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# Recent clinical studies with uridine cream

ESOP is urging hospital pharmacists to collect evidence for the usefulness of uridine products for hand-foot syndrome. Could you arrange a clinical study to collect robust evidence in your hospital?

**P**almar-plantar erythrodysesthesia or hand-foot syndrome (HFS) is a side effect that can occur with several types of chemotherapy. For example, capecitabine, 5FU, doxorubicin and high-dose interleukin-2 can cause this skin reaction for some patients, 45–56% of all patients treated with capecitabine suffer from this syndrome. Following administration of chemotherapy, small amounts of drug leak out of capillaries in the palms of the hands and soles of the feet. The exact pathogenesis of HFS is still unclear. A causal link with the metabolite of 5FU is suspected [1].



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Vitamin B6, painkillers and local glucocorticoids are currently used for treatment and a fresh idea is uridine cream. Uridine is one of several chemicals that could affect cell metabolism of pyrimidine. A detailed pharmacological explanation of the selective effect of uridine rescue is lacking. The administration of uridine to the local skin has

proved to be effective in patients with HFS; however it works well only after 5FU or capecitabine have been administered, but not as a preventive measure. This fact is so far explained by the suggestion that it displaces 5FU from intracellular metabolic pathways due to the increased competition from uridine. Such a hypothesis correlates well with published data.

Despite encouraging practical experience the use of a uridine cream has not so far been supported by a prospective randomised study. The German and European societies for oncological pharmacy (DGOP, ESOP) call on their members and active oncology pharmacists to test the formulations in practice and to provide more evidence for its efficacy. ESOP has received responses from the Czech Republic and Poland.

### Limited studies have been conducted

A small trial has been conducted in SPSK Hospital No.1 in Poznań, Poland. Approval was obtained from the Polish Bioethics Committee before the trial was started.

Ten women over a period of two months were enrolled in a pilot study. They were aged between 37 and 63 years (average 52.3). They were taking capecitabine five days in a row followed by a 2-week break. This cycle was continuously repeated. The date at which HFS first occurred was different in each patient, but it did not start before the second cycle. For seven of the ten patients the hands and feet were affected, for two patients only the hands and for one patient only the feet were affected (see Figures 2 and 3).

The uridine cream was only given to people who had responded insufficiently to glucocorticoids or greasy creams. All of the patients benefited from the cream; in every case the severity of the HFS got better, stage three went to stage two, etc. Success was measured by photographs and by a questionnaire the patients filled in. They were interviewed about symptoms at the beginning of the treatment and at different times while they were using it (2 days, 1, 2, 4, 6 and 8 weeks after starting treatment).

Figure 1: Grade 3 hand-foot syndrome



Exposure of hands and feet to heat as well as friction increases the amount of drug in the capillaries and increases the amount of drug leakage. This leakage of drug results in redness, tenderness, and possibly peeling of the palms and soles. In general hands are more often affected than feet. The erythema looks like sunburn (see Figure 1). The areas affected can become dry and peel, with numbness or tingling developing. HFS is classified in three grades of severity (see Table 1). In severe cases, the chemotherapy might have to be interrupted or the dose reduced.

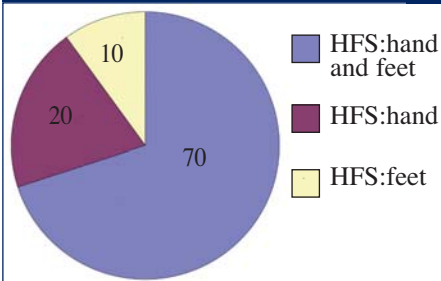
Table 1: Hand-foot Syndrome is divided into three grades

Toxicity	Hand-foot syndrome
Grade 1	Painless erythema, dysesthesia, paraesthesia, discomfort that does not disrupt normal activities
Grade 2	Painful erythema, with swelling (discomfort that affects activities of daily living)
Grade 3	Desquamation, ulceration, blistering, severe pain (severe discomfort, unable to work or perform daily living activities)

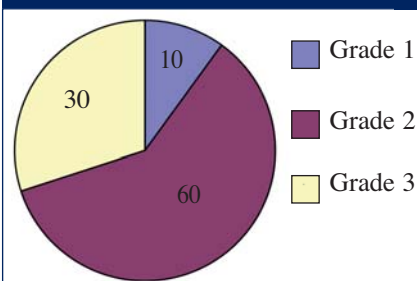
Prevention rather than cure is the standard recommendation, there are relatively simple measures to prevent HFS:

- Keep the skin well hydrated with emollient cream or ointment
- Avoid contact with hot water
- Avoid mechanical stress, such as scratching, clapping, handcrafts
- Cold baths or ice packs for the hands and feet 3–4 times a day.

**Figure 2: Localisation of hand-foot syndrome in the Polish study**



**Figure 3: The frequency of grades 1, 2 and 3 in the Polish study**



Pharmacies in the Czech Republic had to ask the State Institute of Drug Control for permission to use it for human treatment, because uridine is not on the list of authorised substances.

After submitting literature data and the results of a pilot study, the General Teaching Hospital, Prague, was given permission to use it for local administration when HFS was diagnosed. Today the pharmacy

prepares uridine cream not only for patients from this hospital, but occasionally for patients from other hospitals too.

Over a 2-year period 84 patients who were treated with fluoropyrimidine-based chemotherapy (mainly capecitabine) were given the 10% uridine cream 2–3 times daily and were monitored, if conventional treatment (steroids, emollient cream) had been ineffective. The number of chemotherapy cycles, grade and site of HFS, time of local uridine administration and the grade of HFS after treatment, were evaluated. Sixteen patients stopped uridine treatment after the first unit pack (100 g). The reason was a change of therapy after tumour progression or change of hospital.

Of the remaining 68 patients, no effect was seen in 23 patients (34%). In 45 patients (66%) the intensity of HFS decreased after 2–4 weeks of local administration, by about 1–2 grades. We recorded whether treatment was stopped or continued while the HFS was treated. One patient with a history of allergies developed atypical small white skin papules. Other local or systemic allergic reactions were not observed.

### Case study from the Czech Republic

We usually found that treatment could continue if we treated with uridine cream, because it was so effective. In one case, a young girl developed grade 3 HFS. This would usually mean stopping the treatment but her condition was so serious that she continued with the treatment. Improvement started straight away and it took six weeks for the HFS to clear up. If the treatment can be interrupted HFS symptoms are usually relieved much more quickly (in some cases within days).

Uridine 10% formulations were developed by the pharmacist Jürgen Barth in the pharmacy at Essen University Hospital, Germany [2], where it has been used to relieve this problem for the past 10 years (several kilos per year are used – personal communication). The cream is for patients with HFS while the paste is for patients with mucositis. In many countries, uridine is not authorised for routine medical treatment. At present hospitals in Poland are not allowed to use uridine cream, because this substance is not registered in Poland as a medical product. This situation will only change when more reports on its use can be found in the literature.

Hospital Pharmacy of GTH now uses uridine cream regularly and is going to study the mechanism of action. Ms Irena Netikova reports: “We have received financial support from the Czech Ministry of Health for a 4-year research project *The intracellular effect of uridine, and its use for treating palmar-plantar erythrodysesthesia after fluoropyrimidine-based treatment*”. ESOP urges other pharmacies to follow their example. The latest formula for the cream and paste using carbopol 974 can be found on the Pharmazeutische Zeitung site [3].

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