

Hand-foot syndrome, case presentation and literature review

Abstract

Background: Hand-foot syndrome, also called palmoplantar erythrodysesthesia or acral erythema (AS), is a relatively common skin reaction produced by different chemotherapeutic agents. It presents as painful erythema on the palms and soles associated with paresthesias.

Clinical case: We report the case of a 61-year-old woman with basal-like triple-negative breast cancer. She underwent a modified radical mastectomy with a positive node and was administered 8 cycles of adjuvant chemotherapy with Doxorubicin-Cyclophosphamide 4 cycles and Docetaxel 4 cycles 4 cycles, which developed grade 3 hand-foot syndrome due to Docetaxel and its management with topical therapies, corticosteroids and non-steroidal anti-inflammatory drugs, improved and remitted at the end of chemotherapy.

Discussion: A narrative review of the syndrome was carried out; The most common clinical presentation involves the hands and feet, hence the name “hand-foot syndrome,” but it is known by a variety of terms. Originally reported in patients receiving high doses of cytarabine for acute leukemia, it has also been fully described, one theory stating that it may be caused by the accumulation of chemotherapy in the eccrine glands, numerous in the palms and soles of the hands. feet, cause metaplasia and focal necrosis of the eccrine duct epithelium; Its incidence is high when chemotherapy is administered, between 2 and 60%. Symptoms lasted an average of 6.4 days, the hands and feet were involved in 68% of initial episodes, such as pain and discomfort in the hands, limits activities of daily living, such as walking, holding objects and performing simple tasks and for its staging to qualify its severity, different instruments are used and is mainly related to the impact on the quality of life of the patients; 27% require analgesic management and local therapies. Race and sex are not associated, only advanced age and high doses of chemotherapy without dexamethasone are associated.

Conclusion: this syndrome is an adverse effect associated with various cytotoxic drugs. Sometimes it is severe enough to limit symptoms, but complete resolution takes 4 weeks or more and treatment is aimed at relieving symptoms.

Keywords: breast cancer, chemotherapy, erythema dolosum and paresthesias

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Background

The term “chemotherapy toxic erythema” was proposed in 2008 as a diagnostic, descriptive, and unifying entity for the diverse clinical and histopathologic reaction patterns with significant overlapping features reported with chemotherapy.¹

The most common clinical presentation involves the hands and feet, hence the name “hand-foot syndrome” (HFS), which is known by a variety of terms including acral erythema, palmar-plantar erythrodysesthesia, palmar-plantar erythema, toxic acral erythema, toxic erythema of the palms and soles, Burgdorf reaction, and periarticular thenar erythema with onycholysis syndrome.² Originally reported in patients receiving high-dose cytarabine for acute leukemia, HFS has been frequently described in patients receiving pegylated liposomal doxorubicin, capecitabine (an oral fluoropyrimidine that is converted in vivo to fluorouracil, providing prolonged tissue exposure), or fluorouracil, although many other drugs have been implicated (Table 1) (Table 2).²⁻⁸

Table 1 Two other scales, from the World Health Organization (WHO), have four grades of HFS classification and the National Cancer Institute of Canada Clinical Trials Group (CTG-NCIC) scale, which classifies HFS into three grades¹⁰:

- Dermatologic changes, dermatitis without pain (erythema, peeling)
- Dermatologic changes with pain, do not interfere with function
- Dermatologic changes with pain, interfere with function

Table 2 Symptoms of hand-foot syndrome

Symptoms of mild or moderate hand-foot syndrome include

- Redness resembling a sunburn
- Swelling
- Tingling or burning sensation
- Tenderness to touch
- Tightness of the skin
- Thick calluses and blisters on the palms of the hands and soles of the feet

Symptoms of severe hand-foot syndrome include the following

- Cracking or peeling skin
- Blisters, ulcers or sores on the skin
- Severe pain
- Difficulty walking or using hands

Symptoms lasted a median of 6.4 days. Both hands and feet were involved in 68% of initial episodes. 27% of patients required parenteral opioids for pain control. Self-reported race and sex were not associated with HFS, older age and high-dose cytarabine administration without dexamethasone remained associated with HFS ($P = 1.1 \times 10^{-4}$ and $P = 0.038$, respectively). Genome-wide association did not identify any association with palmar-plantar erythrodysesthesia syndrome (PPES) that met the genome-wide significance threshold, but major variants were enriched for cutaneous expression quantitative trait loci, including rs11764092 in AUTS2 ($P = 6.45 \times 10^{-5}$). Multitargeted

tyrosine kinase inhibitors, such as sorafenib, sunitinib and other kinase inhibitors targeting angiogenesis, are associated with a high incidence of hand-foot skin reaction, but the clinical and histological patterns differ from the classic HFS that develops with conventional cytotoxic agents; it is a dermatological toxicity that affects cancer patients undergoing chemotherapy and/or targeted therapy. It presents as a painful erythema in the palms and soles associated with paresthesias in the context of oncological treatment; it is dose-dependent, and both the plasma peak and the cumulative dose of the chemotherapeutic agent determine its appearance. HFS was first described in 1974¹ and is characterized by paresthesias in the palms of the hands, fingers and soles of the feet, which can progress to burning pain, marked erythema with or without edema, skin peeling, fissures and ulceration. When it occurs, HFS is usually classified according to the symptoms and signs presented by the patient. For the staging of HFS, different instruments have been used to rate its severity, but the CTCAE classification⁹ (Common Terminology Criteria for Adverse Events), is the most known and used scale² classifies HFS into three degrees of severity, Grade 1 (mild symptoms), represents minimal skin changes or dermatitis, without pain; grade 2 (moderate symptoms) indicates skin changes, with pain, limiting Instrumental Activity of Daily Living (ADL); and grade 3 (severe symptoms), indicates severe skin changes, with pain, limiting self-care and ADL.⁹

Although the pathogenesis of HFS has not yet been fully elucidated, one theory states that it may be caused by the accumulation of chemotherapy in the eccrine glands, which are more numerous in the palms of the hands and soles of the feet, which can cause metaplasia and focal necrosis of the eccrine duct epithelium.^{11,12} Studies indicate that HFS has a high incidence among patients undergoing chemotherapy, ranging from 2 to 60%,¹³ being even higher among patients using the antineoplastic capecitabine (47 to 71%).¹⁴ The clinical relevance of HFS is mainly related to the impact on the quality of life of patients. Symptoms such as pain and discomfort in the hands limit daily life activities, such as walking, holding objects and performing simple tasks. Skin fissures and lesions affect self-care and personal hygiene, some develop infections as a result of the loss of skin integrity and the severity of symptoms is related to the accumulation of chemotherapy doses and worsens with each cycle¹⁵ and interfere with treatment, having to reduce the dose and even stop it to improve symptoms.^{16,17}

Hand-foot syndrome is generally worse during the first six weeks of treatment with targeted therapies such as axitinib, cabozantinib, regorafenib, sorafenib, sunitinib, and pazopanib. With chemotherapy drugs, it appears after two to three months. Palmar-plantar erythrodysesthesia is an adverse reaction associated with some chemotherapeutic agents. It is thought to be due to a local inflammatory reaction, triggered by the accumulation of antineoplastic metabolites excreted via the eccrine pathway, or microcapillary extravasation from the palms and soles deposited in the stratum corneum, causing a direct cytotoxic reaction, perhaps mediated by cyclooxygenase (COX-2). Other factors implicated include temperature fluctuations in the distal extremities, high pressure points, accelerated cell proliferation, or hyperhidrosis; It is characterized by beginning with a prodrome of palmar-plantar dysesthesia, and between 2 to 4 days, the sensation progresses to a burning pain with edema and erythema in well-defined and symmetrical plaques; they are usually located on the external lateral side of the fingers and the thenar and hypothenar eminences of the hands (Figure 1), but progresses to affect the entire surface. In severe cases, blisters form that leave erosive surfaces, with significant impairment of function.^{12,13}

Although the hands are most frequently affected, the feet are also. The incidence of hand-foot syndrome is difficult to estimate, ranging

from 2-60%, and most cases are of mild to moderate intensity, with signs and symptoms disappearing in a few days, without long-term consequences, when ulcerations have occurred that leave scars. Chemotherapy agents, sometimes, it is difficult to assess the real influence of a given due to the frequency of polychemotherapy regimens. is observed in 34%. Histopathology is not very specific and varies according to the clinical intensity of the lesions. Interface dermatitis with spongiosis and necrosis of keratinocytes and dilatations of the superficial vascular plexus, accompanied by a scarce inflammatory infiltrate.¹⁴⁻¹⁹

Management with urea-based cream on the palms of the hands and soles of the feet is a safe and effective strategy to prevent the appearance and severity of HFS. Due to the keratolytic potential of urea, it reduces hyperkeratosis of the hands and feet, and moisturizes and softens the skin. Topical pyridoxine is recommended due to the similarity with the symptoms of vitamin B6 deficiency and the use of corticosteroids, which reduces inflammation and pain. The clinical and histopathological findings suggest direct cytotoxicity of the acral epidermis due to the high concentrations of chemotherapeutic agents.^{16,20,21}

Causes of hand-foot syndrome

Some anticancer drugs affect the growth of skin cells or small blood vessels in the hands and feet. The types of chemotherapy that can cause this syndrome are related to doxorubicin, 5-fluorouracil and derivatives, cytarabine and docetaxel, Table 3.

Table 3 Types of chemotherapy

Types of chemotherapy that can cause hand-foot syndrome
Capecitabine
Cytarabine
Docetaxel
Doxorubicin
5-Fluorouracil
Floxuridine
Idarubicin
Liposomal doxorubicin
Paclitaxel
Vemurafenib
Targeted therapies most likely to cause it
Axitinib
Cabozantinib
Regorafenib
Sorafenib
Sunitinib
Pazopanib

Not everyone who takes these drugs develops hand-foot syndrome. The severity of this syndrome is different for each person. Even people taking the same drug for the same form of cancer may not have.²²

Clinical summary

A 61-year-old woman, originally from the state of Veracruz, married, with a significant personal history of pathology: dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, and Grade 1 obesity by BMI 32.4 kg/m², has been under control with antidiabetics for 5 years, had rhinoplasty 18 years ago and hysterectomy 23 years ago; physical examination showed vital signs within normal limits. She was diagnosed with breast biopsy, breast cancer, and was treated with modified radical mastectomy modificada (Figure 1) (Figure 2).

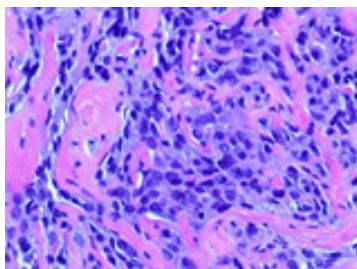


Figure 1 Ultrasound-guided breast biopsy reporting poorly differentiated invasive ductal carcinoma NOS and basal-like triple-negative immunohistochemistry; these are neoplasms with a solid architecture characterized by a great pleomorphism of the tumor cells with a prominent nucleolus, vesicular chromatin and a variable number of mitoses (these mitoses are frequently atypical and appear in groups). The presence of a lymphoid infiltrate in the tumor stroma and extensive areas of necrosis is frequent, which are due to the rapid proliferation capacity of the tumor in contrast to its blood supply capacity. The lack of tubule formation and the presence of apoptotic cells (especially in the periphery of the necrotic area) are also notable.

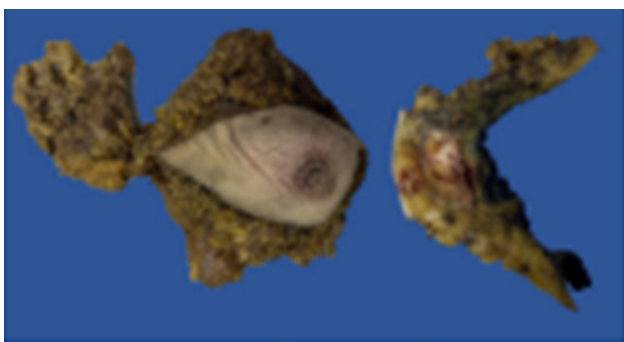


Figure 2 Modified Radical Mastectomy of the right breast with invasive ductal carcinoma of 1.0x0.7cm with 1 positive lymph node with capsular rupture of a total of 17 lymph nodes removed.

She received 8 cycles of chemotherapy, and after 5 cycles the patient presented palmar-plantar lesions, presenting painful edematous erythematous lesions that mainly affected the palms of the hands and soles of the feet (Figure 3). Xerosis and peeling (Figure 4), paresthesias and pain that interfered with functionality (Figure 5) were also noted. Treatment was started with topical corticosteroid creams, non-steroidal anti-inflammatory drugs; the remaining 3 cycles of chemotherapy were not suspended; the lesions returned to the integument (Figure 6). Histopathology (40X) showed nonspecific findings, such as irregular acanthosis, mononuclear dermal infiltrate and vascular dilation, and a diagnosis of palmar-plantar erythrodysesthesia was established (Figure 7), associated with the administration of Docetaxel.



Figure 3 Painful edematous erythematous lesions that primarily affect the palms of the hands and soles of the feet.



Figure 4 Xerosis and scaling.



Figure 5 Paresthesia and pain that interfere with functionality.



Figure 6 Restoration to integument.

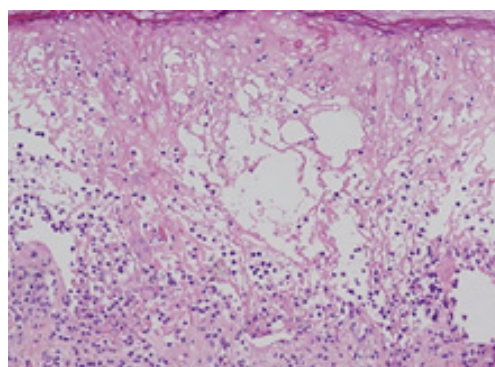


Figure 7 Superficial perivenular and junctional lymphocytic infiltration, epidermal necrosis associated with foci of necrotic keratinocytes and reticular degeneration of epidermal cells (H&E, $\times 100$).

Hand-foot syndrome management

When medications known to cause hand-foot syndrome are ingested, initial treatment is with symptom-reducing topical anti-inflammatory medications, such as corticosteroid creams, such as clobetasol or halobetasol; decreasing the chemotherapy dose or changing the chemotherapy schedule. Even temporarily stopping chemotherapy until symptoms improve. Urea is a polar and hygroscopic molecule produced endogenously by the human body and found naturally in the skin. It originates from the metabolism of proteins and other organic nitrogen compounds excreted in urine and sweat, and has the effect of softening hyperkeratosis and reducing epidermal thickness. Patients who received the urea cream intervention had a significantly lower incidence of grade 2 or higher HFS (OR, 0.72; 95% CI, 0.58–0.90) and a lower incidence of any grade (OR, 0.79; 95% CI, 0.58–1.08) compared with patients who did not receive the urea cream intervention; it is a safe and feasible topical intervention for the prevention of HFS.^{20–35}

Prevention of hand-foot syndrome

Hand-foot syndrome is generally worse during the first 6 weeks of treatment with targeted therapy. With chemotherapy, it usually appears after 2 to 3 months. For patients who apply diclofenac gel to the skin, a 75% reduction in rates of hand-foot syndrome is observed. Avoid prolonged exposure of hands and feet to heat. Heat increases the amount of medication circulating through blood vessels and increases filtration. It is also recommended to avoid hot water when taking baths or long showers. Avoid pressure on hands and feet. Increased pressure irritates the capillaries and activates filtration. Avoid massaging or rubbing the feet and hands, exercises and standing.^{1-8,30-40}

Discussion

Hand-foot syndrome HFS is a side effect of some types of chemotherapy and other drugs to treat cancer, although there is little information on the knowledge of the pathophysiology of this, it makes difficult the pharmacological mechanisms to prevent its appearance; detect a mechanism of action for its development or even genetic markers or predictors that predetermine its incidence and/or severity to determine new strategies to improve the quality of life; capecitabine is the main chemotherapy drug associated with its development, it is a prodrug of 5-fluorouracil, which is administered orally for solid tumors, such as colorectal cancer, gastric cancer and breast cancer. At the cellular level, capecitabine toxicity induces keratinocyte death and reduces the stratum corneum;³⁰ the predictive factors for its development are the concomitant use of a renin-angiotensin system inhibitor, elevated body surface area and albuminemia.¹⁹ In patients with advanced colon cancer treated with capecitabine and oxaliplatin, the rs6783836 variant in ST6GAL1 (ST6 β -galactoside α -2,6-sialyltransferase), a gene that plays a role in inflammation and development of type 2 diabetes mellitus, was associated with its development is a promising biomarker of the syndrome.²⁰ A novel mechanism of individual genetic susceptibility associated with capecitabine, with implications for the prediction of clinically relevant risk; skin in severe HFS shows low levels of R-cadherin and involucrin (proteins essential for the structure and function of the skin barrier) before treatment with capecitabine. Pegylated liposomal doxorubicin (PLD) associated with the appearance of HFS,^{19,20-29} histopathological analysis of HFS in vitro and in animal models found that it induces severe tissue damage, including the destruction of collagen fibers and induction of severe inflammation and apoptosis of epidermal cells; this inflammation and sustained release of PLD generates reactive oxygen species (ROS), unstable and extremely reactive molecules, which transform other molecules with which they collide, causing oxidative damage to keratinocytes; ROS was identified as a crucial factor in the development of HFS and antioxidants are the choice when PLD are used.

Prophylactic strategies for HFS, both topical and non-topical, urea cream (topical) (OR 0.48, 95% CI 0.39-0.60, $p < 0.00001$) and celecoxib (oral) (OR 0.52, 95% CI 0.32-0.85, $p = 0.009$) showed a significant risk reduction, with celecoxib being more effective in preventing capecitabine-induced HFS of all grades (50.5% vs 65%, $p = 0.05$), while urea cream showed more benefit in preventing sorafenib-induced moderate-to-severe HFS (54.9% vs 71.4%, $p < 0.00001$); Research is required on the ideal dose of celecoxib and urea cream.^{12,37}

Moisturizing cream, 10% urea cream, urea and lactic acid cream (12%/6%), 1% silymarin gel and mapisal were analyzed as topical interventions, and as a result, they showed that topical silymarin has the best performance in preventing capecitabine-induced HFS (OR: 0.08; 95% CI: 0.01-0.71). The (30) topical interventions, urea and

lactic acid cream (12%/6%), 10% urea cream and 20% urea cream; the interventions did not demonstrate a significant role in preventing HFS.²⁵⁻³⁰

Hand and foot cream twice daily was evaluated, until the end of capecitabine treatment, versus the use of saline. The overall incidence of HFS with moisturizing cream use was lower than that with saline (56.8% vs. 75.9%, $p = 0.006$). The incidence of grade 1-2 HFS was not statistically significant between the two groups (26/51 vs. 32/54, 52.0% vs. 59.2%, $P = 0.194$).³¹

The use of topical corticosteroids, with local anti-inflammatory action (32,33) demonstrated a significant difference between the global score of HFS receiving corticosteroid cream and cream without corticosteroids (0.83 vs. 1.26, $p = 0.031$). The use of cream with corticosteroids and without any intervention (0.83 vs. 1.24, $p = 0.038$). The time to the onset of HFS was longer with the use of cream with corticosteroids (41 days) vs cream without corticosteroids (22 days) and without intervention (21 days), it was concluded that the use of topical corticosteroids reduces the severity and incidence of HFS; preventive treatment with clobetasol, a high-potency topical corticosteroid, is associated with lower rates of regorafenib-induced HFS. During the second cycle of regorafenib, the frequency of HFS was 30% for grade 1, 8% for grade 2 and 3% for grade 3, with the use of preventive clobetasol, after the development and frequency of HFS was 43% for grade 1, 18% for grade 2 and 7% for grade 3 ($p = 0.12$).²⁹

The use of herbal medicine as alternatives for the prevention of HFS, such as henna, a dye extracted from dried leaves and branches of *Lawsonia inermis*, with antioxidant and immunomodulatory effects;^{22,23} curcumin, the main component of turmeric, with anti-inflammatory and antioxidant activities, to prevent the activation of prostaglandin biosynthesis and c-Jun/AP-1, protein kinases and COX-2 expression;^{23,24} and silymarin, a member of the Asteraceae family, acts as an antioxidant and inhibitor of lipid peroxidation activity, has an immunomodulatory effect, increasing lymphocyte proliferation, interferon gamma (IFN- γ), secretion of IL-4 and IL-10 by lymphocytes and suppression of T cell activation, by affecting the NF-kB pathway.^{20,24,28}

Oncology nurses and their recommendations, number of expected cycles, monitoring of laboratory tests, application of a pain scale, evaluation of mobility, nutritional status, psychological status, local evaluation of the hands and feet (with evaluation of the brachial, dorsalis pedis artery and posterior tibial artery). If there is already a lesion, assess: type of wound; possible causes; location, size and depth; characteristics of the wound bed and edges; presence of exudate and its characteristics; perilesional skin characteristics, improve the results.^{19,20}

Female sex, high hemoglobin and low bilirubin are factors with a high prediction of the risk of HFS and allow the follow-up of patients who have a high risk of developing HFS and the early identification of symptoms and signs.

Health education that improves the communication of symptoms and signs by patients is vital for the management of toxicities caused by chemotherapy and the improvement of the quality of life of patients who develop HFS. The World Health Organization (WHO) recommends that in mild to moderate cases only symptomatic treatment is required, such as emollients, cold compresses and topical corticosteroids of medium to high potency, with or without occlusion, due to their anti-inflammatory effect. In severe cases, the use of vitamin E, COX 2 inhibitors and dexamethasone alone or in combination with pyridoxine at doses of 150-200 mg daily orally. In grades 2 and 3, if support measures are insufficient, the drug can be suspended until

improvement is achieved and then resumed by reducing the dose by 25 to 50%. Or resume the medication, but with a 50% reduction in the dose. Erythrodysesthesia or hand-foot syndrome, in the first instance, does not indicate suspending the chemotherapy treatment that the patient is receiving, as was our case (Table 4).^{25–30}

Table 4 Clinical lesion^{25,26}

Erythema
Grade 1
Grade 2
Grade 3
Dysesthesia/paresthesia, in hands and feet
Discomfort when holding objects, walking, painful swelling or erythema
Grade 1 + edema
Grade 2 + fissures
Painful erythema, swelling of palms and soles, periungual erythema, edema
Grade 4
Desquamation, ulceration, blisters, severe pain
Grade 3 and blisters are added

Doxorubicin is widely recognized as one of the most active drugs in the treatment of cancer, but its clinical utility is limited by dose-dependent cumulative cardiomyopathy, which can lead to severe congestive heart failure.

PPES is an adverse effect associated with treatment with various cytotoxic drugs, including liposomal doxorubicins. It is sometimes severe enough to limit the use of effective polychemotherapy. It presents with dysesthesia and tingling in the hands and feet that appear 2–12 days after chemotherapy treatment. These symptoms progress to edema and erythematous, violaceous plaques. If the chemotherapy cycle is not delayed or the dose is not reduced, desquamation, ulceration, and necrosis of the epidermis may occur.³ Patients usually experience improvement in 1–2 weeks, although in some cases, complete resolution may take up to 4 weeks or more.^{5,11,12} The treatment of PPES is aimed at relieving symptoms through topical nonpharmacological measures such as emollients, aloe vera, ointments such as lanolin, etc. There are no pharmacological treatments except for topical dimethyl sulfoxide (DMSO), which has been investigated in a small number of patients.³ Regarding prophylaxis, there is currently a phase III trial with pyridoxine versus placebo. Other drugs also evaluated are dexamethasone, amifostine and COX-2 inhibitors.^{27–33}

The exact mechanism by which this syndrome occurs is not known, although some studies point to an immunomodulatory response of the drug or a direct toxic effect on basal keratinocytes.⁶ Its incidence is different in pre-marketing studies carried out in breast/ovarian cancer at doses of 50 mg/m²: very frequent for DLP (46.2%) and infrequent for DLNP (0.9%).^{7,8,14,15}

The difference between both liposomal formulations is the speed of elimination of doxorubicin from plasma: DLNP releases 90% of its content in 24 hours, DLP releases less than 10% in 24 hours.^{1,3} In the case of DLP, the longer plasma permanence of the drug may explain the accumulation of doxorubicin in the skin, resulting in the appearance of PPE. This adverse reaction can be considered specific to DLP1, in the case we describe, it was decided to replace DLP with DLNP, although, even so, a PPE appeared that was severe and required hospital admission.

The causal relationship between DLNP and PPE was classified as probable by applying the modified Karl-Lasagna algorithm; which

highlights the importance of reporting adverse reactions to assess the safety of medications.^{34–44}

Conclusion

Hand-foot syndrome is a skin reaction that occurs when a small amount of medicine leaks from capillaries (especially in the palms and soles of the feet) and damages surrounding tissues. It is painful and can affect daily life. Symptoms of hand-foot syndrome include: numbness, tingling, burning or itching, redness, swelling, discomfort, tenderness, rash. In severe cases, it can cause: cracked, peeling or flaking skin, blisters, ulcers or sores that appear on the skin, severe pain, difficulty walking or using your hands. The following chemotherapy drugs for breast cancer can cause hand-foot syndrome: 5-fluorouracil, doxorubicin, ixabepilone, capecitabine; some targeted therapy drugs: margetuximab-cmkb, lapatinib. Not everyone who takes these drugs develops it; topical treatment for prevention of HFS in women with hand-foot syndrome is not recommended. Cancer patients undergoing antineoplastic chemotherapy; mainly topical interventions, with the use of urea and moisturizing creams; evaluation in future studies is required to see their benefits.

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Conflicts of interest

The authors declare that they have no competing interests.

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