

Strategies for Prevention and Treatment of Chemotherapy-Induced Hand-Foot-Skin-Reaction (HFSR)

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Description

Hand-foot-skin-reaction (HFSR), also known as palmoplantar erythrodysesthesia, is a frequently occurring side effect of many antineoplastic therapies. Interruption, dose reduction or even discontinuation of anti-tumor therapy due to missing strategies in prevention or treatment of HFSR can be the consequence. According to severity grade of HFSR restrictions in activities of daily life can occur, which can lead to an impairment of quality of life (QOL). Especially skin-related QOL, which actually can be assessed by a variety of different questionnaires, often decreases when HFSR occurs, which can be underlined by some lately published investigations. Nardone and coworkers used the skindex-16 questionnaire to measure the skin-related QOL of patients treated with sunitinib and sorafenib. Patients with higher grades of HFSR showed lower results in the symptoms and emotions scores of the skindex-16 [1]. Chan et al. report in a lately published review that CTCAE grading of HFSR seems to correlate well with skin-related QOL, irrespective of the available questionnaires used for assessment [2].

Main agents potentially causing HFSR are tyrosine kinase inhibitors such as sorafenib, sunitinib or regorafenib as well as cytostatic agents like pegylated liposomal doxorubicin (PLD), taxanes and pyrimidine analogues (infusional 5-Fluorouracil or capecitabine). The overall incidence rate of HFSR differs from 20% to 60%, depending on trial-designs and analyzed anti-cancer drugs [3-8].

The pathomechanism of HFSR actually seems not to be sufficiently explained. Almost 20 years ago the observed skin reaction in patients treated with a high-dosed chemotherapy led to one of the leading theories for development of HFSR [9]. According to this theory, toxic active metabolites resulting from the applied chemotherapy were eliminated over the eccrine sweat glands of the skin and caused severe damage. Especially at the palms of the hands and the planta of the feet as well as intertriginous areas the count of sweat glands is highest in human body. Additionally, the thick stratum corneum of the skin in these areas serves as a reservoir for the toxic metabolites leading to severe skin reaction. Recently, other potential pathomechanism were suggested by Lademann and coworkers. New optical methods were used to detect fluorescent substances such as anthracyclines on the skin surface and around the sweat glands during or after administration [10]. As a consequence the excretion of toxic metabolites over the sweat glands results in formation of free radicals and hence in damaging cellular components. Thus, a prevention of HFSR using antioxidant agents seemed reasonable.

PROCAPP, an open label randomized phase III trial was conducted to compare the prophylactic effect of Mapisal and urea-cream in

patients receiving capecitabine therapy [11]. Mapisal is a medical device containing a huge variety of antioxidants and other nourishing ingredients. Patients with gastrointestinal or breast cancer not pretreated with tyrosine kinase inhibitors or other substances that could cause HFSR and who should receive a capecitabine based therapy were eligible for this study and were randomized in two groups. In Arm A patients were instructed to use Mapisal three times daily, as well as after washing hands for 6 weeks. Patients of Arm B had to use urea hand-foot-cream in the same frequency and duration as Mapisal in Arm A. The primary endpoint of this study was prevention of HFSR of any grade within six weeks of treatment based on a standardized patient diary. Furthermore skin related QOL was measured with the Quality of Life questionnaire C30 of the European Organization for Research and Treatment of Cancer (EORTC QLQ C30) and Dermatology Life Quality Index (DLQI). 152 patients were evaluable of whom 47 experienced HFSR (30.9%), 39.5% in the Mapisal arm and 22.4% in the urea arm (Stratified Odds Ratio 2.37; $p=0.02$). Time to any-grade HFSR was significantly longer in the urea group ($p=0.03$). Capecitabine dose intensity and time under study were identical in both arms as well as correct application of study medication. Skin related QOL was significantly worse in the Mapisal arm at the end of study treatment. As a conclusion urea showed superiority over Mapisal in preventing HFSR in patients treated with capecitabine.

These results are in keeping with another trial published in 2015 investigating urea as a strategy for prophylaxis of HFSR. Ren and coworkers confirmed superiority of urea over standard local treatment as prophylaxis of HFSR in 871 patients with hepatocellular carcinoma treated with sorafenib [12]. During the 12 week study period 56.0% of the patients in the urea arm and 73.6% of the patients in the best standard local treatment arm suffered from HFSR of any grade ($p<0.001$). Median time to HFSR was 2.5 fold longer for patients in the urea arm (84 days versus 34 days in the standard treatment arm; $p<0.001$). This data as well as the Mapisal trial implicate that urea cream may be an efficient strategy of preventing HFSR regardless of the anti-cancer drug used.

Aside from these positive findings other trials with different settings but also investigating urea-based ointments as a prophylaxis for HFSR have been performed and led to diverse results. In one larger randomized placebo-controlled study by Wolf et al. [13], a mixture of urea (12%) and lactic acid (6%) was used as prophylactic strategy against capecitabine induced HFSR. Amazingly the rate of HFSR in the placebo group was less than in the active treatment group. Wolf et al interpreted these results as a possible irritation of the skin caused by the mixture itself and not the capecitabine therapy.

Investigated Drug	Usage	Anticancer Therapy	Study Design	Result	Reference
urea+lactic acid	prophylactic	capecitabine	randomized, placebo-controlled	no difference between the study arms	Wolf et al. J Clin Oncol. 2010 [13].
pyridoxine (vitamine B6)	prophylactic	capecitabine	randomized, placebo-controlled	no difference between the study arms	Kang et al. J Clin Oncol. 2010 [15].
			meta-analysis	no difference between the study arms	Zhou et al. Biomed Rep. 2013 [16].
			randomized, placebo-controlled	no difference between the study arms	Braik et al. J Community Support Oncol. 2014 [17].
			meta-analysis	no difference between the study arms	Jo et al. Clin Exp Dermatol. 2015 [18].
Mapisal®	prophylactic	pegylated liposomal doxorubicin	observational study, one armed	no HFSR under Mapisal®	Lademann et al. Skin Pharmacol Physiol. 2014 [22.]
	therapeutic	diverse	usage of Mapisal if HFSR grade II or III occurred	reduction of HFSR grade under Mapisal®	Lademann et al. Skin Pharmacol Physiol. 2014 [23].
Mapisal® vs. urea	prophylactic	capecitabine	randomized, controlled	superiority of urea	Hofheinz & Gencer et al. J Clin Oncol. 2015 [11].
urea	prophylactic	sorafenib	randomized, placebo-controlled	superiority of urea	Ren et al. J Clin Oncol. 2015 [12].
urea vs. ceramide / hydrocolloid	therapeutic	sorafenib	randomized, controlled	less worsening of HFSR under hydrocolloid	Shinohara et al. Ann Oncol. 2014 [14].
aluminium chlorohydrate (antiperspirant)	prophylactic	pegylated liposomal doxorubicin	randomized, placebo-controlled	less grade II / III HFSR under antiperspirant	Templeton et al. Breast. 2014 [21].
celecoxib	prophylactic	capecitabine / xelox	randomized, four armed	less grade > I HFSR under celecoxib	Zhang et al. J Cancer Res Clin Oncol. 2011 [20].
	prophylactic	capecitabine	randomized, prospective	less any grade HFSR	Zhang et al.

					under celecoxib	Ann Oncol. 2012 [19].
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Table 1: Selection of studies investigating prophylactic or therapeutic strategies against HFSR.

This observation could be underlined by the fact that 10% of patients reported signs of HFSR on the first day of using the urea and lactic acid containing cream.

Another Phase-II-study from Japan investigated urea containing cream (10%) compared to a ceramide-containing hydrocolloid bandage as a treatment strategy for 33 included patients with HFSR grade I under sorafenib therapy [14]. Intriguingly only the planta of the feet were treated as described above, the hands remained without specific treatment for the observed HFSR. Primary endpoint was worsening of the HFSR to grade 2 or 3, which was reached by 69% of patients in the urea arm and only 29% in the hydrocolloid arm. It can only be speculated whether the observed worsening of HFSR during urea treatment would have also occurred on the palms of the hands or if it is in the realms of possibility that the pathomechanism of the skin damage is different on feet and hands, respectively.

In summary, the pathomechanism of HFSR seems not completely understood and is still to be further investigated. One leading theory for the development of HFSR would be a toxic reaction and cellular damage caused by free radicals that result from active metabolites of the antineoplastic therapeutic agents drifting slowly through the thick stratum corneum on the palms and planta. This theory is underlined by pre-clinic data using new optical methods directly measuring fluorescent agents in the skin. However, the prophylactic and therapeutic effect of antioxidants on HFSR only could be observed within a small count of studies with a limited number of patients [22,23]. A head to head comparison of Mapisal with the empirically used urea cream could not confirm the theory. Contrarily, urea cream tended to be superior over Mapisal as well as over placebo in the Chinese study for patients receiving sunitinib although the specific effect mechanism of urea in this setting apart from the increase of stratum corneum hydration [24] and the inhibition of antimicrobial activity [25] is unclear at the moment. Further randomized controlled trials with larger patient numbers are needed to analyze the efficacy of urea containing ointments for prophylaxis and treatment of HFSR in different tumor entities and using different antineoplastic drugs to optimize supportive care and to enable less treatment interruptions or avoid discontinuation of anticancer therapy.

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