

Tyrosine kinase inhibitors (TKIs) -Induced Hand-Foot Skin Reaction vs Hand-Foot Syndrome: Literature Review

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Abstract

Background: Cutaneous toxicities represent significant dose-limiting factors in systemic anticancer therapy. Among these, Hand-Foot Syndrome (HFS) and Hand-Foot Skin Reaction (HFSR) are frequently conflated despite distinct etiopathogenic and clinical profiles. Our review delineates the divergent characteristics of HFS, associated with conventional cytotoxic chemotherapy, and HFSR, predominantly induced by Tyrosine Kinase Inhibitors (TKIs).

Methods: A comprehensive literature review was conducted across PUBMED, MEDLINE, and other major databases including published articles from 2000 until June 2025 evaluating clinical trials, case reports, observational studies, and literature reviews with meta-analyses concerning TKI-induced HFSR and chemotherapy-associated HFS.

Results: HFSR incidence is particularly high with multi-target TKIs such as regorafenib (45–50%) and sorafenib (30–40%). Pathophysiologically, HFSR stems from VEGFR and PDGFR inhibition, impairing microvascular repair and promoting hyperkeratosis at mechanical pressure points. Clinically, it manifests as well-demarcated, hyperkeratotic plaques appearing within 1–2 weeks of treatment. Conversely, HFS—driven by agents like capecitabine—presents as diffuse, symmetric erythema and edema, typically emerging 2–4 weeks post-initiation. The mechanism involves drug accumulation in eccrine glands and direct keratinocyte apoptosis. While HFS often necessitates dose intensity modifications, HFSR management emphasizes proactive topical keratolytic and pressure-point cushioning. Emerging evidence further suggests that HFSR development may serve as a surrogate biomarker for TKI efficacy.

Conclusion: Precise differentiation between HFS and HFSR is imperative for oncological practice. While HFS requires systemic adjustments to mitigate toxicity, HFSR demands a localized, proactive dermatological approach to maintain therapeutic continuity. Recognizing these nuances allows clinicians to preserve dose intensity while addressing the functional and prognostic implications of these reactions. Crucially, prophylactic management of both conditions include aggressive lipid-replenishing hydration, the use of ergonomic, shock-absorbing footwear, and the proactive mitigation of mechanical pressure points to prevent debilitating hyperkeratotic or erythematous lesions.

Keywords: Tyrosine Kinase Inhibitors (TKIs), Hand-Foot Skin Reaction (HFSR), Hand-Foot Syndrome (HFS), Cutaneous Toxicity, VEGFR Inhibition, Oncologic Dermatology, Hyperkeratosis.

INTRODUCTION

Cutaneous toxicities are among the most frequent adverse events associated with systemic anticancer therapies and may significantly impact treatment adherence, dose intensity, and patient quality of life[1,2]. Among these dermatologic complications, palmoplantar reactions represent a particularly challenging clinical entity due to their functional implications and potential to compromise therapeutic continuity[3].

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Two distinct conditions are commonly observed in this context: Hand-Foot Syndrome (HFS), also known as palmar-plantar erythrodysesthesia, typically associated with conventional cytotoxic chemotherapy agents, and Hand-Foot Skin Reaction (HFSR), predominantly induced by Tyrosine Kinase Inhibitors (TKIs)[4,5]. Although these entities share certain clinical features and they differ substantially in their pathophysiology, clinical presentation, histopathologic characteristics, and management strategies[4,6].

The objective of this article is to provide a comprehensive description of the clinical manifestations, course, and progression of chemotherapy-induced Hand-Foot Syndrome and Tyrosine Kinase Inhibitor-induced Hand-Foot Skin Reaction, to delineate the key distinguishing features between these two adverse cutaneous reactions, and to critically review the impact of their occurrence on patient clinical outcomes.

METHODS

We reviewed the literature published in PUBMED, MEDLINE, EMBASE, SCOPUS, and LILACS on hand-foot reaction (HFSR) associated with tyrosine kinase inhibitors (TKIs) including published articles from 2000 until June. For the search, we used descriptors in English and Spanish and included clinical trials, case reports, observational studies, and literature reviews with meta-analyses concerning TKI-induced HFSR and chemotherapy-associated HFS. The key terms were: regorafenib, hand-foot skin reaction (HFSR), multikinase inhibitors, tyrosine kinase inhibitors (TKIs), palmar-plantar erythrodysesthesia, oncologic dermatologic toxicity.

Hand-Foot Skin Reaction (HFSR) induced by Tyrosine Kinase Inhibitors (TKIs)

Phase II and III clinical trials and subsequent meta-analyses have demonstrated substantial variability in the incidence of tyrosine kinase inhibitor (TKI)-induced hand-foot skin reaction (HFSR) across different agents[7]. In the pivotal phase III TARGET trial evaluating sorafenib in advanced renal cell carcinoma, HFSR was reported in approximately 30–40% of patients, with grade ≥ 3 events in about 8–10%[7]. Similarly, Sunitinib has shown overall incidences ranging from 20% to 30% across large, randomized studies[8]. Notably, higher rates have been observed with regorafenib, as reported in the CORRECT and RESORCE phase III trials, where overall HFSR incidence approached 45–50%, with grade 3 reactions occurring in up to 15–20% of patients[9,10]. Axitinib (AXIS trial) and cabozantinib (METEOR trial) have demonstrated intermediate incidences, generally between 25% and 40%,

depending on tumor type and prior therapies[11,12]. In contrast, pazopanib (VEG105192 trial) and certain other multitarget TKIs have been associated with comparatively lower rates, often below 20%[13]. Pooled analyses of randomized controlled trials confirm this heterogeneity, reporting an overall incidence of TKI-associated HFSR of approximately 30–35% -9.7% high-grade HFSR, with significant differences among VEGFR-targeting agents[14]. These variations likely reflect differences in kinase selectivity, pharmacodynamic profiles, cumulative exposure, and patient populations studied, underscoring the importance of agent-specific risk assessment in clinical practice[14].

The risk of developing HFSR appears to be significantly influenced by the specific VEGFR-TKI utilized and the underlying malignancy[14]. Meta-analytical data indicate that regorafenib carries the highest relative risk (RR 5.4) compared to placebo, while agents like brivanib and axitinib also show high incidences in specific cohorts[14]. Furthermore, the incidence of HFSR is notably higher in patients with renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) compared to those with other solid tumors, potentially due to the different dosing schedules and the duration of therapy required for these indications[14,15]. Patient-related factors, such as female gender and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, have also been associated with an increased risk of high-grade toxicity[16].

The exact molecular mechanism underlying tyrosine kinase inhibitor (TKI)-induced Hand-Foot Skin Reaction (HFSR) remains incompletely elucidated; however, growing experimental and clinical evidence supports a multifactorial pathogenesis[1,4]. Multikinase inhibitors such as sorafenib and regorafenib target several signaling pathways involved in angiogenesis and cellular proliferation, including vascular endothelial growth factor receptors (VEGFR-1, -2, -3), platelet-derived growth factor receptors (PDGFR- α/β), RAF kinases, KIT, and RET[3,17,18]. Inhibition of VEGFR and PDGFR signaling is thought to impair endothelial cell survival and microvascular repair mechanisms, leading to vascular fragility and compromised dermal capillary integrity, particularly in areas subjected to repeated mechanical stress[2]. This antiangiogenic effect may result in reduced regenerative capacity of the epidermis and increased susceptibility to trauma-induced damage[1]. Additionally, direct toxic effects on rapidly proliferating keratinocytes, possibly mediated by RAF pathway inhibition and altered MAPK signaling, may contribute to dysregulated epidermal differentiation and hyperkeratosis[2]. The predilection for pressure-bearing areas suggests that

subclinical mechanical injury, combined with impaired vascular and epithelial repair, plays a central role in lesion development[1,2].

Furthermore, recent evidence suggests that the blockade of the BRAF/MEK/ERK signaling pathway in keratinocytes plays a pivotal role in HFSR[19]. This inhibition triggers a state of premature cellular senescence and the release of pro-inflammatory cytokines, creating a localized 'senescence-associated secretory phenotype' (SASP) that exacerbates tissue damage at sites of mechanical friction[19]. Additionally, the high lipophilicity of certain multikinase inhibitors leads to their preferential accumulation in the stratum corneum and eccrine glands, where they interfere with the mitochondrial function of keratinocytes, leading to reactive oxygen species (ROS) production and subsequent apoptosis[20].

The inhibition of PDGFR and c-KIT is particularly relevant to the unique clinical phenotype of HFSR. PDGFR- β is expressed in pericytes and is crucial for maintaining the structural integrity of dermal capillaries[4,21]. Its blockade, coupled with VEGFR inhibition, synergistically promotes microvascular regression and impairs the response to daily "wear and tear" in acral skin[21]. Moreover, c-KIT is expressed in both eccrine gland epithelium and basal keratinocytes; its inhibition may disrupt normal sweat gland function and keratinocyte homeostasis, potentially explaining the early sensory symptoms and subsequent localized necrosis[22]. This suggests that the clinical manifestation of hyperkeratotic plaques is a secondary compensatory response to chronic, low-grade subepidermal ischemia and direct epithelial toxicity[4].

Clinically, TKI-induced HFSR differs from classic chemotherapy-induced Hand-Foot Syndrome in both morphology and distribution[4]. HFSR typically presents well-demarcated, localized erythematous plaques with overlying hyperkeratosis on the palms and soles, particularly at sites of friction or pressure such as the heels, metatarsal heads, and lateral aspects of the feet[2,4]. Early lesions may manifest as dysesthesia, tingling, or burning sensations, followed by the development of painful callus-like hyperkeratotic plaques[1]. In more severe cases (grade 2–3 according to the Common Terminology Criteria for Adverse Events), lesions may progress to blistering, edema, fissuring, and functional impairment, significantly affecting ambulation and manual activities[2].

Unlike the diffuse changes seen in conventional HFS, the histopathology of HFSR reveals distinct features. Biopsies of HFSR lesions frequently show horizontal layers of keratinocyte necrosis within the stratum granulosum

and spinosum, which often correlate with the duration of drug exposure[3]. Early lesions (<30 days) demonstrate prominent keratinocyte vacuolization and necrosis, whereas later lesions exhibit marked hyperkeratosis and parakeratosis[3,4]. Intracytoplasmic eosinophilic inclusions within keratinocytes have also been described, suggesting a unique cytotoxic metabolic effect of TKIs on the epidermal unit[4].

Hand-foot Syndrome due to Conventional Chemotherapy

Hand-Foot Syndrome (HFS), also referred to as palmar-plantar erythrodysesthesia, is a well-recognized dose-limiting dermatologic toxicity associated with several conventional cytotoxic chemotherapeutic agents[23]. The condition has been most frequently reported with fluoropyrimidines—particularly capecitabine and continuous-infusion 5-fluorouracil (5-FU)—as well as liposomal doxorubicin and, less commonly, cytarabine and docetaxel[24–26]. Across phase II and III clinical trials, the incidence of all-grade HFS with capecitabine ranges from approximately 40% to 60%, with grade 3 events occurring in 10–20% of patients, depending on dose intensity and treatment schedule[27]. Continuous-infusion 5-FU has been associated with HFS rates of 20–40%, while pegylated liposomal doxorubicin demonstrates particularly high incidences, frequently exceeding 50% for all-grade reactions and 15–25% for grade ≥ 3 toxicity[25,26]. Meta-analyses of randomized controlled trials confirm that fluoropyrimidine-based regimens significantly increase the risk of HFS compared with non-fluoropyrimidine chemotherapy backbones[28].

Clinically, chemotherapy-induced HFS presents as symmetric, diffuse erythema and edema involving the palms and soles, often preceded by prodromal dysesthesia, tingling, or burning sensations[5]. As the reaction progresses, patients may develop tenderness, swelling, desquamation, and, in severe cases, blistering, ulceration, or functional impairment affecting ambulation and manual dexterity[5,6]. Lesions are typically non-hyperkeratotic and involve broader acral surfaces[4]. Furthermore, a significant correlation between HFSR severity and the concurrent development of other toxicities—including stomatitis, alopecia, and scalp dysaesthesia—has been documented[15]. This suggests a broader spectrum of dermatologic toxicity associated with this class of biological agents[15]. According to the Common Terminology Criteria for Adverse Events (CTCAE), grade 1 disease is characterized by minimal skin changes without pain; grade 2 includes painful erythema and swelling affecting instrumental activities of daily living; and grade

3 involves severe pain, blistering, or ulceration limiting self-care activities[5,29].

The pathophysiology of chemotherapy-induced HFS is not completely understood but is believed to involve drug accumulation in eccrine sweat glands, which are highly concentrated in palmar and plantar skin[5]. High local concentrations of cytotoxic metabolites may lead to direct damage to basal keratinocytes and endothelial cells, resulting in epidermal apoptosis and inflammatory responses[5,29]. In the case of fluoropyrimidines, the conversion of capecitabine to 5-FU within keratinocytes—mediated by thymidine phosphorylase, which is expressed in higher levels in acral skin—may contribute to localized toxicity[30]. Additionally, mechanical stress and increased vascular permeability in pressure-bearing areas may facilitate extravasation of cytotoxic agents into surrounding tissues[31]. Histopathologic findings typically include vacuolar degeneration of basal keratinocytes, scattered necrotic keratinocytes, mild spongiosis, and superficial perivascular lymphocytic infiltration, without the prominent hyperkeratosis that characterizes TKI-induced reactions[5,27].

In the specific case of pegylated liposomal doxorubicin (PLD), pathogenesis is further complicated by the interaction between the drug and metallic ions in the skin[32]. Studies have suggested that doxorubicin extravasates through the long-term circulation of

pegylated liposomes and interacts with abundant Cu(II) ions in dermal tissues, leading to the generation of reactive oxygen species (ROS)[32,33]. These ROS directly induce keratinocyte-specific apoptosis via the TRPM2 thermoreceptor, which is highly sensitive to oxidative stress[32]. In contrast, high-dose methotrexate and cytarabine, frequently used in pediatric oncology, induce a form of HFS (often called toxic acral erythema) characterized by an earlier onset—sometimes within 2 to 7 days—suggesting a direct, rapid cytotoxic effect on the rapidly dividing cells of the basal layer[23,34,35].

The inter-individual variability in HFS severity is significantly influenced by pharmacogenetic factors, particularly polymorphisms in the *DPYD* gene[36]. Patients with dihydropyridine dehydrogenase (DPD) deficiency are at a substantially higher risk of developing early and severe palmar-plantar erythrodysesthesia due to the impaired catabolism of 5-fluorouracil (5-FU) [36]. Moreover, the involvement of the cyclooxygenase-2 (COX-2) pathway in the pathogenesis of HFS has led to the exploration of prophylactic strategies[37].

Hand-foot Syndrome due to Conventional Chemotherapy vs Hand-Foot Skin Reaction (HFSR) Induced By Tyrosine Kinase Inhibitors (TKIs)

Hand-Foot Skin Reaction (HFSR) induced by tyrosine kinase inhibitors (TKIs) differs markedly from chemotherapy-

Table 1. Differences between regorafenib-induced hand-foot skin reaction vs. classic chemotherapy-induced hand-foot syndrome

Feature	TKI-induced HFSR	Conventional Chemotherapy-induced HFS
Representative Agents	Regorafenib (highest incidence among TKIs), sorafenib, sunitinib, etc.	Capecitabine, 5-fluorouracil, liposomal doxorubicin, cytarabine.
Anatomical Distribution	Focal lesions are localized at mechanical pressure points (heels, metatarsal heads, digital borders).	Diffuse, symmetric involvement of the palmar and plantar surfaces.
Predominant Morphology	Painful hyperkeratosis/calluses with fissures and circumscribed erythema.	Diffuse erythema, edema, pain, paresthesia, desquamation, and blistering. Ulceration in severe cases.
Incidence (Grade ≥ 3)	20.4%; regorafenib carries the highest relative risk of severe HFSR among VEGFR-TKIs.	Grade ≥ 3 is less frequent; incidence depends on the specific agent and cumulative dose intensity.
Prophylactic Management	Use of emollients/keratolytic and friction reduction; pharmacological prophylaxis data remains limited.	Use of emollients/keratolytic and friction reduction; pharmacological prophylaxis data remains limited. Celecoxib is controversial.
Therapeutic Intervention	Emollients combined with keratolytic (urea/salicylic acid), topical corticosteroids, and pressure unloading.	Emollients, topical corticosteroids, and analgesia. Reduction or interruption of the cytotoxic agent.

induced Hand-Foot Syndrome (HFS) in both morphology and distribution (table 1)[26]. While chemotherapy-induced HFS typically presents as symmetric, diffuse erythema and edema affecting the entire palmar and plantar surfaces, often accompanied by desquamation, tenderness, and, in severe cases, blistering, TKI-induced HFSR is characterized by well-demarcated, localized hyperkeratotic plaques predominantly at sites of pressure or friction, such as the heels, metacarpal heads, and lateral aspects of the feet[3]. Pain is often disproportionate to visible erythema in HFSR, whereas in HFS, discomfort generally correlates with the extent of erythema[26]. HFS associated with conventional chemotherapy generally develops after several cycles of treatment, typically two to four weeks after initiation, depending on cumulative dose[38]. By contrast, TKI-induced HFSR often appears earlier, commonly within 1–2 weeks of starting therapy, likely reflecting a combination of direct keratinocyte toxicity and impaired vascular repair mechanisms in acral skin[39].

An emerging concept in the management of these toxicities is their potential role as surrogate biomarkers for treatment efficacy[40]. Several studies and meta-analyses have documented a significant correlation between the development of HFS/HFSR and improved clinical outcomes, including progression-free survival (PFS) and overall survival (OS), for instance, in patients treated with capecitabine or sorafenib, the presence of HFS or HFSR has been predictive of higher objective response rates[40,41]. This association suggests that the same molecular pathways responsible for tumor suppression (e.g., VEGFR or fluorouracil-mediated inhibition) are also driving the cutaneous adverse events, thereby reflecting adequate systemic drug exposure and target engagement[4,41].

Management strategies differ due to underlying mechanisms and lesion characteristics; Chemotherapy-induced HFS primarily requires dose modification or temporary treatment interruption in moderate to severe cases, alongside symptomatic measures such as topical emollients, urea-based creams, cooling of affected areas, and analgesics[38]. Preventive strategies may include dose adjustment or schedule modification to reduce cumulative exposure[26,38].

TKI-induced HFSR often necessitates proactive measures to prevent progression, including early use of keratolytic creams (10–20% urea or salicylic acid), cushioning of pressure points, avoidance of friction, and analgesics[3,42]. Dose interruption or reduction may be required for grade 2–3 toxicity, as recommended in clinical trials of sorafenib, regorafenib, and sunitinib[1].

Unlike chemotherapy-induced HFS, TKI-induced HFSR lesions tend to be more localized, allowing for targeted topical management without always requiring systemic dose adjustments[1,42].

Current clinical evidence strongly supports the prophylactic use of urea-based creams to mitigate the severity of TKI-induced HFSR. A randomized controlled trial demonstrated that the prophylactic application of a 10% urea cream significantly reduced the incidence of grade ≥ 2 HFSR and extended the time to the first occurrence of symptoms in patients receiving sorafenib[4,23]. In contrast, the use of pyridoxine (Vitamin B6) for the prevention of either HFS or HFSR remains controversial[43]. While early anecdotal reports suggested benefits, subsequent high-quality meta-analyses of prospective randomized trials have failed to show a significant reduction in the incidence or severity of HFS with pyridoxine supplementation[23,43]. Furthermore, for chemotherapy-induced HFS, there is emerging evidence that COX-2 inhibitors like celecoxib may reduce the risk of moderate-to-severe reactions (OR 0.39), although their use must be balanced against potential cardiovascular and gastrointestinal risks[37]. For severe HFSR, the use of hydrocolloid dressings containing ceramide has shown some efficacy in reducing friction and promoting lesion healing in patients on sorafenib therapy[2,4,23].

CONCLUSION

Although both entities—TKI-induced hand-foot skin reaction (HFSR) and classic chemotherapy-induced hand-foot syndrome (HFS)—share superficial clinical manifestations (palmar-plantar pain, erythema, desquamation), they differ substantially in anatomic distribution, lesion morphology, pathophysiologic mechanism, chronology of onset, clinical course, and therapeutic approach. In the tyrosine kinase inhibitors context, the development of HFSR represents not only a tolerability challenge but also potentially a prognostic biomarker of efficacy, which requires a management strategy that maximizes continuity treatment with local measures rather than drug discontinuation. This distinction underscores the importance of carefully differentiating both phenomena in clinical protocols, dermatologic management guidelines, and analyses correlating toxicity and efficacy in studies involving TKIs.

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