) higher circulating concentration of the drug and longer half-life in the skin (72 hours as compared to 20-36 hours in other organs). (b) Increased toxic local concentrations of these drugs in eccrine sweat glands which express c-KIT and PDGFR[2-4] (c) Hair depigmentation is thought to be caused by blockade of c-kit signaling which is important for melanocyte proliferation, differentiation and pigment production. (d) Yellow discoloration of skin is due to active drug and its metabolite. (e) Genetic polymorphisms of the tumor necrosis factor-alpha (TNF-α), VEGF, and Uridine diphosphate glucose glucuronosyltransferase 1 family, polypeptide A9 (UGT1A9) genes have also been identified as high risk for severe toxicity.[5]

Cutaneous manifestations of hand-foot skin reaction

The cutaneous toxicities caused by sorafenib and sunitinib are most common during initial five to six weeks, which is considered as the critical period. The most common high grade toxicity is palmar–plantar erythrodysesthesia, also described as Burgdorf reaction[6] commonly known as HFSR. Symptoms of HFSR included paresthesia, tingling, burning or painful sensations on the palms and soles, and a decreased tolerance for touching hot objects. These symptoms usually occur before cutaneous lesions emerge. An early presentation characterized by grade 1 HFSR in the form of erythema and peeling over pressure areas was seen in our patient on sorafenib for metastatic medullary carcinoma of thyroid [Figure 1]. The characteristic cutaneous presentations in HFSR are symmetric acral blisters with erythematous halo, hyperkeratosis followed by desquamation and fissuring. It involves the palmar aspect of digital tips, thenar, hypothenar eminences, heel and forefoot. Hyperkeratosis presents as yellowish, painful plaques on pressure areas of the sole as seen in two of our patients with renal cell carcinoma [Figure 2]. HFSR was observed in 48 percent of patients treated with sorafenib and 36 percent of those treated with sunitinib. Median time to onset was 18.4 days in patients receiving sorafenib and 32.4 days in those receiving sunitinib[7] As per the U. S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE): Version 4.03 HFSR is graded into three grades based on the severity as mentioned in Table 1.

Non-HFSR cutaneous toxicities caused by sunitinib and sorefenib included yellow discoloration of skin occurring in approximately 30 percent of the patients, alopecia, stomatitis, subungual splinter hemorrhages, facial swelling, keratoacanthomas, leukocytoclastic vasculitis. Alternating bands of depigmented and normally pigmented bands of hair was another peculiar effect, which may correlate with on and off periods of treatment. Genital lesions, facial erythema, nevi, lentigenes, epidermal inclusion cysts, and xerosis were the other toxicities noted. Generalized erythema, maculopapular or seborrheic dermatitis-like rashes has been reported with sunitinib therapy. Among these manifestations HFSR, genital lesions in the scrotal region and severe stomatitis were the early toxicities which required therapy modifications in the form of dose reduction and discontinuation [7,8]

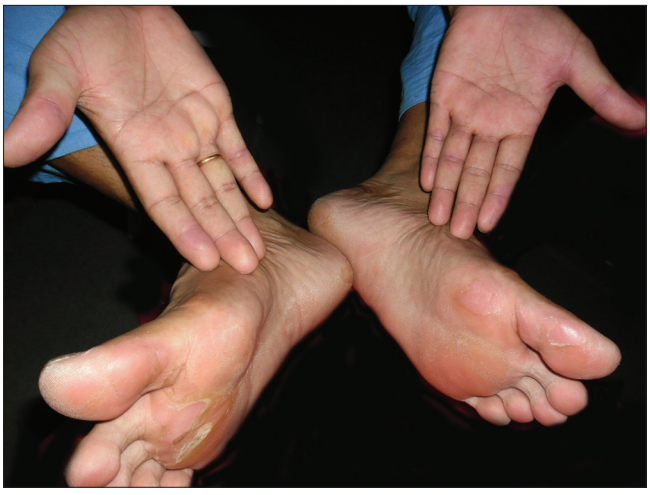

Figure 1: Erythema, hyperkeratoses and peeling over pressure areas in this patient with metastatic medullary carcinoma of thyroid

Differential diagnosis for hand-foot skin reaction

Hand foot syndrome is diagnosed when associated with chemotherapy agents such as cytarabine, capecitabine 5-fluorouracil, and methotrexate, and is characterized by diffuse involvement of palms and soles unlike the focal involvement seen in HFSR. Nails show subungual hyperkeratosis whereas in HFSR subungual hemorrhages were seen.

Neutrophilic eccrine hidradenitis may occur in patients undergoing chemotherapy for acute myeloid leukemia, Hodgkin's lymphoma or solid tumors. It is characterized by erythematous and edematous papules, plaques or nodules located on the trunk, extremities including palms and soles that may be pruritic or tender.

Palmar erythema is characterized by non-tender reddening of the thenar and hypothenar eminences. It may rarely involve the soles (plantar erythema). This presentation may be seen with chronic liver disease, thyrotoxicosis and rheumatoid arthritis. Hyperkeratotic and severe dyshidrotic eczema may also be considered in the differential diagnosis.

Treatment modalities of hand-foot skin reaction

Weekly monitoring of these patients during the initial critical period of five to six weeks is very important. Certain preventive

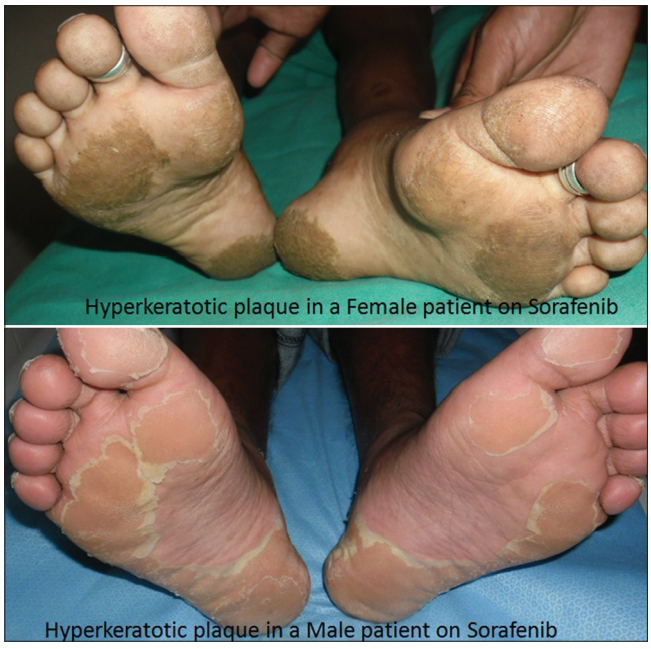

Figure 2: Severe hyperkeratosis in two patients with metastatic renal cell carcinoma on sorafenib

Table 1: Grades of severity in HFSR*

Grade 1	Grade 2	Grade 3
Palmar-plantar erythrodysesthesia syndrome Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL

ADL: Activities of daily living, *U. S. Department of health and human services. Common terminology criteria for adverse events (CTCAE): Version 4.03: June 14, 2010). Available online at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5×11.pdf). HFSR: Hand-foot skin reaction

measures to reduce the severity of HFSR include reducing hot water exposure of their hands and feet, occupational changes to avoid traumatic and frictional activities, wearing thick gloves and socks, avoid ill-fitting shoes, wearing shoes with padded insoles, daily use of salicylic acid and urea preparations, daily inspection of hands and feet for areas of redness and pain. Treatment for oral side effects includes alcohol-free mouthwash with a half teaspoon of baking soda or salt in 1 cup of warm water and rinse several times a day. Viscous lidocaine, non-peroxide toothpaste, use of very soft toothbrush, dietary modifications, such as avoiding hot, spicy foods, alcoholic drinks, and eating soft foods, may be helpful. In case of grade 2 and grade 3 toxicity, treatment may be interrupted for 7 days and restarted at fifty percent of the dose. Drug related therapies under evaluation by various authors include topical emollients, systemic and topical corticosteroids, tazarotene 0.1percent cream, nicotine patch, vitamin E, pyridoxine, and cycloxygenase-2 (COX-2) inhibitors[8,9,10]

CONCLUSION

Sorafenib and Sunitinib are the important inhibitors of tumor angiogenesis and are being used increasingly in various malignancies. Most critical period of HFSR development is during the first 5 weeks of MKIs. In view of the preventable severe cutaneous toxicities, dermatologists must be aware of these specific toxicities, dose modification, preventive and supportive measures that need to be undertaken for early identification and management.

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