

Capecitabine Induced Hand-Foot Syndrome—A Case Report

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ABSTRACT

Hand and foot syndrome (HFS) is a dose limiting dermatological toxic reaction of some chemotherapy agents like Capecitabine. Though not being life threatening, patient's quality of life is compromised secondary to this syndrome. Early detection, dose reduction and interruption of the causative agent have been found to be key in management of HFS. We report a case of a 74-year-old female patient diagnosed with a metastatic rectal adenocarcinoma who received capecitabine as her management, while on treatment she developed signs and symptoms consistent with HFS. The chemotherapy agent was interrupted, and emollients were given to her as management.

Keywords: Cancer, Capecitabine, Colorectal, 5-Fluorouracil, Hand-Food Syndrome, Chemotherapy, Side Effects

INTRODUCTION

The Hand and foot syndrome (HFS) also known as palmar-plantar erythrodysesthesia has been associated with capecitabine as its most common dose limiting side effect [1]. It has been previously reported that 45 to 56% of patients who took capecitabine developed hand and foot syndrome as a major side effect [2]. Capecitabine an oral fluoropyrimidine carbamate is a pro drug of 5-FU (5 fluorouracil), a cytotoxic agent that may have preferential effects on tumor cells as compared to normal cells. In practice, despite its preference to 5-FU due to its tolerability it has shown no decrease in the incidence and severity of HFS.

The use of capecitabine has widely evolved in colorectal cancers where it is has proved to be more efficacious combined with other cytotoxic agents than as a single agent [3]. It is converted to its active form 5-FU through 3 enzymatic reactions; first in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR) then by cytidine deaminase to 5'-deoxy-5-fluorouridine (5'-DFUR) and finally to 5-FU the active drug through hydrolysis by thymidine phosphorylase, a platelet derived endothelial cell growth factor. The mechanism of capecitabine causing HFS is not well understood despite the accumulation of 5-FU or its metabolites have been highlighted as the probable mechanism behind this syndrome [4].

Hand and foot syndrome is characterized by a prodrome of dysesthesias in the palms and soles, that presents with tingling

in hands and foot, later on progressing to erythema, pain and edema for about 3 to 4 days. If the causative agent is not interrupted these symptoms may progress further to skin breakdown and desquamation. HFS onset has been reported to appear often at about 79 days post treatment, the side effect timing ranging from 11 to 360 days[3]. Drug discontinuation induces gradual regeneration of the skin and pigmentation within 5 to 7 days, ascertaining the best treatment approach in patients with severe HFS as interruption of the causative agent. Several other chemotherapy agents like doxorubicin, cytarabine, and docetaxel have also been linked to this syndrome though more pronounced secondary to capecitabine / 5-FU [5].

CASE PRESENTATION

A 74 year- old African woman of Rwandan nationality with a diagnosis of locally advanced rectal adenocarcinoma in November 2017 was treated with neo-adjuvant radiation 25Gy in 5 fractions and thereafter she underwent abdominal perineal resection of the tumor with a permanent colostomy. She did not get any adjuvant chemotherapy then. In February 2019, she presented to the hospital complaining of lower back pain with an onset dating from December 2018 and increasing in intensity.

Clinical findings and therapeutic intervention

On physical examination, she was not able to stand or sit because of back pain and could only walk with assistance. She described

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the back pain as 8/10 as per the WHO pain scale. An MRI of the spine and pelvis was requested which revealed bone marrow infiltrative changes in L4 vertebral body and a 3.5cm lesion on the left iliac blade. A restaging CT chest and abdomen was requested which found bilateral lung metastasis. In February 2019 she was started on palliative chemotherapy with Capecitabine to be taken as 1250mg/m² twice per day for two weeks every 21 days. She was also started on Zoledronic acid. In March 2019 after two cycles, the patient reported significant improvement since she was able to walk alone without assistance. She only complained of tingling in the toes and soles of her feet plus her fingers that she was worse when it was cold. A few days into her third cycle in April 2019, she noticed black pigmentation in her palms and sole of her feet (Figure 1) but there was no numbness or dysesthesia.



Figure 1: Hands after first cycle of capecitabine

We continued her on treatment, but she returned a week later complaining of diarrhea, nausea, vomiting and this time with severe pigmentation and dryness of her palm skin (Figure 2).



Figure 2: Hands after first cycle of capecitabine

Because of these symptoms we held the drug and planned to resume a week later with a dose reduction. She came back with peeling off of the skin but her diarrhea and vomiting resolved. We held the chemotherapy for a total of one month and prescribed topical emollients to be applied on her feet and palms. She returned after a month and all symptoms including her hand discoloration (Figure 3) had resolved.



Figure 3: Hands a month after chemotherapy was held

DISCUSSION

In 1984, Lokich and colleagues described the Hand-Foot Syndrome (HFS) induced by 5-Fluoropyrimidines [6]. Hence it has been well known that most 5FU substrates could cause HFS. Capecitabine is an oral fluoropyrimidine that is designed to allow 5FU activation within the tumor tissue [7]. Usually, Capecitabine is a well-tolerated oral replacement of the intravenous (IV) 5FU but as with IV 5FU, HFS is a well-known common side effect. In cases like the one described above with both metastatic colon cancer and especially with older patients, oral drugs that are usually known to be tolerated are the best choice. HFS has been reported in 43% to 71% of patients treated with a single agent capecitabine [8,9]

The mechanism by which capecitabine causes HFS is not well known. The two hypothesis is that the 5FU metabolites and not the 5FU itself could be the cause of HFS and another theory is that capecitabine might be excreted by eccrine glands and that the resulting excreted metabolites cause HFS [10]. A similar mechanism, the Hand and Foot Skin Reaction (HFSR) has been described as a side effect of Tyrosine Kinase Inhibitors (TKIs) and exhibits similar histopathologic features as HFS [11-13]. As broad as TKIs are in their therapeutic functions, attempts to characterize the pathogenesis have led to conclusion that inhibitions of several pathways (Vascular Endothelial Growth Factor and Platelet Derived Growth Factor among others) could be essential to bring about the HFSR syndrome [14]. Several studies have showed that there are genetic differences that might be associated with increased cytotoxicity including HFS caused by capecitabine [15]. Such biomarkers include genetic polymor-

phisms in MTHFR and TYMS that were found to be associated with capecitabine-induced HFS in patients with metastatic breast cancer [16]. Additionally, deficiency in DPYD gene can result to accumulation of capecitabine in the body [17]

Similar cases have been presented elsewhere, relating to a more distinct thickening of the hands and feet in black populations, with the use of exact daily dosages of capecitabine, hence suggesting an ethnicity background in the syndrome severity, beyond the generalization of the current toxicity grading systems [18-20]. Of note, this patient did not get full course of treatment, as she should have got adjuvant chemotherapy as per standard protocol. With the availability of radiotherapy, chemotherapy and surgical capacities in Rwanda, it is important that multidisciplinary approach to cancer care be encouraged.

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CONCLUSION

Oral capecitabine is a good alternative for 5-FU especially in metastatic settings. It is however associated with Hand and Foot Syndrome (HFS) as its common adverse feature. Several medications including Dihydro-Pyrimidine Dehydrogenase (DPD) inhibitors have been tried but with no success. It is necessary to be very cautious and utilize capecitabine at lower doses especially with older patients. Black patients often have darkening of the skin of the palms and soles not seen in other races. More studies are therefore needed to understand the mechanisms associated with HFS in different races and ethnicities especially of African origin.

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