brief report

# Hand-foot syndrome with docetaxel: a five-case series

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Chemotherapeutic agents may be associated with maculopapular rashes, hyperpigmentation, nail changes, and an acral erythema known as Bergdorf's reaction, palmoplantardysesthesia (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/m$^2$ 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).

**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

*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 (granulocyle conlony-stimulating factor, G-CSF). Two days after the third cycle of docetaxel (100 mg/m2 IV infusion over 3 hours every 2 weeks), she developed erythema, edema, itching, and 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, squamazation 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/m$^2$ 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 (flurouracil, epirubicin, and cyclophosphamide) followed by docetaxel (100mg/m$^2$)

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 vacuolar 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

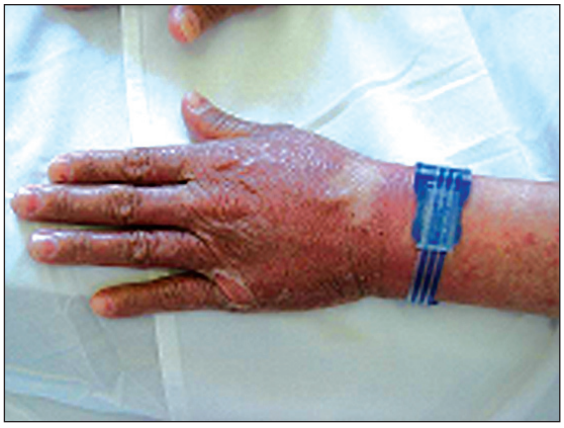

**Figure 1.** Erythema, edema, itching, and desquamation over the hands two days after the third cycle of docetaxel.

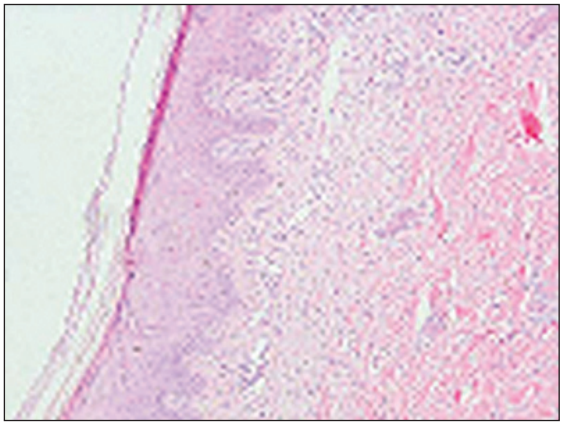

**Figure 2.** Focal parakeratosis in the epidermis with mild spongiosis, scattered dyskeratosis, squamatization of the epithelial cells and maturation disarray (hematoxylin-eosin, × 40).

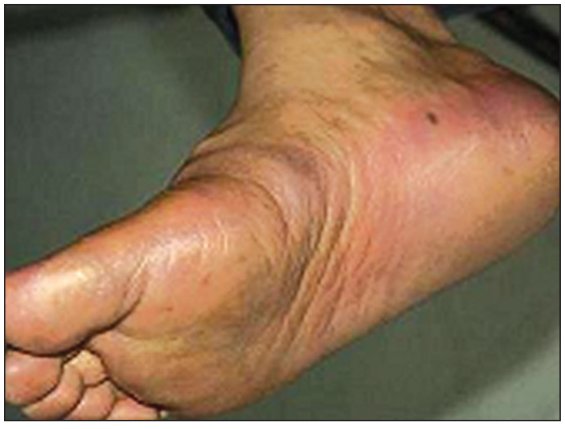

**Figure 3.** Erythema and swelling over heels and soles 4 days following the first dose of docetaxel.

palms and soles, which are believed to rupture under pressure from walking or use, releasing the cytotoxic agent and causing an inflammatory reaction.[23,24] 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.[25]

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,[15] COX-2 inhibitors,[26] oral pyridoxine (50-150 mg/day),[27,28] blood flow reduction and local hypothermia,[29] frozen gloves,[30] topical dimethylsulfoxide,[31] and oral vitamin E therapy (300 mg/day).[32] However, the only proven method for managing HFS is treatment modification, be it interruption or dose reduction.[3,21,33] 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.[19] 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 preceeded by AC, docetaxel preceeded by FEC, docetaxel monotherapy, 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.

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