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**Management of mild hand-foot syndrome associated with medical cancer therapies with an alcohol-free moisturizing and reparative gel containing omental lipids, urea, bromelain, and carnosine: a pilot prospective 12-week study**

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**Key words:** hand-foot syndrome; cancer treatment; purified omental lipid extract; carnosine; bromelain.

**Conflict of interest:** MM is an employee of Cantabria Labs Difa Cooper, the company that sells the tested product. The other authors declare no conflict of interest.

**Ethics approval and consent to participate:** the trial was conducted according to ICH/GCP guidelines and the Declaration of Helsinki. All subjects gave written informed consent to participate in the trial. According to the European Cosmetics Regulation (Regulation (EC) No. 1223/2009), cosmetics are defined and regulated separately from medicines; when used for their intended purpose, studies involving them generally do not fall under clinical trials legislation. Furthermore, the experimental design was low risk, given the already known safety profile of the product.

**Consent for publication:** the patients included in this study provided written informed consent for the publication of their case details.

**Availability of data and materials:** the datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

**Abstract**

Hand-foot syndrome (HFS), also known as palmoplantar erythrodysesthesia, is a frequent and burdensome complication of several anticancer chemotherapies, negatively affecting patients' quality of life. Depending on the treatment regimen, HFS may occur in 5-89% of patients. Currently, no standard therapies are available for its management. A recently commercialized alcohol-free gel containing emollient and skin-reparative components (omental purified lipids, urea, carnosine, and bromelain; POL-Podactive gel (POL-PA; Cantabria Labs, Caronno Pertusella, Varese, Italy) has shown efficacy in treating moderate-to-severe foot xerosis. However, no data are available regarding its potential role in the management of early-stage HFS. The aim of this study was to evaluate, in a pilot open trial, the efficacy and tolerability of POL-PA gel in patients with grade 1 HFS. Twelve patients (2 men and 10 women; mean age 58 years) with grade 1 HFS induced by anticancer treatments (mainly taxanes or antimetabolites) were enrolled in a 12-week pilot study after providing written informed consent. At baseline, all participants presented mild palmoplantar erythrodysesthesia and moderate xerosis. The gel was applied twice daily to the affected areas (hands and feet), with an average daily dose of 12 fingertip units (FTU; 6 g). Efficacy endpoints included the 10-item Dermatology Life Quality Index (DLQI) and subjective pain/dysesthesia assessed using a 10-cm Visual Analogue Scale (VAS; 0 = no pain, 10 = extreme pain). Assessments were performed at baseline, week 6, and week 12. The Common Terminology Criteria for Adverse Events (CTCAE) grade was also recorded at each visit. All patients completed the 12-week study. Mean DLQI decreased from 12±6 at baseline to 8±6 at week 6 and 6±5 at week 12 ($p<0.02$; Wilcoxon signed-rank test). Mean VAS score improved from 5±3 at baseline to 3.7±2 at week 6 and 3.0±2 at week 12, representing a 40% reduction ($p<0.0016$). No worsening of CTCAE grade was observed during the study. In this pilot study, an alcohol-free gel containing emollient and reparative components demonstrated beneficial effects on pain/dysesthesia and quality of life in patients with chemotherapy-induced grade 1 HFS. Controlled, well-designed trials are warranted to further define its therapeutic potential in this clinical setting.

**Introduction**

Hand-foot syndrome (HFS), also referred to as palmoplantar erythrodysesthesia, is a frequent complication of anticancer chemotherapy, with a considerable negative impact on patients' quality of life.[1] Depending on the regimen, HFS occurs in 5-89% of patients.[2] Currently, no standard therapy has been established for its management. POL-Podactive gel (POL-PA; Cantabria Labs, Caronno Pertusella, Varese, Italy), an alcohol-free topical formulation containing omental lipids, urea, carnosine, and bromelain, exhibits emollient, hydrating, antioxidant, and reparative properties and

has been marketed for the treatment of moderate-to-severe foot xerosis. However, no data have been published regarding its potential role in the management of early-stage HFS. The aim of this pilot study was to evaluate the efficacy and tolerability of POL-PA gel in patients with grade 1 HFS.

## Materials and Methods

### *Study design*

This was a single-centre, prospective, exploratory investigation carried out in a tertiary-level dermatological university clinic unit. The protocol and the information sheet were approved internally by the department. Considering that the tested product is classified as a dermocosmetic and the study was low-risk, formal IRB approval was not required under current regulations. Nevertheless, the investigation was conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki.[3]

### *Subjects*

Twelve patients (2 men and 10 women; mean age 58 years) with chemotherapy-induced grade 1 HFS (primarily from taxanes or antimetabolites) were enrolled after providing written informed consent. Inclusion criteria were: age ≥18 years; ongoing chemotherapy treatment; life expectancy >12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 2.[4] At baseline, all patients presented with mild palmoplantar erythrodysesthesia and moderate xerosis.

### *Intervention*

POL-PA gel was applied twice daily to the hands and feet, with an average daily dose of 12 fingertip units (FTU; 6 g) for 12 consecutive weeks.

### *Outcomes*

Efficacy endpoints included: Dermatology Life Quality Index (DLQI), using the 10-item questionnaire by Finlay and Khan (scores 0-30);[5] and pain/dysesthesia severity using a 10-cm Visual Analogue Scale (VAS; 0 = no symptom, 10 = worst symptom).[6] Both DLQI and VAS were assessed at baseline, week 6, and week 12. The Common Terminology Criteria for Adverse Events (CTCAE) grade was also evaluated at each visit.

### *Statistical analysis*

Statistical analysis was performed using GraphPad software. The distribution of variables was assessed to determine the appropriate statistical approach. For longitudinal comparisons between

baseline and follow-up measurements (*e.g.*, DLQI and VAS scores), the paired *t*-test or the Wilcoxon signed-rank test was employed for parametric and non-parametric data, respectively. Statistical significance was defined as $p<0.05$. Given the pilot nature of this exploratory investigation, a formal sample size calculation was not performed; a cohort of 12 subjects was deemed sufficient for these preliminary evaluations.

**Results**

This exploratory investigation was conducted from November 2023 to June 2024 at a tertiary Dermatology Clinic. All subjects completed the 12-week treatment period. Table 1 reports subjects' characteristics at baseline.

At baseline, the mean DLQI score was 12±6. This value significantly decreased to 8±6 at week 6 and to 6±5 at week 12 ($p<0.02$; Wilcoxon signed-rank test) (Figure 1). Similarly, the baseline VAS score was 5±3. The application of the gel significantly reduced the VAS score to 3.7±2 at week 6 and to 3.0±2 at week 12 ($p<0.016$; Wilcoxon signed-rank test) (Figure 2). Overall, after 3 months of treatment, DLQI and VAS scores improved by 50% and 40%, respectively. Figures 3 and 4 show the plantar region of a patient with grade 1 HFS at baseline, showing erythema and xerosis, and after treatment. During the 12-week observation period, no worsening in CTCAE grade occurred.

**Discussion**

HFS, also known as palmoplantar erythrodysesthesia, is frequently observed during chemotherapy.[7] This condition is characterized by erythema and painful skin lesions in acral regions. More specifically, HFS manifests as painful erythema and oedema of the hands and feet, with varying degrees of dysesthesia often followed by skin desquamation.[8] Extensive studies have documented symptoms including numbness, paraesthesia, tingling, and painless swelling; in more severe cases, blisters, ulceration, or intense pain may occur. The reported incidence of chemotherapy-induced HFS is approximately 50% to 60%, with severe forms accounting for 20-30% of cases.[9] Treatments involving capecitabine and taxanes are commonly associated with this condition.[10] While HFS is usually self-limiting, its clinical significance lies in the potential necessity for dose interruptions or permanent discontinuation of anticancer therapy. Erythema, oedema, xerosis, and skin fissuring remain the primary clinical signs.[11]

Some studies support the potential role of topical treatments in reducing the signs and symptoms of HFS. Karimi *et al.*[12] reported that a polyherbal hydrogel containing *Calendula officinalis* was associated with fewer complications in patients receiving fluoropyrimidine drugs. Additionally, research by Aras *et al.*[13] suggested that pyridoxine, vitamin E, emollient creams, and henna might be

effective in alleviating symptoms. However, since exact doses and treatment durations have not been definitively established, the management of HFS continues to represent an unmet clinical need.

In this exploratory pilot trial, we investigated the use of a moisturizing and reparative alcohol-free gel to assess its impact on the skin condition of cancer-treated subjects. The formulation contains purified omental lipids (POL), which are utilized in various topical products.[14] While POL has been reported to be effective in treating fragile skin and severe xerosis[15] and has been characterized by skin reparative activity in other contexts,[16] preliminary clinical data regarding its specific use in HFS are still limited.

The gel's formulation is further characterized by the presence of 15% urea, a known hydrating substance used to improve skin barrier function and reduce xerosis.[17,18] The moisturizing properties are intended to be supported by natural moisturizing factor-like components.[19] Furthermore, the inclusion of carnosine and bromelain provides a rational biochemical basis for the intervention. Carnosine has been shown in *in vitro* and *in vivo* models to act as a scavenger of reactive oxygen species (ROS) and lipid peroxidation products.[20-22] It may also play a role in protecting mast cells from degranulation.[23]

These properties are of particular interest as histological data indicate that HFS-affected tissues exhibit inflammatory changes, such as dilated blood vessels and leucocyte infiltration.[24] Since ROS formation induced by agents like doxorubicin is suggested to be a factor in HFS development,[25] ROS generation and mast cell activation represent potential targets for symptomatic relief.[26] Finally, bromelain is noted for its anti-inflammatory and anti-oedema properties.[27] Based on this pilot observation, the composition of this alcohol-free gel may offer a potential approach to managing the signs and symptoms of HFS, although further large-scale studies are required to confirm these preliminary findings.

## Conclusions

In conclusion, this pilot study suggests that an alcohol-free gel with emollient, anti-inflammatory, antioxidant and reparative components has potential beneficial effects in terms of pain reduction and quality of life improvement in subjects with cancer-treatment-induced HFS. However, due to the small sample size and the lack of a control group, these findings must be interpreted with caution. Future randomized controlled trials are mandatory to definitively establish efficacy. These preliminary data will serve as a basis for proper power analysis and sample size calculation for subsequent studies.

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**Table 1.** Patients' characteristics at baseline (n=12).

| **Characteristic** | | **Value** |
|---|---|---|
| Gender (n) | Male | 2 |
| | Female | 10 |
| Mean age (SD) | | 58 (15) |
| Type of cancer (n) | Breast carcinoma | 8 |
| | Ovarian cancer | 1 |
| | Melanoma | 1 |
| | Gastric cancer | 1 |
| | Colon carcinoma | 1 |
| Anti-tumor regimen (n) | Capecitabine | 3 |
| | Paclitaxel | 4 |
| | Cetuximab | 1 |
| | Trastuzumab | 2 |
| | Ipilimumab | 1 |
| | Regorafenib | 1 |
| CTCAE grade at baseline, n (%) | Grade 1 | 12 (100) |
| Symptoms | Burning sensation | 12 (100) |
| | Paresthesia | 11 (91) |
| | Pain | 1 (8) |

SD, standard deviation; CTCAE, Common Terminology Criteria for Adverse Events.

**Figure 1.** Mean DLQI scores at baseline, week 6, and week 12 in patients with chemotherapy-induced grade 1 HFS treated with POL-PA gel. Significant reductions were observed at weeks 6 and 12 ($p<0.02$, Wilcoxon test).

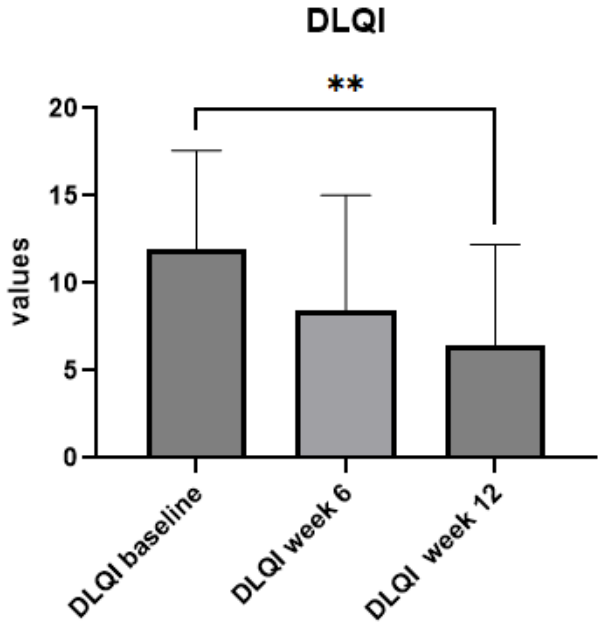


**Figure 2.** Mean VAS scores for pain/dysesthesia at baseline, week 6, and week 12. Treatment with POL-PA gel resulted in a significant 40% reduction in symptoms by week 12 ($p<0.0016$).

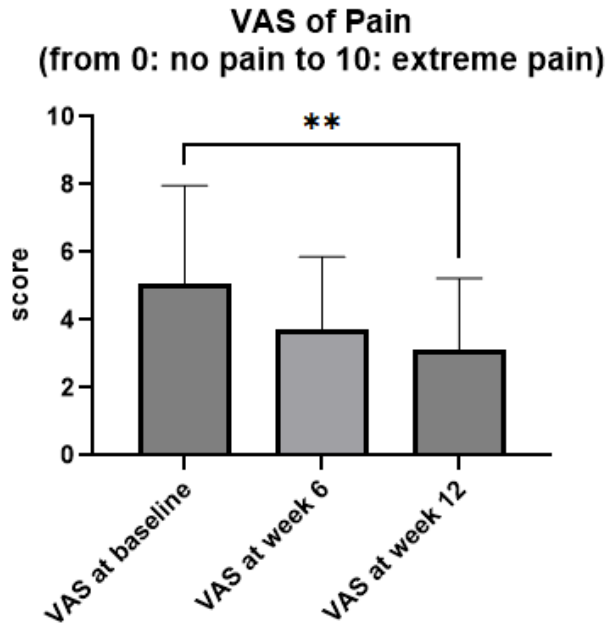

**Figure 3.** Plantar region of a patient with grade 1 HFS at baseline, showing erythema and xerosis.

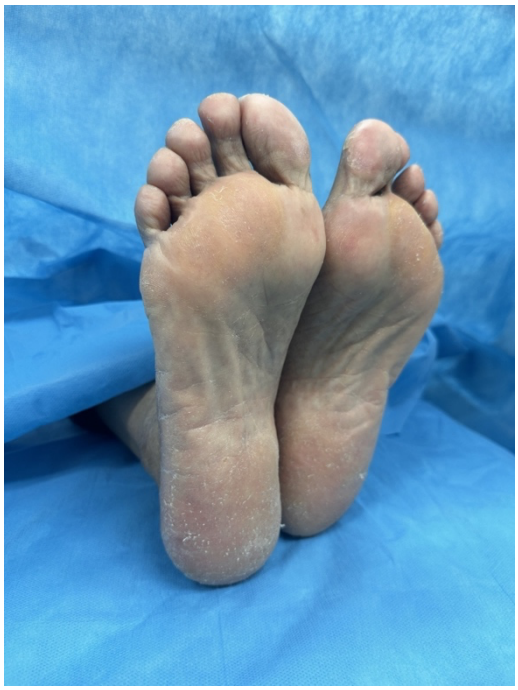

**Figure 4.** Plantar region in the same patient after 12 weeks of treatment. Reduction of erythema and hyperkeratosis is observed throughout the area.