Chemotherapeutic agents may be associated with maculopapular rashes, hyperpigmentation, nail changes, and an acral erythema known as Bergdorff’s reaction, palmoplantar dysesthesia (PPE), or hand-foot syndrome (HFS).1-5 HFS is a rare cutaneous reaction to certain chemotherapeutic agents that can be severe and debilitating and may cause a delay in chemotherapy administration. Docetaxel has been infrequently reported to cause HFS.1-5 We report the clinical and histopathological details of five cases that occurred with docetaxel in different modes and timing of administration.

**Patient 1**
A 54-year-old woman with breast cancer on adjuvant dose-dense chemotherapy AC-T (Adriamycin, cyclophosphamide, Taxotere) developed severe itching and burning in her palms and soles followed by severe facial erythema 2 days after the second cycle of docetaxel (100mg/m² IV infusion over 1 hour every 2 weeks). Toxicity was consistent with HFS. The patient refused the last dose of docetaxel. She was referred for radiation therapy and was given letrozole as adjuvant hormonal therapy (Table 1).

**Patient 2**
A 56-year-old female with breast cancer was treated with modified radical mastectomy (MRM) followed by adjuvant dose dense AC-T chemotherapy supported by filgrastim (granulocyte colony-stimulating factor, G-CSF). Two days after the third cycle of docetaxel (100mg/m² IV infusion over 3 hours every 2 weeks), she developed erythema, edema, itching, and desquamation over the face, feet, and hands (Figure 1). A punch skin biopsy from her upper extremity showed focal parakeratosis in the epidermis with mild spongiosis, scattered dyskeratosis, squamation of the epithelial cells and maturation disarray. Dermal changes included mild to moderate edema, dilated blood vessels, a mild perivascular and interstitial lymphocytic inflammatory cell infiltrate, neutrophils and nuclear debris (Figure 2). She was diagnosed with HFS and her lesions resolved over 2 weeks. The patient refused the fourth dose of docetaxel and was started on adjuvant hormonal therapy.

**Patient 3**
A 61-year-old female with breast cancer treated with 4 cycles of neoadjuvant AC chemotherapy followed by MRM (cyclophosphamide, doxorubicin). After surgery, the patient was given docetaxel at 100 mg/m² IV infusion over 1 hour every 3 weeks. Seven days after the third cycle of docetaxel, she developed a non-pruritic skin erythema over the neck, palms, and soles consistent with HFS. The skin lesions progressed to desquamation and then resolved over 2 weeks. A fourth dose of docetaxel was omitted.

**Patient 4**
An 81-year-old female with left breast cancer was treated with mastectomy and adjuvant chemotherapy with 3 cycles of FEC (5-FU, epirubicin, cyclophosphamide) followed by docetaxel (100mg/m²).

---

**Table 1. Relationship of hand-foot syndrome (HFS) to docetaxel use.**

| Patient | 1 | 2 | 3 | 4 | 5 |
|---------|---|---|---|---|---|
| Adjuvant chemotherapy regimen | AC-T | AC-T | AC | FEC-D | D |
| Timing of HFS after docetaxel dose | 2nd | 3rd | 3rd | 2nd | 1st |
| Dose dense docetaxel | Yes | Yes | No | No | No |
| G-CSF use | Yes | Yes | No | No | No |
| Peg G-CSF | No | No | No | No | No |
| Chemotherapy stopped/delayed/modified | Yes | Yes | Yes | Yes | Yes |

AC-T: Cyclophosphamide, doxorubicin, paclitaxel; FEC: 5-FU, epirubicin, cyclophosphamide, D: docetaxel
brief report

every 3 weeks. After a second cycle of docetaxel, she developed skin erythema, and burning and itching over both hands and feet consistent with HFS. The lesions resolved in one week. Docetaxel was omitted and was replaced by additional cycles of FEC chemotherapy regimen.

Patient 5
A 49-year old female with right breast cancer was on adjuvant docetaxel chemotherapy (100mg/m2) infusion over one hour, without any G-CSF support. Four days following the first dose of docetaxel, the patient complained of erythema, a burning sensation and painful swelling over the heels, soles, and palms (Figure 3). She had red plaques over the dorsa of the hands, wrists, and toes. Pathological findings were mild perivascular inflammatory cell infiltrate composed of lymphocytes and neutrophils with nuclear debris. The clinical presentation was consistent with HFS. The patient was treated with emollient creams and topical steroids with gradual resolution of symptoms over 2 weeks. Docetaxel was replaced by paclitaxel and she had no further reaction.

DISCUSSION
HFS has been described as a cutaneous side effect of cytotoxic chemotherapy with mitotane,6 capecitabine,7,8 cytarabine,9 doxorubicin,10 liposomal daunorubicin,11 liposomal doxorubicin,12 etoposide,13 hydroxyurea,14 gemcitabine and vinorelbine,15 methotrexate,16 and recently, gefitinib.17 Few reports have described HFS as a side effect of docetaxel monotherapy,1-5 or in combination with capecitabine,18 or as a result of concomitant use of pegylated G-CSF.19

Docetaxel-induced acral erythema exhibits a widespread distribution and intense sensation of intolerable pain that may involve areas other than the palms and soles, such as the face and neck as in our patients. Lesions appear as well-defined erythema and edema involving the palmar surfaces. Most reactions occur between day 4 and day 17 after chemotherapy administration.

Histologically, HFS shows mild spongiosis, scattered necrotic and dyskeratotic keratinocytes, and vascular degeneration of the basal layer,20 as seen in our patients. Dermal changes include dilated blood vessels and papillary edema, whereas a perivascular lymphohistiocytic infiltrate is seen in the epidermis.21

The pathogenesis of HFS involves skin keratinocytes which contain increased levels of the enzyme thymidine phosphorylase needed in the breakdown of 5-fluorouracil related drugs, resulting in enhanced breakdown and accumulation of cytotoxic metabolites in the skin,22 in addition to the vulnerability of tiny capillaries in the
palms and soles, which are believed to rupture under pressure from walking or use, releasing the cytotoxic agent and causing an inflammatory reaction. This makes drugs that have sustained or protracted serum levels such as liposomal doxorubicin and capecitabine more likely to cause HFS. Other possible pathophysiologic mechanisms include dihydropyrimidine dehydrogenase deficiency.

HFS is generally self-limited. No standard therapy is recommended, but several symptomatic and prophylactic treatments have been used to alleviate symptoms including steroid ointments, occlusive dressings, COX-2 inhibitors, oral pyridoxine (50-150 mg/day), blood flow reduction and local hypothermia, frozen gloves, topical dimethylsulfoxide, and oral vitamin E therapy (300 mg/day). However, the only proven method for managing HFS is treatment modification, be it interruption or dose reduction. In all of our five patients, HFS lesions were debilitating enough to result in stopping docetaxel therapy and replacing it with other chemotherapy regimens. Patients received palliative therapies consisting of emollient creams, systemic steroids, and pyridoxine 150mg/day over 2 weeks with lesions disappearing gradually over several weeks with no consequences.

HFS was not reported in CALGB trial 9741 in which only nonpegylated G-CSF was used, but was reported in cases treated similarly with the addition of pegylated G-CSF. The authors suggested that pegylation of filgrastim may have contributed to the HFS. They hypothesized that pegylation of filgrastim augments and prolongs the neutrophil infiltration in some patients, mediating the inflammation observed with HFS.

In our present case-series, HFS developed in patients treated with docetaxel in different combinations of therapy: docetaxel preceded by AC, docetaxel preceded by FEC, and docetaxel with and without G-CSF support, but without any pegylated-G-CSF. Moreover, HFS occurred invariably after a single cycle or multiple cycles of docetaxel. Hence, the dose-dense mode of docetaxel administration was not the cause of HFS as symptoms developed after one cycle only (patient number 5). Observations from the five cases reported highlight docetaxel as an etiologic agent of HFS irrespective of the concomitant use of other chemotherapeutic agents, use of G-CSF in its pegylated or non-pegylated forms, or number of cycles and/or time lapse between cycles.
REFERENCES

1. Chu CY, Yang CH, Yang CY, Hsiao GH, Chiu HC. Fixed erythrodysesthesia plaque due to intravenous injection of docetaxel. Br J Dermatol. 2000;142:808-11.
2. Schrijvers D, Van Den Brande J, Vermorken JB. Supraventricular discoloration of the skin due to docetaxel-treatment. Br J Dermatol. 2000;142:1069-70.
3. Eich D, Scharfetter-Kochanek K, Eich HT, Tantcheva-Poor I, Krieg T. Acral erythrodysesthesia syndrome caused by intravenous infusion of docetaxel in breast cancer. Am J Clin Oncol. 2002;25:699-702.
4. Zimmerman GC, Keeling JH, Bursis HA, Cook G, Irvin R, Kuhn J, et al. Acute cutaneous reactions to docetaxel, a new chemotherapeutic agent. Arch Dermatol. 1995;131:202-6.
5. Katah M, Kadota M, Nishimura Y. A case of docetaxel-induced erythrodysesthesia. J Dermatol. 2000;34:403-406.
6. Zuelike RL. Erythematous eruption of the palms and soles associated with mitotane therapy. Dermatologica. 1974;148:90-2.
7. Gressett SM, Stanford BL, Hardwicke F. Management of hand-foot syndrome induced by capecitabine. J Oncol Pharm Pract. 2006;12:131-41.
8. Abushullaih S, Saad ED, Munself M, Hoff PM. Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. Cancer Invest. 2002;20:3-10.
9. Crawford JH, Eikelboom JW, McQuillan A. Recurrent palmar-plantar erythrodysesthesia following high-dose cytarabine treatment for acute lymphoblastic leukemia. Eur J Haematol. 2002;69:315-17.
10. O’Brien ME, Wigler N, Iobar M, Rosso R, Grischke E, Santoro A, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/ Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004;15:440-9.
11. Hui YF, Cortes JE. Palmar-plantar erythrodysesthesia syndrome associated with liposomal daunorubicin. Pharmacotherapy. 2000;20:1221-23.
12. D’Agostino G, Ferrandina G, Ludovisi M, Testa A, Lorusso D, Gbaguidi N, et al. Phase II study of liposomal doxorubicin and gemcitabine in the salvage treatment of ovarian cancer. Br J Cancer. 2000;83:1180-84.
13. Portal I, Cardenal F, Garcia-del-Muro X. Etoposide-related acral erythema. Cancer Chemother Pharmacol. 1994;34:181.
14. Silver FS, Espinoza LR, Hartmann RC. Acral erythema and hydroxyurea. Ann Intern Med. 1983;98:675.
15. Laack E, Mende T, Knuftmann C, Hossfeld DK. Hand-foot syndrome associated with short infusions of combination chemotherapy with gemcitabine and vinorelbine. Ann Oncol. 2001;12:1761-63.
16. Feizy V, Namazi MR, Barikbin B, Ehsani A. Methotrexate-induced acral erythema with bulous reaction. Dermatol Online J. 2003;9:14.
17. Razis E, Karina M, Karanastassi S, Fountzilas G. Three case reports of hand-foot syndrome with gefitinib. Cancer Invest. 2006;24:514-6.
18. Mrozek E, Ramaswamy B, Young D, Rhoades CA, Kendra K, Allen J, et al. Phase II study of weekly docetaxel and capecitabine in patients with metastatic breast cancer. Clin Breast Cancer. 2006;7:141-5.
19. Bardia A, Loprinzi CL, Goetz MP. Hand-foot syndrome after dose-dense adjuvant chemotherapy for breast cancer: a case series. J Clin Oncol. 2006;24:18-9.
20. Gordon KB, Tajuddin A, Guitart J, Kuzel TM, Eramo LR, VonRonnen J. Hand-foot syndrome associated with liposome-encapsulated doxorubicin therapy. Cancer. 1995;75:2169-73.
21. Nagore E, Insa A, Sammartin G. Antineoplastic therapy-induced palmar plantar erythrodysesthesia (‘hand-foot’) syndrome. Incidence, recognition and management. Am J Clin Dermatol. 2000;1:225-34.
22. Agasii MM, Haggerty JG, McNiff JM, Milstone LM, Schwartz PM. Expression and localization of thymidine phosphorylase/platelet-derived endothelial cell growth factor in skin and cutaneous tumors. J Cutan Pathol. 1999;26:287-94.
23. Lin EH, Morris J, Chau NK, Crane C, Wolff R, Janjan, N, et al. Dexamethasone attenuated capecitabine-induced hand-and foot syndrome (HFS) and diarrhea and improved time to tumor progression in metastatic colorectal cancer. Proc Am Soc Clin Oncol. 2002;21 (abstr 2364).
24. Wilkes GM, Doyle D, Palmer-plantar erythrodysesthesia. Clin J Oncol Nurs. 2005;9:105-8.
25. Saif MW, Effky A, Diasio R. Hand-foot syndrome variant in a dihydroxyproline dehydrogenase-deficient patient treated with capecitabine. Clin Colorectal Cancer. 2006;5:219-23.
26. Lin E, Morris JS, Ayers GD. Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. Oncology (Williston Park) 2002;16(suppl):S17-7.
27. Yuvelja SJ, Baker WJ, Bursis HA 3rd, Keeling JH, Von Hoff D. Pyridoxine therapy for palmar-plantar erythrodysesthesia associated with taxotere. J Natl Cancer Inst. 1993;85:1432-33.
28. Vail DM, Chun R, Thamm DH, Garrett LD, Cooley AJ, Obradovich J. Efficacy of Pyridoxine to ameliorate the cutaneous toxicity associated with Doxorubicin containing pegylated ( Stealth) liposomes: a randomized, double-blind clinical trial using a canine model. Clin Cancer Res. 1998;4:1567-71.
29. Zimmerman GC, Keeling JH, Lowry M, Medina J, Von Hoff DD, Bursis HA. Prevention of docetaxel-induced erythrodysesthesia with local hypo-thermia. J Natl Cancer Inst. 1994;86:557-8.
30. Scottle F, Tourani JM, Banu E, Peyroumaur M, Levy E, Marsan S, et al. Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol. 2005;23:4424-9.
31. Lopez AM, Wallace L, Dorr RT, Koff M, Hersh EM, Alberts DS. Topical DMSO treatment for pegylated liposomal doxorubicin-induced palmar-plantar erythrodysesthesia. Cancer Chemother Pharmacol. 1999;44:303-4.
32. Kara ID, Sahin B, Ersikli M. Palmer-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. Breast. 2006;15:414-24.
33. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome. Insights from clinical trials evaluating capecitabine. Oncology (Williston Park). 2004;18:1161-4,1173; discussion 1175-6, 1181-4.