INTRODUCTION

The Hand and foot syndrome (HFS) also known as palmar-plan tar erythrodysthesia 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 prefer- ential 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 [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
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 resting 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 cy-
cles, the patient reported significant improvement since she was
able to walk alone without assistance. She only complained of tin-
gling 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.

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 pre-
scribed 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.

DISCUSSION

In 1984, Lokich and colleagues described the Hand-Foot Syn-
drome (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 al-
low 5 FU activation within the tumor tissue [7]. Usually, Cape-
citabine 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 co-
lon 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
capcitabine [8,9].

The mechanism by which capcitabine 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 capcitabine 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 inhibi-
tions of several pathways (Vascular Endothelial Growth Factor
and Platelet Derived Growth Factor among others) could be es-
sential 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
capcitabine [15]. Such biomarkers include genetic polymor-

Figure 3: Hands a month after chemotherapy was held
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 results 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.

REFERENCES


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.