The Pathogenetic Mechanism of Anthracycline-induced Palmar-plantar Erythrodysesthesia

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Abstract. *Background: Anthracyclines, such as pegylated liposomal doxorubicin (PLD) and epirubicin (EP), are effective for the treatment of malignant tumors. Unfortunately, their implementation in therapy is limited due to severe side-effects such as palmar-plantar erythrodysesthesia (PPE). Patients and Methods: As the exact pathogenesis of PPE still remains unclear, laser scanning microscopy was utilized to detect PLD, EP and their metabolites in and on the skin surface of patients. Results: It was shown that PLD was significantly more frequently detectable on the skin than was EP ($p<0.05$), whereas both substances were most frequently seen in the palms and soles. Additionally, it has been visualized that the substances reach the skin surface via sweat, where they distribute and then penetrate back into the skin. Conclusion: It was concluded that a high density of sweat glands and a thick stratum corneum might represent important predestined factors for the development of PPE. These findings will help to develop efficient prevention and therapy strategies for PPE.*

Anthracyclines are highly effective substances used in the treatment of malignant solid tumours (1). Their efficacy is based on several mechanisms: intercalation between base pairs of the DNA, generation of free radicals, interactions with cell membranes and inhibition of topoisomerase II (2). The implementation of anthracyclines in therapy is limited, however, as a result of their side-effects, which include cardiotoxicity and myelosuppression, and the occurrence of intrinsic or acquired drug resistance (3). Derivatives such as epirubicin (EP) or pegylated liposomal doxorubicin (PLD) were developed in order to improve the therapeutic index by reducing toxicity. Encapsulation of doxorubicin into pegylated liposomes positively modifies pharmacokinetics and toxicity, significantly reducing the severity of cardiotoxicity and myelosuppression (4). An increased incidence, however, can be seen in mucocutaneous reactions (5, 6).

Palmar-plantar erythrodysesthesia (PPE) also known as the hand-foot syndrome, in particular is of importance in this context. This syndrome comprises erythematous skin lesions of the palmae and plantae. The dermatitis may spread to other intertrigeneous sites such as the axilla or groin (4). This syndrome was first described by Zuehlke (7) as a reaction to an infusion with mitotane. The clinical picture is characterized by localized erythema and edema on the palms of the hands and the soles of the feet. The skin becomes increasingly drier and begins to develop varying degrees of scaling. This is usually accompanied by a feeling of tautness and burning on the affected regions. The condition is painful, and the quality of life of the patients thus suffers. In serious cases, the patients can develop such severe blisters and ulcerations, that hospitalization becomes necessary. The incidence of PPE depends on the trigger agent, the dose, as well as the administration interval, and is described as being approximately 50% for PLD (4, 5).

The pathogenetic mechanism of PPE is generally unknown. It has been suggested that PPE is induced by both direct and indirect toxic effects of the cytostatic agents. Fitzpatrick (8) proposed that repeated doses of chemotherapeutic agents or high dosage chemotherapy lead to cumulative toxic damage of the keratinocytes, which are particularly susceptible because of their high turnover rate. Possible associations to anatomic differences such as a high density of sweat glands, absence of folliculo-sebaceous units, a thick stratum corneum and wide dermal papillae have been described by other authors (9). Additionally, it was assumed that palms and soles, and areas of repeated friction or trauma might achieve higher concentrations of chemotherapeutic agents as a result of the rich capillary network at the thickened papillary dermis and increased blood

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Table I. *Patient-relevant data for Group I receiving PLD therapy.*

Patient ID	FIGO	Previous therapies	PLD dose and interval	Body surface (m^2)	Individual dose (mg)	No. of cycles
PLD 1	Relapse	Taxol/carboplatin topotecan/etoposide	20 mg/m^2/*q14d*	1.60	32.0	4+5
PLD 2	III c	Taxol/carboplatin topotecan/etoposide	20 mg/m^2/*q14d*	1.82	36.4	7+8
PLD 3	Relapse	Taxol/carboplatin	40 mg/m^2/*q28d*	1.70	68.0	11+12
PLD 4	III c	Topotecan/carboplatin taxol	20 mg/m^2/*q14d*	1.84	36.8	1
PLD 5	III c	Taxol/carboplatin/ gemcitabine	20 mg/m^2/*q14d*	1.68	33.6	1
PLD 6	III c	Taxol/carboplatin etoposide/topotecan	20 mg/m^2/*q14d*	1.56	31.2	4

flow (6). Other authors suggested that an association with inflammatory processes might exist (10, 11) on the basis that increased vascularisation exists which results in the substances penetrating through the extended capillaries. The hand-foot syndrome has also been observed to occur in combination with other substances, such as 5-fluorouracil, capecitabine and docetaxel (12). It is not yet clear, however, why some substances damage cells, while others do not. Likewise for capecitabine-associated PPE, different theories concerning the etiology exist. Asgari *et al*. (13) suggested that the increase in dermatological effects during treatment with capecitabine is due to the fact that keratinocytes in the skin have increased levels of thymidine phosphorylase, which lead to the accumulation of capecitabine metabolites. Mrozek-Orlowski *et al*. (14) have postulated that the cytostatic drug may be excreted in sweat, making palms and soles more prone to PPE due to the high number of eccrine sweat glands in these extremities.

The penetration of anthracyclines and their derivates into the skin appears to play an important role for the pathogenesis of PPE. To date, it is relatively unclear how such substances arrive at the skin subsequent to intravenous application and why the syndrome predominantly develops on the palms of the hands and the soles of the feet. Recently, new optical methods have become available for the detection of fluorescent substances, such as anthracyclines, in the skin. In this context, two cases have been published by our own group, who showed that doxorubicin was detectable on the skin surface after systemic application (15) and in a sweat duct and around its opening (16). This indicates that the postulations of Mrozek-Orlowski might be correct that the substances are excreted with the sweat, although these initial data need confirmation by further investigations. Therefore, the aim of the present study was to investigate the skin on different body sites and at time points during the therapy of patients receiving anthracyclines, in order to learn about the pathomechanisms of anthracycline-induced PPE. This may lead to the development of new and effective strategies to combat this syndrome which are not available at the present time.

Patients and Methods

Chemotherapeutic agent. The chemical structure of anthracyclines consists of a tetracyclic chromophore which is bound to an amino sugar with a glycosidic bond (1). The chromophore is also present in most metabolites (17). The pegylated liposomal doxorubicin (PLD) and epirubicin (EP) both belong to the class of anthracyclines; EP is an epimer of doxorubicin in which the C4-hydroxyl group is located in an equatorial position instead of the axial position in doxorubicin (18). Both substances, as well as their metabolites, show a fluorescence of 560±40 nm after excitation with light at a wavelength of 480±40 nm (1).

The patients included in this study received their individual doses of either PLD (Caelyx®; Essex Pharma GmbH, Munich, Germany) or EP (Farmorubicin®; Pharmacia GmbH, Karlsruhe, Germany) diluted with 250 ml of a 5% glucose solution. All research was conducted according to the Declaration of Helsinki principle. All patients included in the study gave their written informed consent.

In order to determine how long the anthracyclines demonstrate fluorescence when in contact with air, 5 ml PLD were placed on a glass plate, and the fluorescence was observed up until its quenching. Quenching occurs as a result of exposure to daylight and contact with air.

Patients. A total of 12 patients, each of whom had either a histologically verified mastocarcinoma or ovarian carcinoma, were prospectively examined. The average age was 57.8 years (range 38 to 77 years). In group I, 6 patients received PLD at a medium dosage of 23.3 mg/m^2 (range 20 to 40 mg/m^2). The patients were suffering from advanced or metastatic, platinum-resistant ovarian

Table II. *Patient-relevant data for Group II receiving EP therapy.*

Patient ID	Initial tumor stage	First-line therapy	Body surface (m^2)	Individual dose (mg)	No. of cycles
EP 1	pT2, pN1, M1 c-erbB2 3+	Epirubicin 60 mg/m^2/*q21d* Taxol 90 mg/m^2/*q21d* Herceptin 2 mg/kg/*q7d*	2.00	124.2	3+4
EP 2	pT1c, pN1, G2 c-erbB2 0	Epirubicin 60 mg/m^2/d 1+8, *q28d* CTX 75 mg/m^2/d 1+14, *q28d* 5-FU 500 mg/m^2/d 1+8, *q28d*	1.68	100.8	3+4
EP 3	pT2, pN0, M1 c-erbB2 0	Epirubicin 75 mg/m^2/*q21d* Docetaxel 75 mg/m^2/*q21d*	1.96	147.0	6
EP 4	pT1c, pN0, G3 c-erbB2 3+	Epirubicin 90 mg/m^2/*q21d* CTX 600 mg/m^2/*q21d* 5-FU 500 mg/m^2/*q21d*	1.58	142.2	5
EP 5	pT2, G2, M0 c-erbB2 1+	Epirubicin 90 mg/m^2/*q21d* CTX 600 mg/m^2/*q21d* 5-FU 500 mg/m^2/*q21d*	1.74	156.6	3
EP 6	pT2, pN1, G1 c-erbB2 0	Epirubicin 90 mg/m^2/*q21d* CTX 600 mg/m^2/*q21d* 5-FU 500 mg/m^2/*q21d*	1.93	173.7	6

carcinoma. The individual dosage for each patient was calculated before chemotherapy on the basis of their body weight and height (body surface). The length of the infusion was 30 minutes on average. An overview is given in Table I. The patients were examined at different cycles of their chemotherapy.

In group II, 6 patients with metastatic mastocarcinoma received EP in different chemotherapy regimes (Table II). The medium dosage was 77.8 mg/m^2 (range 60 to 90 mg/m^2). The patients were examined at different cycles of their chemotherapy.

Study design. Dermatological investigation: In a dermatological examination, the skin condition of each patient at the time of the investigation was evaluated. As the patients were at different stages of their chemotherapy cycles (cycles 1 to 12), the medical documents of the previous cycles including the dermatological examinations and the anamnesis were re-evaluated and also considered when identifying the incidence of PPE in the included patients.

PPE was classified according to the Common Toxicity Criteria – V. 1.0 of the National Cancer Institute (19).

Anthracycline detection: Previous to anthracycline therapy, 9 body regions were defined for each patient always including forehead, both axilla, both palmae, both plantae and both underarm areas.

These body regions were examined with laser scanning microscopy before infusion, as well as 1, 2, 3, 4 and 5 hours after the start of the infusion. For each patient, 45 measurements were conducted for hours 1 to 5 (n=45). Due to the reproducibility of the signals of each body region on the left and right sides, these were rated as one area (n=25). In total, 45 measurements for each body region were conducted for the patient group receiving PLD (n=45), while 40 for each body site were conducted for the patient group receiving EP treatment (n=40). A detectable fluorescence signal was recorded of the presence of PLD and EP.

Confocal laser scanning microscopy. The detection of PLD and EP and its fluorescent metabolites in and on the skin was carried out with a dermatological laser scanning microscope (Stratum, Optiscan Ltd, Melbourne, Australia). A comprehensive review of the optical principles has been published elsewhere (20). The fluorescence can be detected at an excitation wavelength of 488 nm. The measuring apparatus consists of an argon laser, which operates at a wavelength of 488 nm, and can be directly projected onto the skin with a flexible hand-held device. The scan can be performed up to a depth of 200 μm in the tissue. The obtained image corresponds to a lateral field of vision of 250×250 μm. Depending on the topographical region, the different layers of the epidermis and the upper region of the dermis can be inspected. The penetration depth varies with different body regions. It is known from previous measurements with the dye sodium fluorescein that the images obtainable for the hands and feet are limited to the upper layer of the epidermis, the stratum corneum; the stratum granulosum can only be observed in very few cases. On other body regions such as the axilla, the forehead and the flexor forearm, it is possible to view all layers of the epidermis, the upper part of the dermis, as well as the papillae and vascular plexus. Hence, it is possible to differentiate whether the substances are localized directly on the skin surface, in deeper skin layers of the stratum corneum, or in the living tissue.

Results

This study was aimed at the analytical detection of the anthracyclines PLD and EP, as well as their metabolites, in and on the skin of patients subsequent to systemic application, using laser scanning microscopy.

Table III. *Occurrence of PPE after intravenous application of PLD and EP.*

	No PPE (no. of patients)	PPE grade I (no. of patients)	PPE grade II (no. of patients)	PPE grade III (no. of patients)	PPE grade IV (no. of patients)
PLD	2	2	1	1	0
EP	6	0	0	0	0

In pre-investigations, PLD was exposed to air and daylight on a glass plate, in order to determine the persistence of fluorescence under these conditions. It was shown that the fluorescence signals were detectable for the course of 2 hours, although the intensity of the signal constantly decreased. The time period in which fluorescence can be detected is not identical to the availability of the anthracyclines in the skin.

The re-evaluation of the case history of the patients revealed that PPE occurred in 67% of all patients treated with pegylated liposomal doxorubicin (PLD) after 3.75 cycles (range 3 to 5) on average. None of the patients who were treated with EP suffered from PPE (Table III).

All patients were examined using laser scanning microscopy on 9 different body regions (forehead, both axilla, both palmae, both plantae and both underarm areas) before and 1, 2, 3, 4, and 5 h after the start of the infusion with either PLD or EP. Previous to infusion, in all patients and on all body regions, no fluorescence signal was detectable. On average, the fluorescence signal initially occurred in all patients 1.4±0.9 hours after the start of the treatment (after 1.4±0.8 hours for PLD and 1.5±1.1 hours for EP). The signal remained detectable throughout the subsequent measurements (up to 5 hours after the start of the infusion) but continuously decreased during the end of the measurement.

Fluorescence was detected predominantly on the palms and on the soles, in comparison to the other body regions measured. The detection of fluorescence was positive in 91% of the cases on the hand (n=45) after the application of PLD and in 82.5% after the application of EP (n=40). On the soles, fluorescence could be seen in 86% of the cases after the PLD infusion (n=45) and in 70% (n=40) subsequent to EP treatment. On the palmae and plantae, extensive intra- and extracellular fluorescence became evident (Figure 1a).

A fluorescent signal was found on the flexor forearms in 66.6% of the cases after PLD infusion (n=45) and in 52.5% after EP infusion (n=40). A positive signal was also found on the forehead after PLD application in 57.7% (n=45), and after EP in 57.5% of the measurements (n=40). In these regions, the fluorescent signal was strongest in the furrows of the skin. In Figure 1 b, fluorescence is visible at the edge of the furrow, which highlights a narrow strip of cells lying at its edge. The detection in the axillar region was 71% for treatment with PLD (n=45) and 35% for treatment with EP (n=40).

Utilizing the Wilcoxon test (SPSS 13.0, Chicago, Illinois), it was calculated that the fluorescent signal in the skin was significantly more frequently detectable in the case of PLD application than of EP application ($p<0.05$).

Additionally, it was detected that the fluorescent signal is firstly verifiable in the sweat duct and around its opening on the skin surface and the superficial layers of the skin and only in the deep layers of the stratum corneum at a later stage. This mechanism is shown in Figure 1c. The ending of a secretory duct of the sweat gland is visible (black) and is surrounded by fluorescence. In Figure 1 d and e, the secretory ducts of the sweat glands which run through the epidermis to the skin surface are visible and show strong fluorescent signals.

These phenomenona were observed after PLD infusion as well as after infusion with EP. No significant difference concerning intensity and occurrence of fluorescence could be detected between the patients treated with 40 mg/m^2/*q28d* and those who were treated with 20 mg/m^2/*q14d*. However, the intensity and occurrence of the fluorescence signal showed interindividual differences.

Discussion

In the present study, 67% of the patients treated with PLD developed a PPE, which is in the range of previous reports (21, 22).

The known fact that anthracyclines show fluorescence has widely been used for the detection of these substances, for example in plasma (1). With the help of dermatological laser scanning microscopy, it is now possible to detect the fluorescence in the skin after intravenous application. Because of the fluorescence, cellular structures such as the cells of the stratum corneum, skin furrows and wrinkles, as well as sweat glands, can be visualized.

The analysis of the penetration pathway here confirmed the postulations of previous authors (14, 16) that anthracyclines and/or their metabolites are transported to the skin surface *via* the sweat glands. Here, they spread laterally and penetrate back into the skin. At 1.4±0.9 hours after the start of the treatment with either PLD or EP, a fluorescent signal was detected in all patients. These results support studies that have shown that substances are secreted with the sweat 1 to 2 hours after systemic application. Harris *et al.* (23), for example, observed the secretion of ketoconazol

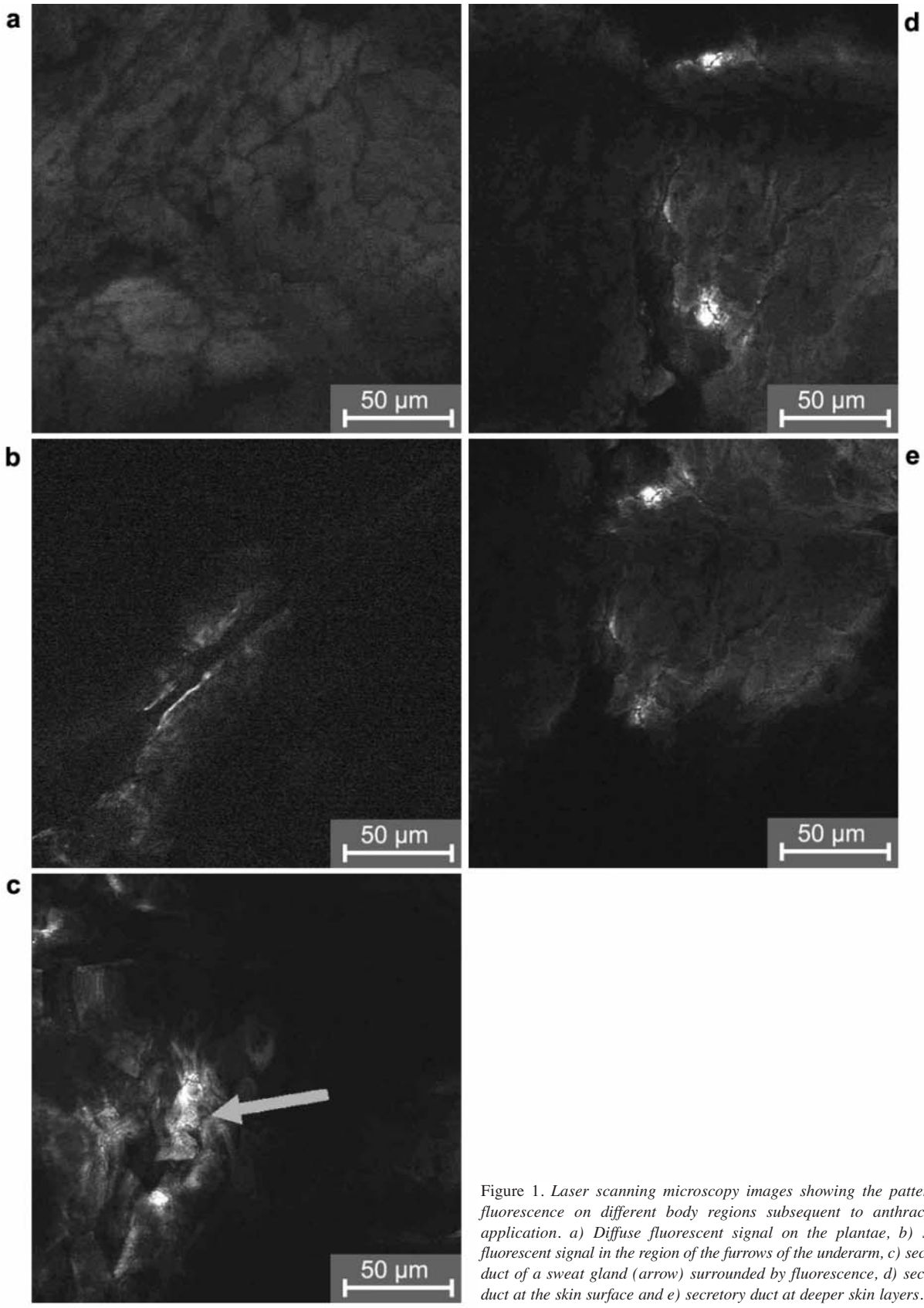

Figure 1. *Laser scanning microscopy images showing the patterns of fluorescence on different body regions subsequent to anthracycline application. a) Diffuse fluorescent signal on the plantae, b) strong fluorescent signal in the region of the furrows of the underarm, c) secretory duct of a sweat gland (arrow) surrounded by fluorescence, d) secretory duct at the skin surface and e) secretory duct at deeper skin layers.*

with sweat 1 to 2 hours after systemic application and described a positive correlation between therapeutic concentrations in the skin and very high secretion rates through sweat glands. While there are elaborate studies regarding the penetration of topically applied substances into and through the skin, investigations are rare regarding inverse penetration of systemically applied substances into the skin. Theoretical inverse penetration routes should include the intercellular, the follicular, and the intracellular routes, as well as transport *via* sebaceous glands or *via* desquamation (24). Reviewing the available literature revealed that apart from inverse intercellular penetration, all pathways might be of relevance, whereas sweat and sebaceous glands appeared to be the most fast and effective inverse penetration pathways for systemically applied substances, depending on the physicochemical properties of the latter (24). With the help of the laser scanning microscope, it was possible to visualize PLD and EP, or their metabolites, arriving at the skin through the sweat glands, and then spreading out laterally on the surface before penetrating back into the stratum corneum, as if applied topically. Therefore, it is highly likely that the sweat glands have to be considered as the most relevant inverse penetration pathway for these substances. The extent of the participation of the other possible inverse penetration pathways, however, is not yet clear.

The results of the present study revealed that a fluorescent signal was most frequently detectable in the region of the palms and soles (up to 91% for PLD on the palms) in comparison to other regions (only in 52.5% for EP on the flexor forearm). These data might be able to explain the predilection of PPE for the palms and the soles, as both these regions have a high number of sweat glands (25) and a thicker stratum corneum (26) in comparison to other regions. Other authors have also postulated that high density of sweat glands and a thick stratum corneum may be the reason for a heightened concentration of such substances in the skin (9). On the forehead, which also has a high density of sweat glands but only a thin stratum corneum, the detection was more seldom. A thick stratum corneum can therefore be considered as an additional factor for the development of PPE because a thick stratum corneum represents a large reservoir for penetrating substances. Being stored for a longer time, the anthracyclines can induce oxidative processes and the formation of free radicals in the skin, which might be responsible for the development of the skin lesions.

For PLD, in our study we revealed an incidence of 67% for the development of PPE, which is in the range of data from literature, whereas for EP, none of the investigated patients developed this type of side-effect. This variation of incidence of PPE for PLD and EP might be explained by the liposomal encapsulation of doxorubicin. It may be assumed that the pegylated liposomes disintegrate in the stratum corneum as liposomes are known to interact with various lipids of the stratum corneum. As pegylated liposomes are more hydrophilic than conventional liposomes, the disintegration presumably occurs more slowly. As a result of the longer half-life of PLD, higher local concentrations of this substance can be found in the skin. Additionally, it has to be considered that PLD has been detected significantly more frequently on different skin sites than EP, which also might play a role.

As yet, PPE can only be treated by interrupting therapy or by dosage reduction (5, 27, 28) which, however, presumably also affects therapy effectiveness (29). Behaviour modifications such as limiting pressure applied, avoidance of extremes in temperature, as well as creaming of these regions, can be viewed as supportive therapy (27). Several other topical and systemic therapy regimes exist, such as cooling (30), topical dimethylsulfoxide (DMSO) application (31), oral and local steroids (32-34), or oral pyridoxine (35), although these have not shown convincing success throughout clinical studies.

An improved understanding of the pathomechanism of PPE may now lead to the development of new strategies for prevention and therapy of PPE. Pyridoxine, for example, which is an antioxidant, might be used in the correct management of PPE as the formation of free radicals represents an important mechanism of action of anthracyclines and might also be responsible for the development of skin lesions. On the basis of the present findings, it can be assumed that prevention strategies should focus on topical application, as the skin surface and the upper layers of the skin represent the site of action and systemic application might be able to reduce the effectiveness of the chemotherapeutic substance by decreasing the action of the free radicals.

Therefore, the findings of the present study offer opportunities for further clinical studies developing and investigating prevention and therapy strategies for PPE, as anthracyclines represent a popular and effective group of cytostatic substances.

References

1 de Bruijn P, Verweij J, Loos WJ, Kolker HJ, Planting AS, Nooter K, Stoter G and Sparreboom A: Determination of doxorubicin and doxorubicinol in plasma of cancer patients by high-performance liquid chromatography. Anal Biochem *266*: 216-221, 1999.

2 van Asperen J., van TO and Beijnen JH: Determination of doxorubicin and metabolites in murine specimens by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl *712*: 129-143, 1998.

3 Speth PA, van Hoesel QG and Haanen C: Clinical pharmacokinetics of doxorubicin. Clin Pharmacokinet *15*: 15-31, 1988.

4 Charrois GJ and Allen TM: Multiple injections of pegylated liposomal doxorubicin: pharmacokinetics and therapeutic activity. J Pharmacol Exp Ther *306*: 1058-1067, 2003.

5 Gordon KB, Tajuddin A, Guitart J, Kuzel TM, Eramo LR and VonRoenn J: Hand-foot syndrome associated with liposome-encapsulated doxorubicin therapy. Cancer *75*: 2169-2173, 1995.
6 Lotem M, Hubert A, Lyass O, Goldenhersh MA, Ingber A, Peretz T and Gabizon A: Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. Arch Dermatol *136*: 1475-1480, 2000.
7 Zuehlke RL: Erythematous eruption of the palms and soles associated with mitotane therapy. Dermatologica *148*: 90-92, 1974.
8 Fitzpatrick JE: The cutaneous histopathology of chemotherapeutic reactions. J Cutan Pathol *20*: 1-14, 1993.
9 Cox GJ and Robertson DB: Toxic erythema of palms and soles associated with high-dose mercaptopurine chemotherapy. Arch Dermatol *122*: 1413-1414, 1986.
10 DeSpain JD: Dermatologic toxicity of chemotherapy. Semin Oncol *19*: 501-507, 1992.
11 Skelton H, Linstrum J and Smith K: Host *vs*.-altered-host eruptions in patients on liposomal doxorubicin. J Cutan Pathol *29*: 148-153, 2002.
12 Susser WS, Whitaker-Worth DL and Grant-Kels JM: Mucocutaneous reactions to chemotherapy. J Am Acad Dermatol *40*: 367-398, 1999.
13 Asgari MM, Haggerty JG, McNiff JM, Milstone LM and Schwartz PM: Expression and localization of thymidine phosphorylase/platelet-derived endothelial cell growth factor in skin and cutaneous tumors. J Cutan Pathol *26*: 287-294, 1999.
14 Mrozek-Orlowski ME, Frye DK and Sanborn HM: Capecitabine: nursing implications of a new oral chemotherapeutic agent. Oncol Nurs Forum *26*: 753-762, 1999.
15 Schmook T, Jacobi U, Lademann J, Worm M and Stockfleth E: Detection of doxorubicin in the horny layer in a patient suffering from palmar-plantar erythrodysaesthesia. Dermatology *210*: 237-238, 2005.
16 Jacobi U, Waibler E, Schulze P, Sehouli J, Oskay-Ozcelik G, Schmook T, Sterry W and Lademann J: Release of doxorubicin in sweat: first step to induce the palmar-plantar erythrodysesthesia syndrome? Ann Oncol *16*: 1210-1211, 2005.
17 Drummond DC, Meyer O, Hong K, Kirpotin DB and Papahadjopoulos D: Optimizing liposomes for delivery of chemotherapeutic agents to solid tumors. Pharmacol Rev *51*: 691-743, 1999.
18 Mahnik SN, Rizovski B, Fuerhacker M and Mader RM: Development of an analytical method for the determination of anthracyclines in hospital effluents. Chemosphere *65*: 1419-1425, 2006.
19 Common Toxicity Criteria - V. 1.0 of the National Cancer Institute. www.ucdmc.ucdavis.edu/clinicaltrials/documents/ NCI_ toxicity_table pdf 2007.
20 Meyer L, Otberg N, Richter H, Sterry W and Lademann J: New prospects in dermatology: Fiber-based confocal scanning laser microscopy. Laser Physics *16*: 758-764, 2006.
21 Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, Roman L, Uziely B, Muderspach L, Garcia A, Burnett A, Greco FA, Morrow CP, Paradiso LJ and Liang LJ: Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. J Clin Oncol *15*: 987-993, 1997.
22 Hackbarth M, Haas N, Fotopoulou C, Lichtenegger W and Sehouli J: Chemotherapy-induced dermatological toxicity: frequencies and impact on quality of life in women's cancers. Results of a prospective study. Support Care Cancer 2007.
23Harris R, Jones HE and Artis WM: Orally administered ketoconazole: route of delivery to the human stratum corneum. Antimicrob Agents Chemother *24*: 876-882, 1983.
24 Patzelt A, Lademann J and Sterry W: Skin penetration from the inside to the outside: a mini review. Drug Discovery Today, 2008.
25 Hwang K and Baik SH: Distribution of hairs and sweat glands on the bodies of Korean adults: a morphometric study. Acta Anat (Basel) *158*: 112-120, 1997.
26 Ya-Xian Z, Suetake T and Tagami H: Number of cell layers of the stratum corneum in normal skin – relationship to the anatomical location on the body, age, sex and physical parameters. Arch Dermatol Res *291*: 555-559, 1999.
27 Gerbrecht BM: Current Canadian experience with capecitabine: partnering with patients to optimize therapy. Cancer Nurs *26*: 161-167, 2003.
28 Nagore E, Insa A and Sanmartin O: Antineoplastic therapy-induced palmar plantar erythrodysesthesia ("hand-foot") syndrome. Incidence, recognition and management. Am J Clin Dermatol *1*: 225-234, 2000.
29 Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA and Fryer JG: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncol *7*: 425-432, 1989.
30 Molpus KL, Anderson LB, Craig CL and Puleo JG: The effect of regional cooling on toxicity associated with intravenous infusion of pegylated liposomal doxorubicin in recurrent ovarian carcinoma. Gynecol Oncol *93*: 513-516, 2004.
31 Lopez AM, Wallace L, Dorr RT, Koff M, Hersh EM and Alberts DS: Topical DMSO treatment for pegylated liposomal doxorubicin-induced palmar-plantar erythrodysesthesia. Cancer Chemother Pharmacol *44*: 303-306, 1999.
32 Atkins JN: Fluorouracil and the palmar-plantar erythrodysesthesia syndrome. Ann Intern Med 102: 419, 1985.
33 Brown J, Burck K, Black D and Collins C: Treatment of cytarabine acral erythema with corticosteroids. J Am Acad Dermatol *24*: 1023-1025, 1991.
34 Hoff PM, Valero V, Ibrahim N, Willey J and Hortobagyi GN: Hand-foot syndrome following prolonged infusion of high doses of vinorelbine. Cancer *82*: 965-969, 1998.
35 Hui YF and Cortes JE: Palmar-plantar erythrodysesthesia syndrome associated with liposomal daunorubicin. Pharmacotherapy *20*: 1221-1223, 2000.

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