Oral Capecitabine - Can It Cause The Hand-Foot Syndrome?

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ABSTRACT

The Hand Foot Syndrome (HFS) or palmo-plantar erythrodysesthaesia (PPE) manifests as acral erythema with swelling and dysesthaesia of the palms and the plantar aspects of the feet, which in the absence of dosage reduction or drug cessation, progresses to moist desquamation and ulceration, resulting in serious infections and loss of function [1].

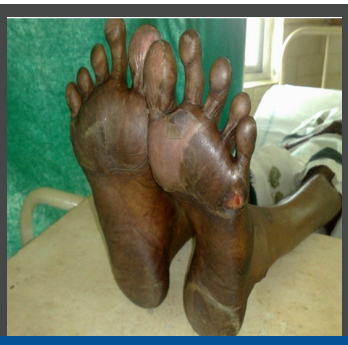
The Hand –foot syndrome is a cutaneous adverse event which is associated with various anti- cancerous chemotherapeutic drugs viz; capecitabine, 5-fluorouracil, cytarabine, doxorubicin, epirubicin, fluorodeoxyuridine(FUDR), mercaptopurine, cyclophosphamide, docetaxel, [2] gemcitabine, sunitinib, erlotinib and sorafenib [3], idarubicin [4], vinorelbine [1], high dose interleukin(IL2) [5] , hydroxyurea [6], mitotane, and thiotepa. Although the pathogenesis of HFS is not fully understood, it is suspected that it may be caused due to damaged deep capillaries in the soles of the feet and on the palms of the hands, leading to a COX inflammatory-type reaction, or that it is related to the enzymes which are involved in the metabolism of capecitabine, namely, thymidine phosphorylase and dihydropyrimidine dehydrogenase. Ethnic variations in the clinical manifestation of HFS warrant further attention, and an alternative system for grading HFS in non-white patients has been proposed [7].

We report here, a case of HFS, induced by oral capecitabine, with moist desquamation and ulceration over the feet and hands.

Key Words: Hand-foot syndrome, Capecitabine, Palmo-plantar erythrodysesthesia

CASE REPORT

A 50 year old female who was diagnosed with carcinoma of the breast, stage 3 ,was advised tab capecitabine 900mg per day, tab lapatinib 250mg.qid and inj.docetaxel 110 mg i.v over 1hr, after undergoing right sided modified radical mastectomy.The patient did not reveal any adverse effects other than nausea; vomiting and anorexia during the first cycle of chemotherapy and neither did her laboratory reports detect any abnormality. After the second cycle of chemotherapy, the patient complained of severe diarrhoea, for which she was adequately treated. After the third cycle, it was noticed that the patient was suffering from mild erythema and black discolouration of the palms and soles, and her laboratory reports revealed that she had normocytic hypochromic anaemia. The patient was advised to use moisturizing creams on the hands and soles, and to use lukewarm water or cold water for daily use. Fourteen days after the fourth cycle of chemotherapy, the patient was admitted to the ward with complaints of painful desquamation of the skin over the hands and the soles.She was diagnosed as HFS, grade 3. Her chemotherapy was stopped and she was treated with tab pyridoxine, inj ceftriaxone, inj metronidazole, tab B-complex, cap Rabeprazole, Iron supplements, urease cream, moisturizing cream and gentian violet paint for local application. Gradual improvement was noticed and the symptoms resolved completely within four months. [Table/Fig 1]



[Table/Fig 1]:]: Photo showing grade 3 HFS

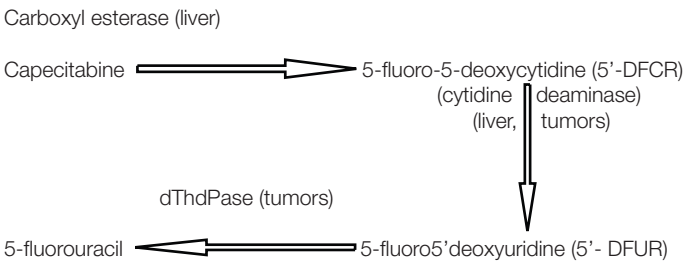
DISCUSSION

Capecitabine is a fluoropyrimidine carbamate which is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is converted eventually to 5'-FU (5-Fluorouracil).

The conversion of 5'-deoxy-5-fluorouridine (5'-DFUR) to 5-FU is enzymatically catalyzed by thymidine phosphorylase (dThdPase), which is much highly expressed in many types of human tumours than in the healthy tissues. For this reason, it is thought that capecitabine has an improved bioavailability and selective distribution and that it is more effective than 5-FU. Capecitabine undergoes a three step enzymatic conversion, as shown in the figure below [8].

The hand-foot syndrome occurs when small amounts of chemotherapy leak out of the capillaries (small blood vessels) in the hands and feet. Once out of the blood vessels, the chemotherapy damages the surrounding tissues. Although it is less common, the hand-foot syndrome can also occur on other areas of the skin, such as on the knees and elbows [9].

Another theory states that many chemotherapeutic drugs concentrate in the endocrine sweat glands or ducts, such as those found in the palms and soles, the damage to which is then caused by local drug accumulation [10].

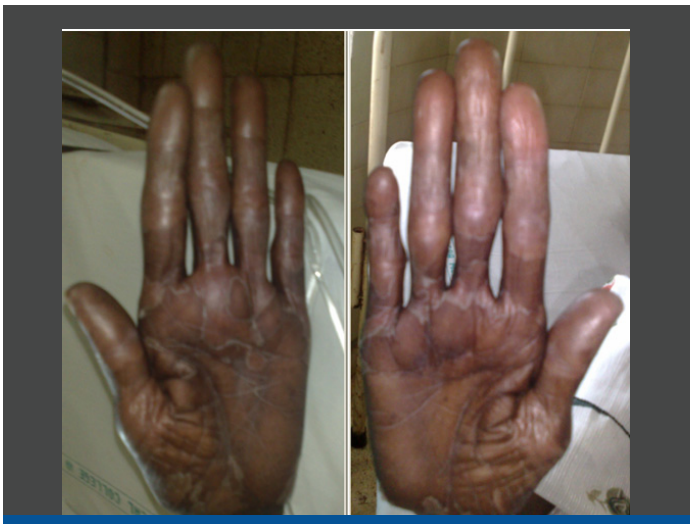


HFS is characterized by paresthaesiae in a sock-and-glove distri-

bution, followed by painful swelling and erythema. The skin may break down; and in severely affected patients, it desquamates upon the discontinuation of therapy. Different histological patterns have been described in the past. More recently, Gordon et al. described two cases of HFS which were caused by the administration of liposomal doxorubicin and suggested the possibility of the drug having a direct toxic effect on the basal keratinocytes[11].

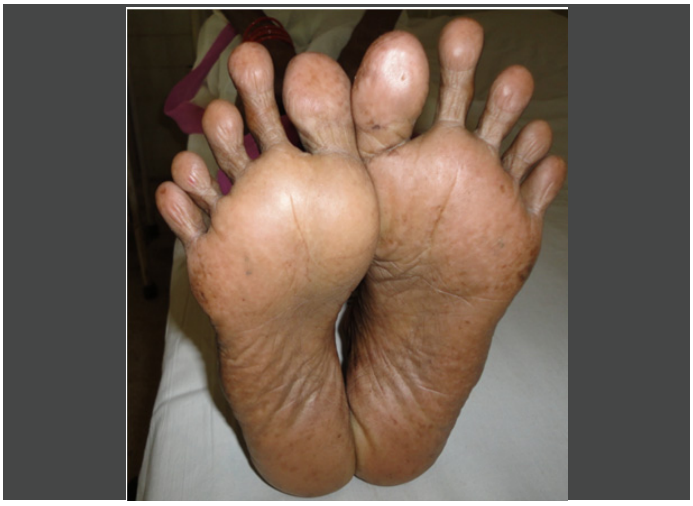
Unfortunately, no biopsy samples were obtained from our patients during the acute phase of the HFS. The dose limiting adverse effects which are associated with capecitabine are diarrhoea, hand-foot syndrome and hyperbilirubinaemia. Nausea, stomatitis, fatigue, abdominal pain, anorexia, sores in the mouth and throat numbness, tingling, itching on the hands or feet, decreased white blood cell count with an increased risk of infection, decreased platelet count with an increased risk of bleeding, decreased red blood cell count with an increased risk of tiredness (fatigue) and the feeling of pins and needles in the hands and feet, are the other observable adverse effects [12].

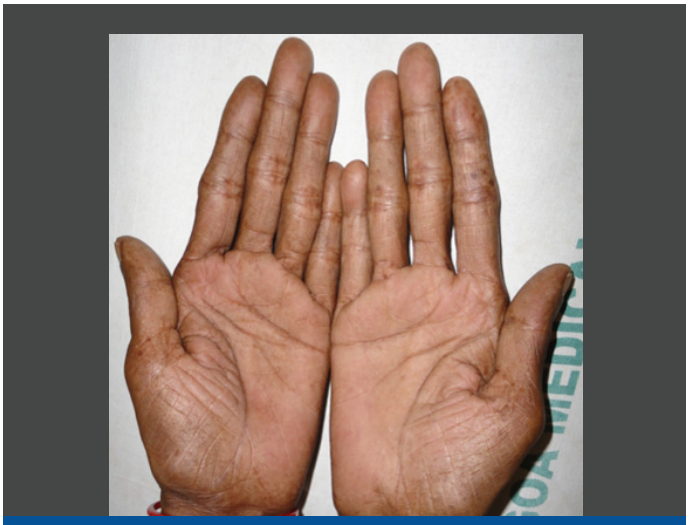
The most notable toxicities which are observed with oral capecitabine and i.v.docetaxel combination therapy are neutropaenia, hand-foot syndrome, infection, myalgias, fatigue, and diarrhoea, in this order of incidence [13]. [Table/Fig 2]



[Table/Fig 2]: Photo showing grade 3 HFS

The manifestations of HFS are graded [14] according to severity as-Grade 1 -consists of erythema of the lateral aspects of the fingers that progress to the thenar and hypothenar eminences, with swelling, numbness, dysesthaesia/ paresthaesia and tingling, especially over the pads of the distal phalanges. The same manifestations occur on the soles, but less frequently on the dorsal aspects of the hands and feet. The discomfort does not disrupt the normal activities. [Table/Fig 3]





[Table/Fig 3]: Photo taken after treatment

Grade 2- a progression of grade-1 manifestations, where pain and discomfort affect the daily activities of the patient. Grade 3- is the superimposition of blistering and moist desquamation and ulceration, coupled with severe pain, severe discomfort, and inabililty to work or perform the activities of daily living.

The pathophysiology of HFS is largely unknown, with only a few cases having been investigated via biopsies. The pathological changes which have been described thus far include the vacuolar degeneration of the basal keratinocytes, dermal perivascular lymphocytic infiltration, apoptotic keratinocytes and dermal oedema [4].

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