

REVIEW

Hand-Foot Syndrome in cancer patients: concepts, assessment and management of symptoms

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ABSTRACT

The purpose of this study is to present an update on Hand-Foot Syndrome, a common side effect of certain chemotherapeutic agents. Initial symptoms include erythema, dysesthesia and tingling in the palms of the hand and soles of the feet, which can develop into a burning sensation with dryness and pain, cracking, desquamation, ulceration and edema. Due to its negative impact on the quality of life of patients and its penchant for being a dose-limiting reaction, it is important for professionals on oncology teams to be knowledgeable about this condition so they can use assessment and classification tools recommended for the prevention and control of side effects. There is little evidence regarding the effectiveness of options for hand-foot syndrome prevention and treatment, which may include the use of moisturizers vegetable based oils, use of COX-2 inhibitors, corticosteroids, cryotherapy, among others. Further studies are needed to support this clinical practice.

Keywords: drug therapy; hand-foot syndrome; palmarplantar erythrodysesthesia; toxicity.

INTRODUCTION

Hand-Foot Syndrome (HFS) is a cutaneous adverse effect induced by certain antineoplastic chemotherapeutic agents and characterized by painful erythema that affects the palms of the hands and soles of the feet. Also known as Palmar-Plantar Erythrodysesthesia (PPE) or Acral Erythema, it was first described in 1974 and was connected with the use of Mitotane for treating renal carcinoma. The importance of acquiring knowledge about this syndrome stems from the fact that it is dose-limiting and has a negative impact on the quality of life of affected patients^{1,2}. The cytotoxic agents most often associated with the development of HFS are: capecitabine, pegylated liposomal doxorubicin (PLD) and 5-fluorouracil (5-FU),

although there are reports in the literature of less frequent occurrences linked to cytarabine, cyclophosphamide, paclitaxel, docetaxel, etoposide, vinorelbine, methotrexate, daunorubicin, mercaptopurine, tegafur and hydroxyurea^{2,3}.

The incidence varies depending on the drug, but HFS generally occurs in 6 to 64% of patients undergoing chemotherapy. Capecitabine is the cytotoxic agent responsible for most cases of HFS, with a prevalence of 50% to 60%. This orally administered agent is a fluoropyrimidine carbamate derivative that, *in vivo*, is sequentially converted to the 5-fluorouracil cytotoxic fraction. Regarding 5-FU, there is an incidence of HFS from 6 to 13% with bolus infusion and 35% with continuous infusion. With the use of PLD, HFS occurs in 40 to 60% of patients³⁻⁵. Recently, two orally administered drugs, sunitinib maleate (a drug with antiangiogenic activity and an inhibitor of tyrosine kinase enzymatic activity) and sorafenib (a molecular inhibitor of tyrosine and Raf kinases) were recognized as important causative agents, with an incidence of 10 to 28% and 10 to 62%, respectively⁶.

The occurrence of HFS is apparently dose-dependent and influenced by both the peak concentration of the cytotoxic drug and the total accumulated dose in consecutive applications²⁻⁷. This reaction occurs mainly on the soles of the feet and palms of the hands, but can also affect other areas such as the armpits, groin, backs of the knees, elbows, waist, creases on the wrist, breast folds and sacral region⁵.

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The pathophysiology of HFS is not fully understood, although there are inconclusive studies which indicate some possible mechanisms that may be involved. A number of reported cases manifested similar histological changes regardless of the causative agent, namely: vacuolar degeneration of the basal cell layer, keratinocyte necrosis, blood vessel dilation, dermal papillary edema, mild spongiosis, lymphohistiocytic infiltration and partial separation of the epidermis and dermis. Also, the presence of eccrine glands and the high rate of cell division in these areas are presumably related to the condition. These histological findings suggest two possible pathophysiological theories. The first is related to the metabolism of 5-FU and capecitabine and suggests a “graft *versus* host” response, where the cells whose membranes are altered by the action of the drug would be recognized as foreign and attacked by the immune system. The second and more accepted theory among experts is based on direct toxic action in specific regions via different mechanisms: 1) The high concentration of enzymes (thymidine phosphorylase and uridine phosphorylase) in keratinocytes, involved in the metabolism of the chemotherapeutic agents, results in drug accumulation in these cells and consequent inflammation of the skin; 2) The palms of the hands and soles of the feet have a large concentration of the body’s eccrine glands, which increases the possibility that the accumulation of drugs in certain regions is due to the movement of the drug or its metabolites through sweat, thus causing local tissue damage; and 3) Rapid cell division of skin in acral areas, absence of hair follicles or sebaceous glands and the high number of dermal papillae and frequent pressure on these areas results in the rupture of capillaries, releasing chemotherapeutic agents into the interstice^{2,4,6}.

The signs and symptoms associated with HFS are progressive and start with dysesthesia (a neurological disorder characterized by a weakening or change in sensitivity, especially touch) with or without local symmetrical erythema, itching and tingling in the palms of the hands and soles of the feet. The clinical presentation is similar, regardless of the causative agent. These symptoms may develop into a painful local burning sensation, dry skin, swelling, edema, cracking, peeling and formation of keratosis plaques, blisters and ulcers if there is no intervention. For reasons still unknown, the palm of the hand is affected more than the soles of the feet^{2,5-7}.

HFS can directly affect everyday activities, such as walking and holding objects, as well as cause pain, which undermines quality of life and reduces rates of adherence to antineoplastic treatment. Although uncommon, severe cases can lead to local and generalized infections, resulting in life-threatening risk to the patient^{3,8}.

In order to treat HFS it is necessary to identify and evaluate the symptoms. As integral members of interdisciplinary oncology teams, nurses can both identify and grade

symptoms, as well as instruct and guide patients on how to recognize changes and control the symptoms⁷. Given the lack of scientific literature on the subject in Portuguese and the need to inform and update oncology nurses on the topic, the goal of this paper is to present assessment and classification methods, in addition to recommending interventions for the prevention and control of HFS.

EVALUATION AND MANAGEMENT OF HAND-FOOT SYNDROME SYMPTOMS

The first evaluation must take place immediately before the administration of antineoplastic drugs which may cause HSF, so that the patient’s dermal and sensory status can be properly assessed and recorded^{3,9}. The use of classification tools is recommended for best practice. Different instruments to classify HFS signs and symptoms have been developed; among the most frequently used are those from the National Cancer Institute (NCI) and the World Health Organization (WHO), presented in Table 1, along with the main histopathological changes observed for each grade^{2,3,10}.

There are no conclusive studies regarding control of the signs and symptoms described above, but certain courses of action may be applied. Among possible treatments, reduction of the dose of the antineoplastic chemotherapeutic agent or increasing the interval between applications are actions that have proven most effective in lowering the grade of the symptoms without interfering with the destruction of tumors, thus avoiding the discontinuation of the use of the chemotherapeutic agent^{9,11,12}.

Different measures can be taken to treat each grade of symptoms, and there are predetermined specifications for reducing the dose of each antineoplastic chemotherapeutic agent, depending on the severity of symptoms and impact on quality of life, so as not to compromise its anti-tumor action. As a general rule, when symptoms occur: Grade 1 - do not alter the dose; Grade 2 - suspend application until the regression of symptoms to Grade 1, with the option to either maintain or reduce the dose (by 25% or 50%) in the next cycle; and Grade 3 or 4 - suspend application until the regression of symptoms to Grade 1 and reduce the dose by 50%, in addition to considering suspension of the treatment if the same grade of symptoms reappears^{5,9,13-16}.

However, regardless of the grade of symptoms or the drug used, all patients need to receive teaching and instruction to recognize signs and symptoms, and also in relation to supportive care (Table 2). The progression of the condition must also be monitored by the multidisciplinary team^{2,5,9,15,17}.

In practice, it is widespread practice among oncology professionals to prescribe the use of moisturizers, although some studies contradict their effectiveness in treating hand-foot syndrome. Research studies have been

Table 1. Tool for evaluating signs and symptoms of Hand-Foot Syndrome (HFS), from the NCI and WHO. São Paulo, 2013.

Grade	NCI (CTCAE* Version 3.0)	WHO	Histological Findings
1	Minimal skin changes or dermatitis (e.g., erythema) without pain	Dyesthesia/paraesthesia, tingling in the hands and feet	Dilated blood vessels of the superficial dermal plexus
2	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Discomfort in holding objects and upon walking, painless swelling or erythema	
3	Ulcerative dermatitis or skin changes with pain interfering with function	Painful erythema and swelling of palms and soles, periungual erythema and swelling	Isolated necrotic keratinocytes in the higher layer of the epidermis
4	_____	Desquamation, ulceration, blistering, severe pain	Complete epidermal necrosis

* National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 2. Supportive care for HFS prevention and treatment. São Paulo, 2013.

Supportive Care for HFS Prevention and Treatment	
Educate patients so that they are able to assess their own hands and feet and know how to recognize the symptoms of HFS, so that they can notify the medical and/or nursing team.	
Guidelines - AVOID	Guidelines - DO/USE
<ul style="list-style-type: none"> Exposure of the skin to high temperatures (e.g. sauna, hot baths, steam) Tight clothes, coarse or synthetic fabrics Walking barefoot or wearing open sandals Use of adhesive bandages Contact of the skin with chemicals such as detergent and bleach Repetitive activities that apply friction or pressure to the risk areas Products with alcohol in their composition Use of creams and lotions on non-intact skin, except for specific products under medical prescription Overexposure to the sun 	<ul style="list-style-type: none"> Comfortable clothes and footwear Rubber gloves for handling cleaning products Sunscreen and moisturizers Cotton socks and gloves while sleeping to increase moisturizer absorption Hydration (if no contraindication) - Drink 8 to 12 glasses of liquids per day Balanced diet rich in vitamins B and C Wherever possible, leave skin uncovered to prevent excessive sweating Keep the affected area elevated Analgesics and antibiotics according to medical prescription, when needed

conducted to determine the best formula for prevention and treatment, but thus far none of the results have been conclusive. Among the various active ingredients of moisturizers available, urea is still highly recommended for its moisturizing and keratolytic properties, which help it penetrate the outer layers of the stratum corneum, promoting desquamation and facilitating the absorption of other topically applied substances. On the other hand, some adverse effects have been observed, such as burning and irritation, and the optimal concentration (which ranges from 10 to 40%) has not yet been established. Although a control group study found that the use of urea and lactic acid-based creams (as well as keratolytics) are ineffective in preventing HFS symptoms, specialists recommend their use in cases where there is keratosis plaque formation (grade 3), since these agents facilitate the penetration of other moisturizers and the removal of this necrotic layer^{3,17-19}. Another highly recommended skin hydration product is lanolin, a complex substance formed by fatty acids arising from the secretion of the sebaceous glands of sheep and accumulated in their wool, and used as an emollient and vehicle for cosmetics and medicines due to its excellent penetration and skin hydration maintenance

properties. Although several studies emphasize a high frequency of allergic reactions associated with it, lanolin (up to a concentration of 2%) does not seem to affect the healing process or have any toxic effects²⁰.

In clinical practice, the best results were obtained with emollients containing hyaluronic acid, allantoin and aloe vera, many of which are developed primarily for treating radiodermatitis^{6,21}. Hyaluronic acid has high water retention capacity, and its topical application has been found to improve healing due to its rheological (viscosity), viscoelastic and hygroscopic (water absorption) properties, as well as its potential to stimulate cellular regeneration²¹. Allantoin serves to control itching due to its anti-irritant effect and facilitates the penetration of other agents into the deeper layers of the skin, as well as through keratolytic action and humidity retention²². Aloe Vera assists in the repair of epithelial tissue due to its anti-inflammatory, antibiotic, astringent, coagulable, analgesic and healing properties, by stimulating the action and proliferation of fibroblasts and increasing collagen synthesis²³. A recent study discovered benefits in the use of uridine, alone or in combination with thymine at a 10% concentration, for controlling HFS symptoms induced by 5-FU, due to the

protective action of keratinocytes against damage caused by chemotherapy²⁴.

The famous creams Bag Balm® and Udderly Smooth®, although strongly recommended, have not yielded results demonstrating consistent effectiveness. A phase II study not yet published, conducted at Northwestern University (Chicago, USA), will contain an assessment regarding the effectiveness of using 40% urea cream, cream with 0.05% fluocinonide (a high-power steroid), 0.1% tazarotene cream (part of the vitamin A, retinoid family of products) and creams using Udderly Smooth® (composed of deionized water and containing moisturizing, emollient, occlusive, antibacterial and antifungal ingredients) for treating HFS induced by sorafenibe^{6,7,9,25}.

Among possible pharmacological interventions, experts are unanimous about prescribing analgesics to control pain. Recent studies having a high degree of scientific evidence have demonstrated the effectiveness of the prophylactic use of COX-2 inhibitors (enzyme involved in the inflammatory process of the skin) in patients being treated with capecitabine, alone or in combination with oxaliplatin, as well as a reduced incidence of HFS in patients using celecoxib (200mg) twice a day; however, this drug is contraindicated for patients with cardiovascular diseases and was not studied in conjunction with other causative agents^{26,27}. Although several case reports have found benefits in the use of pyridoxine (vitamin B6) in daily doses for the prevention of hand-foot syndrome in patients undergoing treatment with PLD, recent randomized studies have proven their ineffectiveness, even in treatments with capecitabine^{5,28,29}. Corticosteroids administered both intravenously and topically were tested for prevention of symptoms. One prospective study found good results in the prophylactic use of intravenous dexamethasone in patients being treated with PLD, but the data is insufficient to recommend the routine use of corticosteroids, mainly due to their known side effects^{5,30}. Vitamin E has been proven effective in preventing dermal ulcers through its interaction with glucocorticoids to avert lipid peroxidation, thus resulting in more stable cell membranes. Its systemic action inhibits inflammatory response and collagen synthesis, which is why it was found to be effective in treating HFS caused by docetaxel and capecitabine in a study using daily doses of 300mg of Vitamin E. This study, however, was likewise inconclusive³¹.

International guidelines and articles cite the topical use of DMSO or the application of henna (*Lawsonia inermis*) as options for managing HFS symptoms, but the few published studies have yielded inconclusive results and a low degree of evidence. Formulas with 99% DMSO have proven effective in treating doxorubicin extravasation, thus taking into account one of the possible pathophysiological mechanisms, DMSO could carry PLD freely into the systemic circulation or act as an antioxidant, thereby

preventing toxic effects in soft tissues. Another study suggests the use of henna powder, alleged to have antioxidant and immunomodulatory effects. It is mixed with water until becoming clay, and this mixture is then applied to the palms of the hands and soles of the feet, wrapped with a bandage and washed off after 5-6 hours^{9,32,33}.

Cryotherapy during the administration of chemotherapy drugs is another prevention hypothesis that is being tested. The use of Elastogel® gloves and slippers, as well as the immersion of hands and feet in cold water or wrapping the wrists and ankles with ice bags during infusion have shown promising results, but all of them are inconclusive as of yet^{5,34-36}.

CONCLUSION

Hand-foot syndrome is a painful and stressful condition which directly affects the quality of life of patients. Since only changes in chemotherapy dosage or discontinuation of treatment have proven to be effective in controlling symptoms, the prevention of this condition continues to be the determining factor in maintaining antineoplastic chemotherapy. Nurses play a key role in preventing and assessing the development of symptoms by directly guiding and instructing patients. Updated information on drugs that cause HFS, the use of instruments for grading and assessing symptoms and evidence-based interventions ensure that high quality care is provided.

IMPLICATIONS FOR PRACTICE

This literature review will subsidize an experimental study in which get up-to compare two different strategies for management of the syndrome Hand-Foot, from the use of the substances described above and subject to be adopted in a population of cancer patients treated at public or private hospital.

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