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Hand-Foot Syndrome - Induce Chemotherapy Drugs: A Mini-Review and Literature Review

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Abstract

Introduction: Hand–foot syndrome (HFS), also known as palmar–plantar erythrodysesthesia (PPE), is a clinically significant dermatologic toxicity associated with several conventional chemotherapeutic agents and targeted anticancer therapies. Although HFS is rarely life-threatening, it may substantially impair patients' quality of life, interfere with daily functional activities, and compromise treatment adherence through dose reduction, treatment interruption, or premature discontinuation of therapy. The incidence and severity of HFS vary according to the causative agent, cumulative drug exposure, treatment duration, and individual patient susceptibility. Fluoropyrimidines, pegylated liposomal doxorubicin, and multikinase inhibitors remain among the most frequently implicated agents. Clinically, HFS is characterized by erythema, edema, dysesthesia, pain, hyperkeratosis, desquamation, and, in severe cases, blistering and ulceration predominantly involving the palms and soles. Despite increasing recognition of this toxicity, the underlying pathophysiological mechanisms remain incompletely understood. Proposed mechanisms include direct cytotoxic injury to keratinocytes, eccrine gland-mediated drug accumulation, inflammatory cytokine activation, oxidative stress, endothelial dysfunction, and micro- vascular injury. This mini- review provides a comprehensive overview of epidemiology, molecular pathogenesis, clinical manifestations, histopathologic features, diagnostic criteria, grading systems, differential diagnosis, prevention strategies, and contemporary management approaches for chemotherapy-induced HFS. Evidence-based supportive care interventions, topical therapies, dose-modification strategies, and emerging therapeutic modalities are critically discussed. Furthermore, the review highlights the importance of multidisciplinary supportive care and early intervention in minimizing morbidity and optimizing oncologic treatment continuity.

Conclusion: Early recognition and proactive management of HFS are essential to reduce symptom burden, preserve functional status, maintain quality of life, and ensure uninterrupted delivery of anticancer therapy. Continued research into predictive biomarkers and targeted preventive strategies may further improve clinical outcomes in patients at risk of chemotherapy-induced HFS.

Keywords: Hand-Foot Syndrome; Palmar-Planter Erytherodysesthesia; Chemotherapy Toxicity; Dermatologic Toxicity; Capecitiabine

Abbreviations: HFS: Hand-Foot Syndrome; PPE: Palmar–Plantar Erythrodysesthesia; EGFRI: Epidermal Growth Factor Receptor Inhibitor; WHO: World Health Organization; NCI: National Cancer Institute; HFSR: Hand-Foot Skin Reaction; CTCAE: Common Terminology Criteria for Adverse Event

Introduction

Hand–foot syndrome (HFS), also known as "acral erythema" or "palmar-plantar erythrodysesthesia" or "toxic erythema of palms and soles" or "Burgdorf syndrome," is a known and relatively rare side effect of chemotherapy drugs. Although HFS is not life threatening, it can cause significant discomfort and impairment of function, especially in elderly patients, and may seriously impact quality of life. Even if it is not life-threatening, HFS, without proper management, can cause serious skin lesions and thus deteriorate the life quality of a patient, which often leads to the interruption of chemotherapy [1,2]. Several hypotheses have been proposed to explain the pathogenesis's of HFS; however exact mechanism remains unclear. Its management remains palliative and discussed [3].

Clinically; HFS is characterized by erythema, edema, pain, dysesthesia and desquamation affected the palms and/or the soles [4]. Commonly reported skin toxicities include epidermal

growth factor receptor inhibitor (EGFRI) rash, hand-foot skin reaction, hand-foot syndrome or palmar-plantar erythroderma, and chemotherapy-induced alopecia [5,6]. It is important to distinguish HFS from hand-foot skin reaction (HFSR), which is more commonly associated with multikines inhabitore such as sorafenib, sunitinib, axitinib, pazopanib, and regorafenib, and the BRAF inhibitors vemurafenib and dabrafenib [7] approximately 30% of patients receiving this agent may develop HFSR.

Accurate grading of HFS is essential because it guides dose reduction, treatment interruption, and supportive management. The World Health Organization (WHO) and the National Cancer Institute (NCI) common Terminology Criteria for Adverse Event (NCI-CTCAE) are commonly used grading systems [5,6] [8,9]. The pathogenesis of HFS appears to differ according to the causative drug class. Histologically, HFSR demonstrates acantholytic dyskeratotic keratinocytes, whereas HFS lesions exhibit non-specific cytotoxic skin damage, including keratinocyte necrosis, basal vacuolar degeneration, epidermal necrosis, blister formation, papillary dermal edema, vascular dilation, lymphocytic infiltration, and eccrine squamous syringometaplasia [10,11].

The human skin microbiome consists of millions of bacteria, fungi, archaea, and viruses that function cooperatively to protect against pathogens, support immunity, and metabolize natural products [12,13]. Commonly reported skin toxicities associated with cancer therapies include epidermal growth factor receptor inhibitor (EGFRI)-associated rash, hand–foot syndrome, hand–foot skin reaction, and chemotherapy-induced alopecia [5,6]. Management of HFS primarily involves dose delay, dose reduction, treatment discontinuation, or switching to alternative regimens [9,14]. Supportive care includes the use of topical corticosteroids, urea-based creams, regional cooling, wound care, pain control, thick cotton socks, gel shoe inserts, and orthotic devices to reduce plantar pressure [15,16].

Discussion

The World Health Organization defines an adverse drug reaction as a harmful and unintended response occurring at doses normally used in humans for prophylaxis, diagnosis, or treatment [17]. In oncology patients, adverse reactions may be severe or fatal, necessitating careful monitoring by healthcare providers [18]. Hand–foot syndrome was first described in association with chemotherapy in 1974 [19]. Since then, it has been referred to by several terms, including palmar–plantar erythrodysesthesia, acral erythema, toxic erythema of the palms and soles, and Burgdorf reaction.

Clinically, HFS commonly presents symmetrical erythema and edema of the palms and soles, progressing in severe cases to blistering, ulceration, and necrosis. HFSR associated with kinase inhibitors often presents with more localized hyperkeratotic lesions distinct from classic HFS. Patients receiving kinase inhibitors may also develop folliculitis, xerosis, periungual inflammation, hair changes, splinter hemorrhages, and periocular edema [20]. Differential diagnoses include allergic reactions, contact dermatitis, erythromelalgia, and [21]. Because the presentation may initially be subtle, delayed diagnosis can lead either to worsening toxicity due to continued drug exposure or unnecessary interruption of anticancer therapy.

Diagnosis is mainly clinical. Histopathological examination is rarely required but may demonstrate parakeratosis, dyskeratosis, necrotic keratinocytes, and superficial bullous changes [20]. Modern cancer treatment strategies include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Despite therapeutic benefits, many anticancer drugs cause cutaneous toxicities. HFS manifests clinically with erythema, edema, dryness, scaling, pain, burning sensation, and paresthesia affecting the hands and feet. Severe cases may involve blistering and ulceration requiring hospitalization or interruption of cancer therapy [22].

Pharmacovigilance studies suggest that women experience chemotherapy-related adverse drug reactions more frequently than men, accounting for approximately 65-70% of reported cases [23]. Severe HFS may impair walking and hand function, significantly affecting daily activities and treatment adherence. Palaniappan et al. reported that breast cancer was the most common malignancy associated with HFS (32%), followed by colorectal cancer [24]. Similarly, Law et al. [25] identified colorectal and breast cancers as major indications for capecitabine-associated PPE.

Several Anticancer Agents are Strongly Associated with HFS:

Capecitabine causes PPE in more than 50% of patients, with severe (grade 3) toxicity occurring in 10-15% [26,27]. Sunitinib is associated with HFS in approximately 14-21% of patients [28,29]. Regorafenib causes PPE in approximately 50% of patients, with severe toxicity in nearly 17% [30,31]. Cabozantinib is associated with PPE in approximately 50% of patients, including grade 3 toxicity in about 13% [32].

Supportive care measures remain the cornerstone of management. Standard emollients, topical corticosteroids, urea creams, pain management, regional cooling, and pressure redistribution techniques are commonly recommended [33]. According to the NCI-CTCAE grading system, grade 3 HFS represents severe symptoms that interfere significantly with activities of daily living [34,35]. Pyridoxine (vitamin B6) has been investigated for prevention and treatment of HFS because of similarities between HFS and pyridoxine-deficiency syndromes [36,37]. Although pyridoxine is inexpensive and relatively safe, randomized studies have shown inconsistent efficacy in preventing capecitabine-induced HFS [38]. Drug that is harmful and unintended, and that occurs at doses normally used in humans for the prophylaxis, diagnosis and treatment of diseases or for the modification of physiological function [17]. Effective treatment measures include topical medications (analgesics, corticosteroids, emollients), chemotherapy dose reductions, and switching to other drugs of the same class

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with lower HFS rates [21]. In cancer patients, some of these reactions can be fatal, requiring greater caution by the healthcare provider [18].

Conclusion

Chemotherapy-induced hand-foot syndrome remains a clinically significant adverse effect that can negatively affect patient quality of life and treatment adherence. Early recognition, accurate grading, preventive strategies, and prompt supportive management are essential to minimize morbidity and avoid unnecessary interruption of anticancer therapy. For more severe disease, topical steroids and temporal discontinuation or dosage reduction of the offensive agent can be attempted. Keratolytic can be used, if necessary [39], the prognosis of this disease is excellent. Further prospective studies are needed to establish standardized preventive and therapeutic approaches for HFS and HFSR. Artificial intelligence-based toxicity predication models and digital dermatologic monitoring systems may improve early detection and clinical management.

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