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Recommendations for Cosmetology Procedures in the Chemotherapy – Induced Palmar-Plantar Erythrodysesthesia

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Abstract

Palmar-plantar erythrodysesthesia (PPE), also called to as hand-foot syndrome (HFS) or hand-foot skin reaction (HFSR), is a cutaneous complication in patients receiving some oncology drugs. It often makes normal daily activity impossible, it deteriorates the patient's quality of life and frequently limits chances of effective treatment. There are several approaches to ameliorating the symptoms of this complication. The purpose of the paper is to systematize and present information on PPE (HFS/HFSR), prevention and conservative treatment recommended in cosmetology procedures.

Keywords: Palmar-plantar erythrodysesthesia (PPE); Hand-foot syndrome (HFS); Hand-foot skin reaction (HFSR); Prevention; Conservative treatment; Cosmetology procedure

Introduction

Palmar-plantar erythrodysesthesia (PPE) is a limited skin reaction located on the palms and / or soles of the feet as a toxic side effect of certain types of medication used to treat cancer, commonly known as hand-foot syndrome (HFS) - when associated with classical chemotherapy, or hand and foot skin reaction / hand-foot skin reaction (HFSR) - when associated with certain molecularly targeted drugs. It is characterized by a sensation of hypersensitivity and tingling progressing to severe pain and tenderness with erythematous changes, edema, blisters and hyperkeratosis, mainly on the palms and soles. It is never life threatening, but it may interfere with the patient's daily activities [1-5].

Differences between HFS and HFSR

The skin toxicity associated with anticancer therapy with cytostatics in the form of PPE is an important issue in oncological practice. Several new cytotoxic drugs in the form of multi-kinase inhibitors (MKIs), such as sorafenib, sunitinib, axitinib, regorafenib and BRAF inhibitors (dabrafenib, vemurafenib), are associated with skin toxicity known as hand and foot skin reaction (HFSR) [6-8]. HFSR is histopathologically and clinically often defined as a variant of the more known hand-foot syndrome (HFS) following administration of older chemotherapeutic drugs such as 5-fluorouracil, capecitabine or doxorubicin [1,9-13]. Although the clinical features of HFS and HFSR such as bilateral occurrence, palmar-plantar localization, tenderness and pain are present in both, HFS is more diffuse and HFSR is localized to pressure points and includes conditions such as inflammatory hyperkeratosis. HFS and HFSR may occur simultaneously when older chemotherapeutic agents are used in combination with molecularly targeted therapy [14,15].

As mentioned above, the similarities between HFS and

HFSR are alike localization of lesions, pain, and resolution after treatment discontinuation. Nevertheless, the clinical picture of HFSR differs from that of HFS and is mainly characterized by well-defined areas of hyperkeratosis arising on an erythematous, inflammatory substrate. It is not uncommon that the layers of the epidermis are very thick, which causes pain and makes it difficult to walk and perform daily activity. In more severe cases, painful blisters may appear in places that are repeatedly exposed to pressure [1,11,16]. The most important differences in the clinical picture between HFS and HFSR are presented in Table1.

Symptoms	HFS	HFSR
Erythema	X	X
Swelling	X	
Blisters	X	X
Peeling of the skin	X	
Effects on the surfaces of the hands and soles	X	X
Effects on pressure-free areas of the hands and soles (fingertips, lateral parts of the foot, skin around the anus)		X
Hyperkeratotic calluses		X

Table 1: Differences between HFS and HFSR.
Source: [1,2].

Pathophysiological Mechanism

The exact mechanism that leads to the emergence of PPE associated with the administration of certain anticancer drugs is not yet known. Researchers have put forward several theories about its formation, but indicate that more research is needed to determine the complete pathophysiology and pathobiology of this common undesirable skin complication of chemotherapy. Some are shown below.

Since this condition affects primarily the hands and soles of the feet, scientists postulate that PPE is caused by drug accumulation in the eccrine sweat glands of the hands and feet, causing characteristic damage in these areas resulting from the toxicity of the drug administered [2]. This was observed, for example, in the case of, among others pegylated liposomal form of doxorubicin (PLD), which accumulates in greater amounts in eccrine sweat glands, located mainly on the palms and soles of the feet, and eccrine sweat, which may explain the frequent location of skin lesions in this area [9,17]. It is also indicated that the individual tendency to excessive sweating of the hands and feet may contribute to the occurrence and intensification of changes [18].

Some researchers postulate that cytostatics leak from the capillaries in the deeper layers of the skin due to local trauma associated with daily activities, which may explain the occurrence of changes in other areas of the body, such as the axillary, groin and sacral regions [19]. Taking into account their typical location, it is therefore assumed that as a result of mechanical factors such as friction, pressure or high temperature, small blood vessels are damaged. This requires the constant activation of repair processes involving VEGF and PDGF receptors. For example, sunitinib inhibits VEGFR-2 and PDGFR-β kinases, which show the greatest expression in capillaries among the other receptor subtypes. Inhibition of these kinases disrupts the processes of epithelial cell reconstruction, which is clinically manifested by edema, inflammation, erythema, blistering, and even necrosis [11,16,20-22].

Another report describes the mechanism by which HFS is a consequence of an inflammatory response that may result from overexpression of the enzyme COX-2, a prostacyclin precursor, which is expressed in inflammation. Scientists have noticed that the level of COX-2 increases significantly after administration of chemotherapy, which may lead to an inflammatory reaction of the COX type [23].

In the case of treatment with combined inhibitors of MEK and BRAF - although it gives high response rates with lower toxicity of skin therapy - the occurrence of skin lesions of the HFSR type is explained by the theory of paradoxical activation of the CRAF pathway in keratinocytes under the influence of therapy [24].

Clinical Symptoms

The first symptoms appear several days after the commencement of chemotherapy on the hands and / or

soles of the feet. Patients usually first notice an unpleasant disturbance of sensation (so-called dysesthesia / paresthesia), characterized by impaired sensitivity, especially to touch, tingling and numbness. They feel a clear change in skin temperature (a feeling of strong heat), or a "electricity passing" through hands and soles of the feet. These changes can progress and worsen over the following days and weeks, leading to burning pain, well-defined symmetrical erythema (especially in the pads of the distal phalanges) and swelling, sometimes with slight exfoliation, blistering, painful skin cracks, and deep ulceration on the hands and feet. The type and pace of symptoms depends on the treatment regimen chosen for the patient [11,12,16,20-26].

Thus, PPE (HFS / HFSR) can progress from mild to moderate to severe symptoms:

- Erythema
- Numbness
- Tingling
- Sensitivity (hypersensitivity to touch)
- Thickening of the skin
- Bright redness (symmetrical and sharply separated from unchanged skin)
- Burning, severe pain
- Swelling
- Peeling of the skin
- Fissures, blisters, erosions, ulcers
- Loss of fingerprints (as a possible result of peeling / peeling of the skin after some medications) [11,12,16,20-26].

Histological Symptoms

Histological examination of the altered skin reveals changes in keratinocytes: parakeratosis, i.e. pathological keratosis consisting in the presence of cell nuclei in the cells of the stratum corneum, where physiologically these cells are devoid of nuclei, and dyskeratosis, i.e. pathological keratinization of individual cells in the layers below the stratum corneum in which physiologically, keratosis does not occur. In the epidermis, scattered necrotic areas are also observed - numerous necrotic keratinocytes (necrosis - a series of morphological changes occurring after cell death) and numerous pyknotic keratinocytes (pyknosis - degenerative changes in the cell nucleus involving the transformation of chromatin into an irregular, compact mass, hydrolyzed by cytoplasmic sequences; of this is cell degeneration); and mild sponginess - intercellular edema. Focal vacuolar degeneration of the basal layer is also observed. The basement membrane is intact and there is no damage to the glands or sweat ducts. Melanin deposits, dilated blood vessels and perivascular lymphocytic infiltration - papillary edema are visible in the dermis [14].

Localization of Changes

As mentioned previously, HFS / HFSR is mostly limited to the hands and / or feet. The hands are usually more affected than the feet, or may be the only area affected. Initially, the changes concern the hands and soles of the feet. Sensory disturbances, erythema, skin exfoliation and wounds may appear in other areas of the body, especially those exposed to pressure, friction or elevated temperature, such as the groin [19]. These changes may also appear on the buttocks, vulva or scrotum [27,28].

Occurrence

Various sources report that PPE (HFS / HFSR) occurs in cases of the 6-64% patients treated with various chemotherapy regimens, in most cases with less severe grades and approximately 5% with severe severity. It seems that the onset and the severity of PPE depend mainly on the type of drug and its dose (peak plasma drug concentration, total cumulative dose, administration schedule) [16,22,24,25].

Prevention and Minimization of Symptoms

PPE (HFS / HFSR) is a common and very troublesome complication of chemotherapy, which significantly worsens the patient's quality of life, sometimes even preventing normal functioning. Therefore, numerous attempts are made to find a supportive therapeutic method (in addition to discontinuing treatment and reducing the dose of the cytostatics) that can effectively prevent or alleviate its symptoms. Unfortunately, there are still no guidelines for the prevention and treatment of this syndrome of palmar-plantar erythrodysaesthesia, both induced by tyrosine kinase inhibitors and following classic chemotherapy. The available recommendations and recommendations are based on the experience of clinicians and expert opinions. There are data from several randomized clinical trials on the prevention and minimization of PPE. Some trials to assess the efficacy of supportive therapies have been collected and described in Table 2 [29-37].

Author	Description of the study	Study result	Recommendations
Lopez i inni, 1999 [29]	DMSO was administered topically to 2 patients undergoing chemotherapy with liposomal doxorubicin who developed Grade 3 PPE.	After topical application of DMSO 4 times a day for 14 days, PPE resolved within 1-3 weeks.	A larger sample study to prove therapeutic efficacy is suggested in the future.
Leuman i inni, 2001 [30]	A retrospective study investigated 3 groups of patients: taking capecitabine only, treatment preceded by pyridoxine prophylaxis, treated with concomitant pyridoxine therapy to ameliorate the effects of HFS.	Patients who took> 200 mg / d of pyridoxine had milder symptoms of HFS compared to those who took the lower dose.	Patients may need higher doses of pyridoxine to relieve symptoms of HFS.
Cin i inni, 2001 [31]	13 HFS patients used "bag-balm" (emollients) in the non-control study.	12 out of 13 patients reported improvement after using "bag balm". 55% were able to continue chemotherapy without delaying or reducing doses.	Confirmation of effectiveness requires a large placebo-controlled study.
Karo i inni, 2006 [32]	Group of 5 patients with MBC treated with docetaxel and capecitabine: all patients with stage 2-3 PPE. Vitamin E was administered at a dose of 300 mg / day without dose reduction related to the therapy.	After one week, the symptoms related to PPE began to fade away.	Vitamin E can be considered as a PPE-related preventive drug.
Lee i inni, 2007 [33]	A prospective, randomized, placebo-controlled study (N = 360) of pyridoxine (vitamin B6) administered for the prevention of HFS / PPE.	Pyridoxine was not effective in preventing HFS associated with capecitabine treatment.	There are no clinical benefits of administering pyridoxine as a preventive measure for HFS.
Yamamoto i inni, 2008 [34]	Patients taking capecitabine were monitored for HFS. 42 cases of level 2 HFS were identified; all patients were taking vitamin E during chemotherapy.	Reducing peeling and pain, and improving the quality of life of all patients; symptoms of neuroticism decreased. All patients were able to complete chemotherapy without interruptions or delays; 38/42 HFS did not develop and 4 had grade 1 toxicity.	It can be assumed that vitamin E will prevent discontinuation of therapy and will allow the planned dose level to be maintained.
Wolf i inni, 2010 [35]	Topical urea lactic acid keratolytic agents were administered twice daily for 36 days in 137 patients with HFS treated with capecitabine. Compared to a placebo-control group.	The percentage of patients with moderate and severe symptoms of HFS did not differ between groups.	The data do not confirm the effectiveness of the tested cream.
Hofheinz i inni, 2015 [36] Iwase i inni, 2016 [37]	For 6 weeks, a new ointment containing an antioxidant complex was compared with urea cream on a group of 152 patients.	Urea cream showed greater effectiveness in preventing HFS than cream with antioxidants.	There is no clinical benefit to using an antioxidant cream.
Abbreviations: DMSO = dimethyl sulfoxide; MBC = metastatic breast cancer.			

Table 2: Selected clinical trials on methods to prevent and minimize HFS / HFSR.
Source: [29-37].

The list of tested pharmacological agents is wider than presented in Table 2, includes, among others emolytes, antioxidants, vitamin B6 (pyridoxine), painkillers and anti-inflammatory drugs (such as ibuprofen, naproxen, celecoxib, acetominophen, which by inhibiting the action of the COX2 enzyme involved in the formation of the factor responsible for pain and inflammation, would alleviate the symptoms of PPE), corticosteroids, dimethylsulfoxide. Although the effectiveness of these substances in preventing lesions has not been confirmed in randomized clinical trials and will not replace cytostatic dose modification, some authors suggest prophylactic or therapeutic supplementation (especially pyridoxine) to prevent and / or minimize PPE [17].

Taking into account all the recommendations from scientific research, symptomatic treatment consists of the local application of moisturizing, softening, keratolytic and anesthetic agents. It is also recommended to use preparations containing vasoconstrictors, such as phenylephrine, and astringents, such as witch hazel extract [12]. In patients who develop hyperkeratotic changes, keratinocyte necrosis and inflammatory infiltrates, it seems important to use topical urea cream (10-40%), both independently as well as in combination with 0.1% tazarotene cream or 5% 5-fluorouracil cream [11,16,26,38]. Urea has a keratolytic and softening effect, tazarotene reduces the proliferation of keratinocytes, normalizes their differentiation and reduces inflammation, while 5-fluorouracil inhibits cell proliferation in hyperkeratotic foci. The intensification of hyperkeratotic changes is also helped by preparations with salicylic acid (INCI: Salicylic Acid) (5-10%) [10]. These preparations should be applied twice a day, only to the affected areas. Topical corticosteroids (0.05% clobetasol propionate) or their combination with 3.5% salicylic acid are most effective in treating inflammation. However, these preparations should not be used for more than 14 days due to the risk of exacerbation of the lesions [12]. In the case of strong sensitivity and pain within the lesions, the use of 2-4% anesthetic gel with lidocaine brings beneficial effects. Strong pain that persists despite the use of local therapy is an indication for the implementation of oral painkillers from the group of NSAIDs or opioids [12,16,26]. Pharmacological treatment, with the help of, among others DMSO (INCI: Dimethyl Sulfoxide), vitamin B6 (INCI: Pyridoxine Hydrochloride), vitamin E (INCI: Tocopherol Acetate), celexoxib, as well as oral glucocorticosteroids may be of benefit, but data are still insufficient [10,11,22].

As there are no effective methods of PPE prevention and treatment, therapists are often forced to extend the interval between chemotherapy pulses and reduce drug doses, which often limits the possibility of effective treatment of oncological patients [39]. Interruption of treatment or dose reduction of chemotherapy, as recommended for dose modification, remain the most important action in the treatment of PPE. Proper patient education on the hygiene and care of the affected skin areas is also important.

As PPE can be very severe and adversely affect the quality of life of cancer patients by interfering with their ability to carry out normal daily activities, it is important to educate patients about the possible changes: first and foremost, they should be aware of the first symptoms. HFS / HFSR is manageable, but if not diagnosed early and left untreated, it can progress rapidly from a mild skin reaction to a painful, debilitating condition. Early communication with a physician or nursing staff member will identify and assess the degree of PPE, enabling care interventions to manage symptoms. Early implementation of therapeutic procedures will give a chance for a quick reversal of symptoms without any consequences for the functioning of the patients. Moreover, the physician may modify the treatment regimen by reducing the dose of the drug, dosing it less frequently or, ultimately, discontinuing it until the end of PPE, or permanently, if necessary, to prevent the patient's condition from worsening [1].

There are many non-pharmacological ways of managing the symptoms of HFS / HFSR and prevent it from worsening. For some time after treatment (about one week after intravenous administration, possibly while taking oral medications) it is important to avoid activities that rub the skin of the hands and soles, put pressure on the palms and soles, and / or expose them to heat. This can be achieved by modification of selected daily activities [10,11,16].

Strategies for non-pharmacological prevention / minimization of PPE include educating the patient to care for the areas of the body most at risk of change. The following tips can help you avoid factors that cause excessive exposure of your hands and feet to heat, pressure, and friction (which can heat and irritate the skin, dilate blood vessels and increase the amount of cytostatic in them). They can also be a list of indications for patients starting chemotherapy or suffering from PPE who are clients of cosmetology clinics [17,40-52]:

- Avoid long exposure of hands and feet to hot water, especially during hot baths in a hot tub, hot water showers, hand washing and washing dishes in hot water, staying in a steam bath - cooling baths and summer / cool showers are recommended, washing in cool water.
- Avoid strong, vigorous rubbing of the skin when wiping it with a towel - it is recommended to gently press the water with a material that absorbs water easily.
- Do not overheat the skin while in a sauna or exposure to the sun - it is recommended to stay in cool rooms.

- Avoid strong detergents, perfumes and cosmetics containing potentially irritating ingredients: alcohol, dyes, fragrances, preservatives - it is recommended to keep the skin of hands and feet moisturized: regularly and often gently apply mild, moisturizing skin care creams containing emollients, urea, petroleum jelly or lanolin.
- Avoid rubbing, vigorously massaging or rubbing while applying cosmetics - tap them gently.
- Avoid strenuous physical activity such as running, aerobics, jumping, walking, racket sports, long periods of walking - especially during the first weeks of chemotherapy - plenty of rest - sitting or lying down and raising your hands and feet.
- Avoid tight clothing, especially gloves, socks, tights and stockings - it is recommended that you wear loose cotton clothing, especially gloves and socks.
- Do not go barefoot, wear loose, well-ventilated, comfortable shoes and, if possible, wear comfortable slippers.
- Avoid using knives and tools such as a shovel, screwdrivers, hammers or garden tools (chopping motion, squeezing hands on a hard surface may cause excessive pressure and rubbing on the hands) - it is recommended to use protective gloves, not rubber, if necessary.
- It is recommended that you use cold compresses or baths, which can be helpful in relieving symptoms that can be used with ice, but be sure not to apply it directly to the skin.
- Alcohol consumption should be avoided [18,40-52].

Conservative Management Depending on the Severity of the Lesions

A very important step in the prevention / treatment of PPE symptoms is the assessment of their severity [1]. There are two popular systems used to classify HFS / HFSR: the NCI (National Cancer Institute) classification criteria and the WHO (World Health Organization) classification criteria. The NCI has a 3-tier grading system. The WHO classification system is based on 4 levels. Guidelines for the palmar-plantar erythrodysaesthesia syndrome are presented in Table 3.

Grade according to NCI	Definition according to NCI	Clinical changes	
1	Changes without pain	Abnormal sensation, fainting, tingling, painless swelling or erythema of the hands and / soles of the feet, causing disturbances that do not interfere with normal functioning	
2	Skin lesions with pain, not disturbing the functioning	Painful swelling and erythema of the hands and / or soles of the feet, causing discomfort affecting daily activities	
3	Skin lesions with pain, disrupting functioning	Wet peeling, ulceration, blistering, severe pain in the hands and / or feet, causing severe discomfort that prevents you from working or carrying out daily activities	
Grade according to WHO	Definition according to WHO	Clinical symptoms	Histological symtoms
1	Dysesthesia / paresthesia in the hands and feet	Erythema	Dilated superficial blood vessels
2	Discomfort when holding an object and walking, painless erythema and swelling of the hands and / or soles of the feet	1 + swelling	Spongy - intercellular edema
3	Painful erythema and swelling of the hands and / or feet, erythema and periungual edema	2 + skin cracks	Isolated necrotic keratinocytes in the upper layers of the epidermis
4	Peeling, severe pain, blisters, ulceration	3 + blisters	Total epidermal necrosis

Table 3: Classification of PPE (HFS / HFSR) according to the criteria of NCI (National Cancer Institute) vs. WHO (World Health Organization).
Source: [14].

Suggested principles of patient management depending on the degree of HFS / HFSR are summarized in table 4.

Grade	Symptoms	Functional status	Management suggested to patients
1	Abnormal sensation, numbness, tingling, painless swelling or erythema of the hands and / or soles of the feet	Activities or daily life are generally not impeded	Notify your doctor, nurse or cosmetologist as soon as you notice the first symptoms. Do not wait!
2	Painful erythema and swelling of the hands and / or soles of the feet, skin remaining intact	Hardship in daily life or activities\	Properly care for your skin:
			• Reduce friction and pressure during: kneeling for a long time, leaning on your elbows, brisk walking, jogging or walking regularly for a long time, using hand tools, gardening
			• Apply sunscreen, avoid exposure to heat
			• Use mild skin cleansers, do not rub the skin when wiping, but gently squeeze water with a material that absorbs water easily
			• For bathing and showering, use lukewarm water or cool water, avoid hot tubs and long exposure to hot water
			• Keep skin hydrated, use topical emollients, apply moisturizing creams frequently
			• Put your hands in cool water to relieve symptoms
			Dress appropriately:
			• Wear comfortable, loose-fitting clothes, shoes and gloves
			• Wear loose cotton gloves at night
			• Avoid using rubber gloves as they trap heat
			• Do not go barefoot, wear shoes, and when possible - comfortable slippers
3	Moist peeling, ulceration, blistering or severe pain in the hands and / or feet, tissue breakdown	Activity or daily life substantially interrupted, inability to work, difficulties with walking and using hands	

Table 4: Suggested management depending on the degree of HFS / HFSR. Source: [42,44-51].

Summary

Palmar-plantar erythrodysaesthesia syndrome is an undesirable effect of not only classical cytotoxic drugs, but also of molecularly targeted drugs [46-51]. This cutaneous side effect of oncological treatment, although not life-threatening, is very inconvenient for the patient and results in a significant reduction in the quality of life. In most cases, the symptoms associated with both HFS and HFSR can be effectively managed without compromising treatment. That is why cooperation between oncologists, dermatologists and cosmetologists in this matter seems so important. Appropriate prophylaxis should be instituted as soon as possible to all the patients who begin classical chemotherapy, as well as therapy with one of the aforementioned molecularly targeted drugs. The most recommended ingredients of cosmetics are: urea (INCI: Urea) and vitamin E (INCI: Tocopherol). The patient should be informed about the procedures that will reduce

the risk of skin complications and prevent the progression of the emerging lesions [52,53].

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