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Review

Pegylated liposomal doxorubicin-associated hand–foot syndrome: Recommendations of an international panel of experts

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ABSTRACT

Background: Hand–foot syndrome (HFS) is dose-limiting and the most common cumulative toxicity associated with pegylated liposomal doxorubicin (PLD). It can cause considerable discomfort and lead to therapy interruption. Numerous approaches to HFS management have been reported, but there is no consensus.

Methods: Published literature (identified via Medline and internet search) and expert experience regarding HFS and its pathogenesis, incidence, risk factors, prevention and treatment in patients undergoing treatment with PLD were collected and reviewed by a panel of experts. A consensus technique was used to develop recommendations.

Findings: The pathogenesis of PLD-associated HFS has been recently elucidated. Systems used to grade, prevent and treat HFS in individuals treated with PLD vary widely. A randomised clinical study demonstrated that PLD dose intensity reduction can prevent HFS. While there is limited literature support, patient education and supportive measures were endorsed by the expert panel as effective strategies for HFS prevention and treatment. An easy to use HFS grading and management algorithm was developed, early signs and symptoms of HFS outlined and specific recommendations for supportive care developed.

Interpretation: The paucity of data on the management of PLD-associated HFS led the expert panel to develop consensus-based recommendations. Patient education and supportive

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measures are important elements in the management of HFS and dose intensity reduction has documented efficacy in prevention. At a PLD dose intensity not exceeding 10 mg/m^2 weekly, HFS can be easily managed. Phase III research to support the efficacy other interventions is lacking.

1. Introduction

Hand–foot syndrome (HFS) or palmar–plantar erythrodysesthesia (PPE) is characterised by a patchy or confluent erythema involving the palmar aspect of the hands and soles of the feet. The erythema may become painful and progress to desquamation, bullae formation and functional limitation (Fig. 1). HFS was first reported in 1974[1] and has most commonly been associated with cytotoxic drug administration.[2] It can also arise as a paraneoplastic phenomenon[3,4] and has been reported following total body irradiation and high-dose combination chemotherapy prior to allogeneic bone marrow transplantation,[2,5] where it may be an indicator of impending development of post-transplant graft-versus-host disease (GVHD).[6] It has also been suggested that HFS induced by one agent can be recalled following treatment with other agents also known to cause HFS.[7]

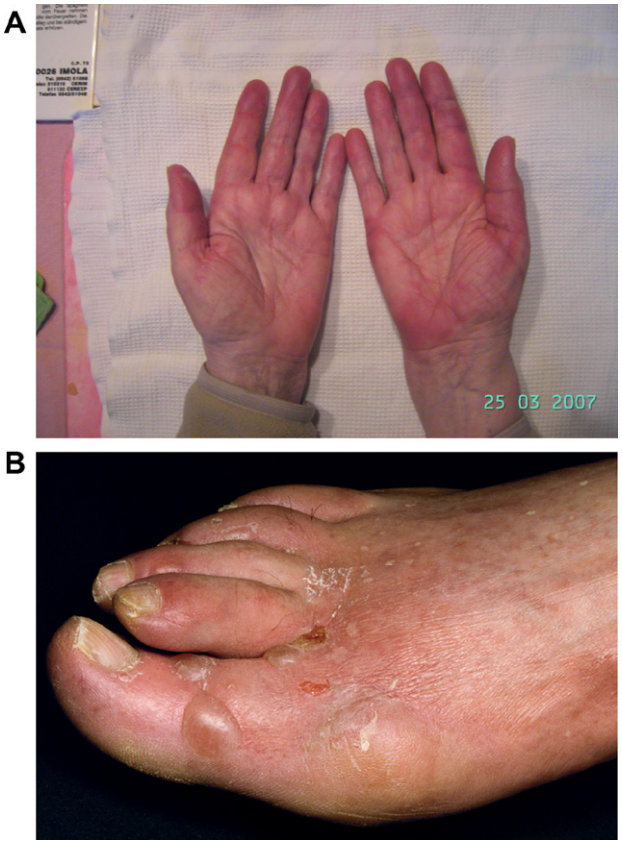

Fig. 1 – Hand–foot syndrome with (A) severe redness and swelling on the thenar and hypothenar eminences and lateral aspects of the fingers and pads of the distal phalanges and (B) desquamation, blistering and ulceration of the feet, particularly the toes.

While numerous cytotoxic agents are associated with HFS, our focus is on the pathogenesis, prevention and treatment of HFS in patients receiving pegylated liposomal doxorubicin (PLD). Our original intent was to address HFS of all causes; however, we limited our discussion because most of the literature on HFS is in patients receiving PLD and there is no clear evidence that other drugs share the same pathophysiologic mechanism for HFS.

Hand–foot syndrome is dose-limiting and the most common cumulative toxicity experienced by patients treated with PLD.[8] In pooled analysis of data in patients with breast or ovarian cancer treated with PLD, the incidence of HFS was approximately 45%. Severe (Grade 4) HFS occurred in <1% of patients and 4–7% of patients permanently discontinued PLD due to HFS.[9]

While most cases of HFS are mild, even mild cases may be associated with considerable discomfort and therapy interruption, which has the potential to alter treatment outcome. There is a paucity of data regarding the prevention and treatment of HFS. Therefore, an international panel of experts was convened to develop recommendations for the management of PLD-associated HFS.

2. Patients and methods

The international panel of experts was composed of physicians and a nurse involved in the care of patients with cancer and in the management of HFS. The panel met initially to review current practices, discuss ongoing research and come to agreement on the scope and content of the manuscript. The panel agreed to address the following as it relates to HFS in patients receiving PLD:

- What is HFS and how is it graded?
- What is the pathogenesis of HFS?
- What are the risk factors for HFS?
- What interventions have been shown to reduce the incidence or severity of HFS?
- How does HFS affect quality of life?
- What recommendations can be made for the prevention and treatment of HFS and for future research?

After the initial meeting, PubMed was searched from 1974 to the present for English language articles relevant to PLD and HFS and the findings were shared with the panel members. Consensus recommendations were developed during teleconferences and via e-mail communication.

Search terms included acral erythema, hand-foot syndrome, palmar–plantar erythrodysesthesia and palmoplantar erythema. Bibliographies of the retrieved articles were scanned for additional data to be included with the secondary searches based on the key authors and agents known to cause HFS. Google searches were performed using the same terms, and additional information was sought from dermatology and oncology textbooks. Web sites for dermatology and oncology medical associations (American Society of Clinical Oncology, European Society for Medical Oncology, Oncology Nursing Society, American, Association of Cancer Research, American Society of Hematology, American Academy of Dermatology, British Association of Dermatology) were searched for meeting abstracts, clinical practice guidelines and other resources associated with HFS and PLD.

3. Results

3.1. What is HFS and how is it graded?

Hand–foot syndrome (HFS) has numerous synonyms, including palmar–plantar erythrodysesthesia (PPE), plantar–palmar erythroderma, palmar–plantar erythema, toxic erythema of the palms and soles, Burgdorf's syndrome and chemotherapy-induced acral erythema. HFS remains a clinical diagnosis with no specific diagnostic testing recommended for confirmation. While tissue biopsy may be useful in the research setting to gain additional insight into the mechanism and pathophysiology of HFS, it is not appropriate in routine clinical practice.

The syndrome is typically described as a localised, non-specific dermatologic reaction affecting the palmar and plantar surfaces of the hands and feet. Preexisting inflammatory skin disease may contribute to the involvement of skin areas other than the palms and soles. Compressed skin regions as well as scars anywhere on the body can also be affected.

The earliest symptom is typically a tingling sensation followed within 2–4 d by painful sharply demarcated bilateral erythematous changes. Subsequently, the area can become oedematous and violaceous, after which it may dry and desquamate. In severe cases, bullae develop and may subsequently erode, and full-thickness ischaemic necrosis can occur. Erythema and swelling most commonly appear on the thenar and hypothenar eminences, as well as the lateral aspect of the fingers and the pads of the distal phalanges (Fig. 1). The hands are affected more often than are the feet and may be the only area involved.[10,11] Patients with dark complexions may present with hyperpigmentation instead of erythema and exhibit a thickening of the skin of the palms and soles that results in stiffness.[10–12] Less commonly, other skin areas such as the axilla, groin, waist, inner side of knees, posterior side of elbows, anterior folding lines of wrists, sacral area and bra line may be involved, particularly those exposed to occlusion, friction or frequent contact pressure.[10,11,13]

Neurologically, strength, reflexes and position senses are preserved despite potential functional limitations due to pain and swelling. Light touch may induce burning dysesthesias, while pin prick and temperature sensation may be absent or reduced.[14]

Reports detailing the onset and severity of HFS vary widely. Generally, symptoms have been reported within days of initiating the offending agent, but the onset may be months (2–10 months) after initiating therapy due to cumulative exposure.[11,15] In patients treated with PLD, HFS onset is often within the first 2–3 courses of treatment, but may also arise later in therapy.[13,16]

The natural history of HFS is usually self-limiting, with resolution often reported within 1–5 weeks of interrupting therapy with the offending agent. Due to the long half-life of PLD, HFS can take longer to resolve with each course of therapy, requiring dose reduction and delays of increasing duration.[17] Functional limitations due to HFS depend on the severity of the symptoms as well as other underlying general medical conditions or functional status limitations that may modify the impact of the syndrome.

Several different classification schemes have been devised to grade the severity of HFS, including the systems described in the National Cancer Institute common toxicity criteria (NCI CTC),[18] by the World Health Organization[19] and in PLD clinical trials.[20] While these systems may be useful in the research setting, they are not easily applied in clinical practice. No data are available to assess how well these classification schemes accurately reflect the clinical severity of HFS. Importantly, they do not provide for easy differentiation between grades. Thus, we find these classification systems to be inadequate for use in the clinical setting.

3.2. What is the pathogenesis of HFS?

The pathogenesis of HFS is an area of active investigation. The degree to which potentially causative agents share pathogenetic mechanisms is unclear, as no commonalities across all agents have been identified. The reaction, however, arises in anatomic areas that share common features, including temperature gradients, vascular anatomy, rapidly dividing epidermis, high concentrations of eccrine glands and significant exposure to friction and trauma, suggesting that local factors may play a role in pathogenesis.[12,21]

Histologic features of HFS are non-specific and are based on small numbers of patients. These include vacuolar degeneration of the basal cell layer, mild spongiosis, keratinocyte necrosis, papillary dermal oedema, lymphohistiocytic infiltrates and partial separation of the epidermis from the dermis. Perivascular infiltrates composed of lymphocytes and eosinophils are often seen in the dermis.[5,17,22] There may also be evidence of eccrine squamous syringometaplasia or neutrophilic eccrine hidradenitis.[23] Skin biopsies from 2 patients with PLD-associated HFS showed vacuolar degeneration of the basal layer of the epidermis, along with mild perivascular lymphocytic infiltration of the dermis, hyperkeratosis and apoptotic keratinocytes.[24] Clinical, electrophysiologic and biopsy data suggest that small-fibre neuropathy may be the cause of pain and dysesthesia.[14]

Research has uncovered the likely mechanism for HFS in patients treated with PLD. PLD is known to preferentially localise in both tumour and skin,[25,26] with pre-clinical models finding higher PLD levels in paws than in skin.[26,27] In another study, PLD fluorescence was quantitatively evaluated in humans using a dermatological laser scanning microscope.

Three hours after PLD administration, fluorescence was observed in the uppermost part of the skin of the flexor forearm, palm, sole, axilla and forehead of a male patient.[28] A fluorescence signal was also detected, deep in the sweat glands and orifices of the palms, suggesting that the drug is transported by sweat to the skin's surface, perhaps facilitated by the hydrophilic coating of the liposome. Once on the surface of the skin, the drug was observed to be carried in sweat and to penetrate into the stratum corneum, which may serve as a reservoir, allowing penetration of the drug into the deeper layers of skin. Once penetration occurs, free radicals are formed and react with epidermal cells, leading to HFS.[29] The palmar and plantar areas are characterised by high numbers of eccrine sweat glands that continuously secrete fluid and are thus most at risk for HFS.[28,29]

3.3. *What are the risk factors for HFS?*

Currently, there are no validated, predictive models identifying the risk of developing HFS. Neither tumour type nor body mass has been found to be an independent risk factor for HFS[30] and the impact of race is unclear.[12]

Based on the review of the available literature and through panel consensus, the major identified risk factors for HFS in patients treated with PLD are the schedule of administration and cumulative dose received.

Pre-clinical models demonstrated that the probability of PLD-associated HFS in dogs is related to PLD dose intensity which can be modified by changing either dose interval or level.[31] These findings were further explored amongst women with metastatic breast cancer in whom the half-life of the drug was significantly correlated with HFS, whereas dose delivered was not. The authors postulated that the importance of dose interval was related to keratinocyte turnover and epidermal transit time, which are both approximately 3–4 weeks. They suggested that the administration of PLD on an every 3 week schedule may coincide with the timing of skin repair, thus increasing the risk of HFS.[13]

3.4. *What interventions have been shown to reduce the incidence or severity of HFS?*

Numerous approaches have been employed in attempts to prevent and/or reduce the severity of HFS. Two nearly universally accepted approaches to the management of HFS are supportive care in conjunction with patient education and, for moderate to severe symptoms, treatment delay with or without dosage reduction. However, the efficacy of these approaches has not been demonstrated in controlled clinical trials. For the most part, observational studies, case series/reports and retrospective reviews have been used to support the usefulness of interventions. Only dose intensity modification for the prevention of HFS in patients treated with PLD[32] has been evaluated in randomised clinical trials.

3.4.1. *Dose intensity modification*

Reducing PLD dose intensity is a standard approach used to reduce the risk of or to ameliorate HFS and has been used in patients with several different tumour types. Collectively, studies demonstrate that PLD administered at a dose intensity of 10 mg/m^2/week, regardless of the dosing interval, is well tolerated and effective. At this dose intensity, most HFS is mild to moderate and potentially disabling HFS does not occur.

A randomised phase II study compared the incidence of HFS (graded using a 4-step scale) in 116 women with metastatic breast cancer (MBC) treated with 60 mg/m^2 PLD every 6 weeks versus 50 mg/m^2 every 4 weeks. In the former, weekly delivered dose intensity was 9.8 mg/m^2, with 69% of women achieving a dose intensity >90%, compared to a delivered dose intensity of 11.9 mg/m^2, with 65% of women achieving a dose intensity >90% in the latter treatment arm. HFS was more frequent (58% versus 33%) and more severe (Grade 3 or 4, 16% versus 2%) in women treated with 50 mg/m^2 every 4 weeks. The efficacies of the two schedules were similar.[32]

In an observational study, 46 patients with MBC were treated with 40 mg/m^2 PLD and compared to a matched patient population treated with 50 mg/m^2 PLD, both given every 4 weeks. NCI CTC Grade 1 or 2 HFS was seen in 41% of patients. There was no Grade 3 HFS, compared to a rate of all grade HFS of 52%, with 9% of patients experiencing Grade 3 or 4 HFS in the higher dose group. There were no significant differences in response or survival rates between the two populations.[33]

Sehouli and colleagues[34] evaluated the incidence of HFS in 64 heavily pre-treated patients with ovarian cancer treated with 20 mg/m^2 PLD every 2 weeks. HFS, graded using the NCI CTC, was reported in 48% of women, with 28% having Grade 1, 14% Grade 2 and 5% Grade 3 HFS. Efficacy was similar to that typically achieved at a dose of 50 mg/m^2 every 4 weeks.[34]

Lorusso et al.[35] evaluated the safety of 35 mg/m^2 PLD every 3 weeks in heavily pre-treated patients with epithelial ovarian cancer. The incidence of HFS was 22%, with 1 patient (2.8%) experiencing a Grade 3 reaction. Response rates were comparable to those achieved at a dose of 50 mg/m^2 every 3 or 4 weeks, but the incidence of HFS was considerably lower than the 23–29% incidence of Grade 3–4 HFS reported at the higher dose and using a 4-step grading criteria described in PLD clinical trials.[36,37]

In a retrospective review of 90 patients with gynaecologic tumours treated with 40 mg/m^2 PLD every 4–6 weeks, the incidence of Grades 1, 2 and 3 HFS was 26%, 10% and 1%, respectively. HFS was graded using NCI/GOG criteria. Patients were managed successfully with dose reductions of 5–20 mg/m^2 and did not experience subsequent events.[38]

Rose and colleagues[39] conducted a retrospective review of patients treated every 4 weeks with 40 mg/m^2 PLD (n = 38) and 50 mg/m^2 PLD (n = 40) to assess the relative activity and tolerability of these regimens in patients with gynaecologic malignancies. HFS was graded on the same scale as that used in PLD clinical trials (Table 1).[20] Dose reductions due to Grade 3 HFS were reported in 25% of patients treated at the 50 mg/m^2 dose and in no patients at the 40 mg/m^2 dose. There was no Grade 4 HFS and no difference in efficacy outcomes between the two doses.[39] Rose subsequently reviewed the incidence of HFS in several studies using PLD and suggested that 40 mg/m^2 PLD every 4 weeks (dose intensity of 10 mg/m^2

Table 1 – The proposed hand–foot syndrome (HFS) grading and management algorithm

Grade	Symptoms	Findings	Measures	
			First occurrence[a]	Second or greater occurrence[a]
1	None or only slight dysesthesia	Mild redness	Supportive care (Table 3)	Supportive care (Table 3)
2	Dysesthesia but no pain	Severe redness and/or swelling	Delay treatment until Grade 1 or less and consider dose reduction for subsequent courses	Delay treatment until Grade 1 or less and reduce dose 25%
3	Dysesthesia with pain	Severe redness and/or swelling	Delay treatment until Grade 1 or less and reduce dose 25%	Delay treatment until Grade 1 or less and reduce dose an additional 25%
4	Pain and impaired function in the activities of daily living (ADL)	Desquamation, blistering and ulceration	Delay treatment until Grade 1 or less and reduce dose 50%	Discontinue treatment

a Supportive care (Table 3) is recommended for all Grades of HFS.

per week) represents the optimal clinical efficacy while minimising the risk of HFS and other dose or schedule dependent toxicities.[40]

The benefit of initiating therapy with PLD at a reduced dose intensity in patients with Kaposi's sarcoma has been reported. At a dose of 20 mg/m^2 every 3 weeks, HFS was not reported.[41,42]

3.4.2. *Supportive care and patient education*

There are no formal evaluations of supportive care in the management of HFS, but panel members have extensive experience using this approach and consider it an integral component of HFS management along with patient education.

Supportive care includes topical wound care to aid healing and prevent infection and pain management with analgesics. Emollient creams may also be helpful.[43]

Avoidance of hot baths/showers, tight clothing and vigorous rubbing of the skin for 24 h before and 72 h after PLD administration have been recommended,[44] but supportive data are lacking. Other recommendations have included sitting or lying on padded surfaces, raising legs whenever possible, avoidance of jogging or vigorous exercise and wearing loose-fitting clothing and shoes.[45,46]

Patient education and monitoring may reduce the incidence and severity of HFS allowing early identification and reporting of signs and symptoms.[47,48] To be maximally beneficial, patients should be educated about HFS prior to beginning therapy with PLD.

In a nursing support programme aimed at reducing the incidence of adverse events in women with recurrent epithelial ovarian cancer treated with PLD (40 mg/m^2 every 4 weeks), the incidence of Grade 3 or 4 HFS (grading system not specified) was 4%[49] compared with an incidence of 21% in a large phase III trial conducted in a similar population.[50] The nursing support programme included patient education about potential PLD toxicities and instructions on prevention and treatment of side-effects. Patients were also asked to maintain a diary of symptoms and interventions.

3.4.3. *Pyridoxine*

There are numerous case reports of the successful use of oral pyridoxine at doses up to 800 mg daily for the management of HFS caused by a wide range of agents. In a case report, pyridoxine 100 mg three times daily was used successfully to treat PLD-associated HFS.[51] In contrast to these case reports, a large prospective, randomised double-blind study evaluating the efficacy of pyridoxine in the prevention of capecitabine-associated HFS found no benefit.[52]

Pyridoxine cream has been used alone or in combination with pyridoxine tablets for the management of HFS, but data are limited.[53]

Pre-clinical data support the efficacy of pyridoxine to ameliorate PLD-associated HFS. Dogs ($n = 41$) undergoing treatment with PLD for non-Hodgkin's lymphoma were randomised to receive either oral pyridoxine or placebo. The risk of developing serious HFS requiring PLD dosage adjustment or discontinuation was 4.2 times greater in the placebo group ($P = .032$). The onset of HFS was late and it was less severe in pyridoxine-treated dogs. Dogs receiving pyridoxine received a higher cumulative dose of PLD (mean, 4.1 mg/kg) compared with placebo-treated dogs (mean, 2.9 mg/kg; $P < .028$).[54]

The use of pyridoxine for PLD-associated HFS is not well supported and it cannot be recommended outside the research setting.

3.4.4. *Regional cooling*

The effects of regional cooling for HFS prevention were retrospectively reviewed in 20 women treated with single-agent PLD (30–50 mg/m^2 every 4 weeks) for recurrent ovarian cancer. HFS was graded using a 4-step scale. Seventeen patients (85%) kept ice packs around their wrists and ankles and consumed iced liquids during PLD administration and were encouraged to continue the procedure for 24 h. They were instructed to avoid direct sunlight, hot foods and liquids, contact with hot water and undue friction to the hands and feet for 72 h. A single dose of a 5-hydroxytryptamine agonist was administered before PLD infusion. Grades 0–2 HFS was reported in 94% (16 of 17) and Grade 3 HFS in 6% (1 of 17) of

patients using regional cooling. Of the 3 patients who did not use regional cooling, 33% (1 of 3) had none to Grade 2 HFS and 67% (2 of 3) had Grade 3 HFS. There was no Grade 4 HFS.[55]

A second retrospective review included 73 women with recurrent ovarian cancer treated with a median of five courses (range 2–27) of PLD. Of the 69 patients for whom PLD dose was available, 64 received 40 mg/m^2, 4 patients received 30 mg/m^2 and 1 patient received 50 mg/m^2. Approximately one-third of patients (25/73) followed the regional cooling protocol, which involved placing hands and feet in ice water during chemotherapy infusion. HFS was graded using a 4-step scale. All cases of HFS occurred in patients treated with a dose of 40 mg/m^2. The incidence of HFS in the regional cooling group was 24% versus 54% in the non-regional cooling group ($P = .0067$). The distribution of HFS in the regional cooling group versus the non-regional cooling group was 12% versus 19% for Grade 1, 8% versus 15% for Grade 2, 4% versus 15% for Grade 3 and 0 versus 4% for Grade 4. Discontinuation of PLD due to HFS was required in 4% (1/25) of patients treated with regional cooling compared with 23% (11/48) who did not receive regional cooling ($P = .048$).[56]

While regional cooling appears promising for the prevention of HFS, data are not sufficient to support the routine use in clinical practice.

3.4.5. *Oral corticosteroids*

The effectiveness of oral dexamethasone for HFS prevention was evaluated in a prospective case study conducted in patients with gynaecologic malignancies receiving PLD. Of 23 patients treated with 50 mg/m^2 PLD every 4 weeks, 39% ($n = 9$) developed Grade 2 or higher HFS. HFS was graded using the NCI CTC. After the resolution of HFS, 6 of the 9 patients were subsequently re-treated with PLD (without dose modification) in combination with oral dexamethasone (8 mg twice daily for 5 d beginning the day before PLD followed by 4 mg twice daily for 1 day, then 4 mg once daily for 1 day); 3 of 9 patients did not receive prophylaxis with dexamethasone. None of the patients treated with dexamethasone required PLD dosage adjustment for Grade 2 or higher HFS, while each of the 3 patients who did not receive dexamethasone required treatment delay or dose reduction for Grade 2 or higher HFS.[57]

A retrospective case study in patients with gynaecologic malignancies treated with 50 mg/m^2 PLD every 4 weeks addressed the effectiveness of oral dexamethasone for HFS. Six of nine patients with Grade 2–4 HFS were treated with a tapering oral dose of dexamethasone (8 mg twice daily [BID] Days 1–5, 4 mg BID Day 6, 4 mg Day 7). PLD was resumed without dose reduction but after resolution of HFS. The 6 patients treated with dexamethasone had complete or near complete resolution of HFS and were able to continue treatment without dose modification. Three patients who were not treated with dexamethasone required multiple treatment delays and dose reduction.[58]

Data are not sufficient to recommend the routine use of corticosteroids for HFS. Corticosteroid side-effects should be considered before using this approach in the management of HFS, particularly when using corticosteroids for prophylaxis.

3.4.6. *Other treatments*

Symptoms of HFS were reported to have resolved after topical application of dimethylsulphoxide (DMSO; 99% four times daily for 14 d) to 2 patients treated with 50 mg/m^2 PLD every 4 weeks, but treatment was also interrupted.[59] Concerns regarding the toxicity of DMSO[60–63] must be resolved before serious consideration should be given to evaluating its efficacy in HFS.

The administration of amifostine 200 mg/m^2 IV prior to PLD administration followed by pyridoxine 200 mg orally daily was successful in ameliorating or preventing HFS in a phase II study conducted in 12 patients with multiple myeloma.[64] Preclinical studies demonstrated the efficacy of amifostine in reducing the severity and incidence of PLD-associated HFS without altering the tumour response or pharmacokinetics of PLD in rodents.[65] Data are insufficient to recommend amifostine for routine use.

Primary results of a pilot non-randomised study of 20 patients who received a specially designed antioxidative ointment (characterised by defined radical protection factor [RPF] values) for HFS were very promising.[66] Twelve chemotherapy-naïve patients did not develop any degree of HFS.[67] Four patients interrupting the application of the ointment developed Grade 1 or 2 HFS, which was reduced after reapplication. Three patients with HFS from previous chemotherapy had very small reactions, and one patient was excluded. Further randomised studies will be performed.

3.5. *How does HFS affect the quality of life?*

HFS can adversely affect quality of life (QOL). While there was no meaningful impact on the overall QOL when the European Organization for Research and Treatment of Cancer QOQ-30 instrument was used to assess the impact of HFS on QOL in 404 women with MBC treated with PLD[68], most reports indicate that severe HFS can lead to significant morbidity and poor patient compliance with therapy.[10,48,69]

A prospective study was conducted in 91 patients with gynaecologic malignancies to investigate the impact of skin side-effects on health-related quality of life (HRQL). All patients were receiving systemic chemotherapy (46% taxanes, 7% PLD, 19% other anthracyclines, 14% topotecan, 14% other drugs) and were routinely examined for skin, hair and nail side-effects. Patients were interviewed using a standardised questionnaire that probed for information regarding side-effects and their impact on QOL. Side-effects affecting skin (e.g. HFS, nail loss, nail changes, alopecia) were categorised using the NCI CTC criteria, and photographed. The overall prevalence of skin, nail and hair side-effects was 87%. HFS was reported in 19% of patients (Grade 1 HFS in 3 (3%), Grade 2 in 5 (5.5%) and Grade 3 in 9 patients (10%)). The highest incidence of HFS was reported by patients treated with PLD, but was seen in all patients groups. Of patients with HFS (any Grade), 47% identified it as the most unpleasant side effect, while 78% of patients with Grade 3 symptoms reported HFS as the most unpleasant side-effect.[69]

4. Recommendations

The paucity of data on PLD-associated HFS led the expert panel to develop consensus-based recommendations.

- *HFS Grading and Management Algorithm*: A uniform grading system for HFS, with clear delineation of factors associated with each grade, is essential. We developed an algorithm for HFS grading and management (Table 1).
- *HFS Management*: While it is difficult to assess the impact of intervention for HFS without the availability of data from randomised controlled trials, the panel agreed that
  1. Dose intensity modification currently is the most effective and well-documented approach to the *prevention* of HFS. At a PLD dose intensity not exceeding 10 mg/m^2/week (typically administered as 40 mg/m^2 every 4 weeks), HFS, should it occur, is typically mild and easily managed and Grade 4 HFS should not occur.
  2. While large, phase 3 randomised controlled clinical trials have not evaluated the effectiveness of dose intensity modification in the *treatment* of HFS, the available data and clinical experience suggest that this intervention most reproducibly impacts the natural history and severity of PLD-induced HFS.
  3. Patient education regarding the early signs and symptoms of HFS (Table 2) and the importance of prevention and early intervention using supportive care approaches (Table 3)[48,70] are essential components in the prevention and management of HFS.
  4. Other strategies should be avoided outside the research setting, as their efficacy has not been demonstrated in phase III studies.
- *Future research*: More attention should be given to conducting phase III research on HFS prevention and treatment. For example, pyridoxine, regional cooling and systemic corticosteroids have only limited data to support their use and cannot be recommended without the support of phase III data. Additional research is required to assess QOL in patients with PLD-induced HFS and to what extent HFS prevention and treatment strategies alter QOL.

Table 2 – Early signs and symptoms of hand–foot syndrome (HFS)

- *Skin reactions*
  - *Symptoms*: tightness, tingling, pain or stiffness in the hands and/or feet
  - *Signs*: redness, scaliness and blistering, which can progress to ulcerations. Patients with dark complexions may present with hyperpigmentation and thickening of the skin
  - *Location*: most commonly on the palms of the hands and soles of the feet, but other areas may also be involved, such as axilla, groin, waist, inner side of knees, posterior side of elbows, anterior folding likes of wrists, sacral area and bra line
- *Onset*: may appear as early as 3–5 d after starting therapy
- Changes may arise in the skin, blood vessels and nails
- Wounds and injuries may heal less well

Table 3 – Supportive care for the prevention and management of hand–foot syndrome (HFS)[48,70]

Stage	Recommendations
Prior to treatment	*Educate the patient about the early signs and symptoms of HFS (Table 2) and discuss the importance of early reporting
Prevention of HFS	*Monitor the patient for signs and symptoms of HFS *Instruct the patient to • Apply emollient cream regularly to hands and feet • Avoid skin irritants (e.g. perfumes, alcohol, harsh cleaning agents) • Wear cotton socks or gloves to bed to enhance the absorption of creams • Avoid tight, irritating or ill-fitting clothing and shoes[a] • Avoid the use of band aides or other types of adhesive bandages or tape • Avoid repetitive activity or staying in one position for long periods of time • Keep the skin uncovered when possible to minimise perspiration • Wear rubber gloves while doing dishes • Pat (do not rub) skin dry with towels • Avoid extremes of temperature, pressure and friction • Avoid performing mechanically stressful manual work • Minimise exposure to strong, direct sunlight • Elevate affected limbs
Treatment of HFS	*Ensure that patient follows treatment interruption or dosage reduction guidelines *Monitor the patient for progression/resolution of HFS *Prescribe analgesics if necessary *Instruct the patient to • Continue the use of prevention strategies • Cushion sore skin • Submerge hands and feet in cool water baths or apply cold compresses for relief

a Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras.

Patient education and supportive measures are important to ensure the use of preventive strategies and ensure accurate and early communication of toxicities to clinic staff so that appropriate intervention can be initiated. The panel believes that in this way, quality of life can be maximised, pain and functional limitations minimised and potential benefits of systemic therapy more fully realised. More research is required to identify effective treatments for PLD-induced HFS, focusing on approaches that allow dose intensity to be maintained while minimising the risk of HFS.

Conflicts of interest statement

Roger von Moos has consultant or advisory relationships with Essex AB and Roche to disclose. Beat J.K. Thuerlimann has no conflict of interest to disclose. Matti Aapro (Chair)

has a consultant or advisory relationship with Schering-Plough, Roche and Pfizer to disclose, and receives research funding from Roche and Schering-Plough. Daniel Rayson has a consultant or advisory relationship with Schering-Plough and honoraria to disclose. Karen Harrold has no conflict of interest to disclose. Jalid Sehouli receives research funding from Schering-Plough. Florian Scotte has no conflict of interest to disclose. Domenica Lorusso has no conflict of interest to disclose. Reinhard Dummer has a consultant or advisory relationship with Schering-Plough and honoraria to disclose. Mario E. Lacouture has no conflict of interest to disclose. Jürgen Lademann has no conflict of interest to disclose. Axel Hauschild has a consultant or advisory relationship with Schering-Plough and honoraria to disclose.

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