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CAPECITABINE INDUCED HAND-FOOT SYNDROME IN COLON CANCER PATIENTS -A CASE REPORT OF TWO CASES

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ABSTRACT

Hand Foot Syndrome (HFS), also known as "Palmoplantar erythrodysesthesia, Acral erythema" is a cutaneous reaction caused by certain chemotherapeutic agents that manifests as varying degrees of dysesthesia, painful erythema, edema and desquamation of palms and soles. In more severe cases, the symptoms interfere with the normal activities of daily living. We report two cases of capecitabine induced HFS who received adjuvant chemotherapy with capecitabine for carcinoma of colon. While on treatment, they developed signs and symptoms of Grade 1 and Grade 2 capecitabine induced HFS. They were managed with reduction of dosage and use of topical emollients. The adverse drug reaction assessment was done using "Naranjo's causality assessment scale" which showed 'probable' type of reaction with capecitabine in both the cases. Although Hand-foot syndrome is widely regarded as a non-lifethreatning toxic reaction to cancer treatment, infectious complications of this condition can prove fatal. Prevention, early recognition and implementation of various management strategies for HFS play a vital role in minimizing unfavourable outcomes.

KEYWORDS: Capecitabine, 5FU, Hand-Foot syndrome, Adverse drug reactions, Naranjo's causality assessment scale.

INTRODUCTION

Capecitabine is a novel oral fluoropyrimide carbamate that was rationally designed to allow for selective 5-FU(5-fluorouracil) activation in tumor tissue.[1] It is converted to its only active metabolite FU(flourouracil), by thymidine phosphorylase. Higher levels of this enzyme are found in several tumors as well as in the liver, compared with normal healthy tissue.

The oral agent was initially approved by the FDA in 1998 as salvage therapy in anthracycline and taxane-resistant breast cancer. In addition, this agent is FDA approved for use in the first line treatment of metastatic colorectal cancer and as adjuvant therapy of stage III colon cancer when fluoropyramidine therapy alone is preferred.[2]

Currently capecitabine is used in combination with Oxaliplatin/Irinotecan for the treatment of advanced colorectal cancer and incorporating capecitabine in combination with radiation therapy as part of neoadjuvant therapy for locally advanced rectal cancer. Capecitabine is also active in a wide range of other solid tumors including pancreatic, gastroesophageal, ovarian and head and neck cancers.

The main toxicities include diarrhoea and hand-foot syndrome(HFS). The incidence of myelosuppression, neutropenic fever, mucositis, alopecia and nausea/vomiting is lower with capecitabine when compared with 5FU. Elevation in serum bilirubin can be observed which is usually transient and clinically asyptomatic.

Hand-foot syndrome(HFS) also referred as palmoplantar erythrodysesthesia or acral erythema is a cutaneous reaction caused by certain chemotherapeutic agents that manifests as varying degrees of dysesthesia, painful erythema, edema and desquamation of palms and soles. In more severe cases, the symptoms interfere with the normal activities of daily living. Drugs that have been associated with HFS include 5FU, capecitabine, cytarabine, doxorubicin, epirubicin, fluorodeoxyuridine(FUDR), hydroxyl urea, mercaptopurine, cyclophosphamide and docetaxel.[3,4]

We report two cases of capecitabine induced HFS managed with reduction of dosage and use of topical emollients. Our study aims to lay emphasis on the significance of patient education attempting to prevent predictable adverse drug reactions(ADR's) and therefore, it is crucial to report this ADR for better treatment outcome and improving quality of life of patients and timely recognition of its toxicities.

CASE 1

A 55 year old female patient, was presented with pain in abdomen since 1 month associated with vomiting, constipation, obstipation and no H/O hematochezia. She was diagnosed as carcinoma of colon-left side(spleen flexure growth with liver mets) with intestinal obstruction – PT3N2a, HbsAg 'positive' chronic carrier state.

Colonoscopy revealed circumferential friable polypoidal growth at splenic flexbone narrowly the lumen, scope could not be negotiated beyond growth. Biopsy confirmed adenocarcinoma. CECT abdomen reports: i) Liver- normal size with two ill defined hypodense foci with subtle peripheral rim enhancement in delayed scar seg-7 (11mm), IV B (13mm) possible mets. ii) Short segment circumferential enhancing intramucosal wall thickening causing narrowing at splenic flexure of colon(involved seg-2.4cm length and 10mm thickness).

Laboratory tests for serum electrolytes, complete blood picture, serum creatinine, complete urine examination, blood urea, uric acid levels, 2D echo (EF-70%) were with normal limits. She was planned for adjuvant chemotherapy with capeox 8 cycles (Oxaliplatin and capecitabine). She was started with oral capecitabine 500mg twice daily for 14 days followed by a 7-day tablet free interval and was asked to review on the 21st day after start of treatment.

Patient tolerated cycle 1 well. After the third cycle, she experienced tingling sensation in both her palms. Over the next 3 days, she developed erythema on her palms and soles. The patient ignored the symptoms which progressed to burning type of pain, blackish discolouration with peeling of skin and fissuring of both palms and soles. On examination, there was a patchy hyperpigmentation(blackish discolouration) of both the palms and soles [figure 1], which were more diffuse over the dorsa of all fingers and both soles. In addition, there was a moist desquamation around the toes [figure 2].

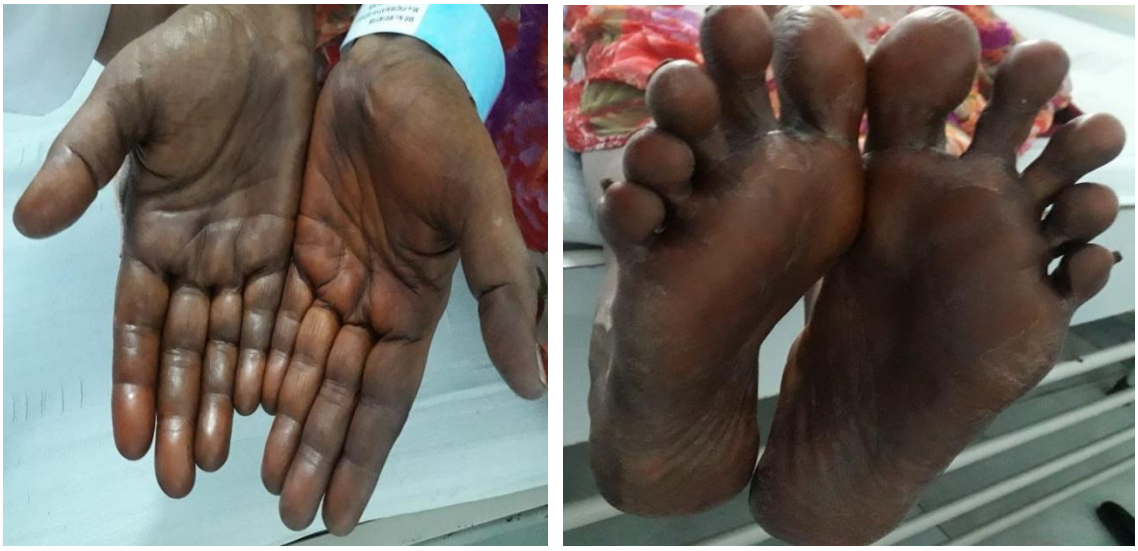

Figure 1: Views of the palms and soles in patient 1.

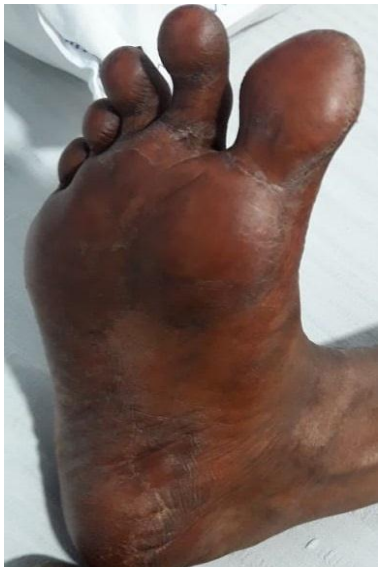

Figure 2: Discoloured peeling of skin on sole.

She was diagnosed as a case of capecitabine induced Grade-2 HFS. She was prescribed with Hafoos cream (containing urea, lactic acid and glycerine) for local application twice daily on palms and soles. On follow-up of the patient, 3 weeks later (i.e. after 21 days), there was significant reduction in the pain, peeling and the tingling and burning sensation. However, there was only a minimal decrease in the hyperpigmentation (discolouration) of the hands and feet. The adverse drug reaction assessment was done using "Naranjo's causality assessment scale" which showed 'probable' type of reaction with capecitabine. Treatment was restarted with a reduced dose of capecitabine. The patient was advised to continue topical emollients, NSAID's (Naprosyn) and follow-up after every cycle for her chemotherapy.

CASE 2

A 42 year old male patient was presented with complaints of recurrent abdominal pain, blood in stools and incomplete bowel emptying since 4 months. He was occasionally alcoholic, on physical examination P/A-soft, diffuse palpable lump in the left iliac fossa. He underwent laproscopic surgery suggestive of assisted anterior resection with colo-rectal anastomosis + jejunal resection anastomosis in 2018, He was diagnosed with carcinoma sigmoid colon PT3N0M0, Stage-II. He received palliative chemotherapy with 5 FU, oxaliplatin and leucovarin for 2 cycles.

Histology of the patient revealed sigmoid colon, Biopsy suggestive of adenocarcinoma, moderately differentiated (Tumour measures 5.5cm in greatest dimension). Colonoscopy-proliferative growth at sigmoid colon. CECT abdomen showed distal (L) colonic growth. CT abdomen revealed heterogeneously enhancing circumferential wall thickening of sigmoid colon (for a length of 77mm) with adjacent fat stranding and tiny pericolic nodes (max thickness 17mm). Chest X-ray, 2D-Echo, Serum electrolytes, Complete blood picture, liver function tests were normal. Serum CEA-1.52ng/ml (normal range: 0.0-5.0 ng/ml).

Patient developed poor tolerance and was planned for 6 cycles of oral capecitabine at a daily dosage of 1000 mg/m^2 (i.e., 500mg 3-0-3 x 14 days) every 21 days. Each cycle of therapy consisted of a 2 week of capecitabine administration, followed by a 1-week resting period. After the fourth cycle, the patient developed dry, desquamation and brownish to black hyperpigmentation on the palms, fingers and soles [Fig.3]. The patient complained of mild pain in palms and soles. He had no dysesthesia.

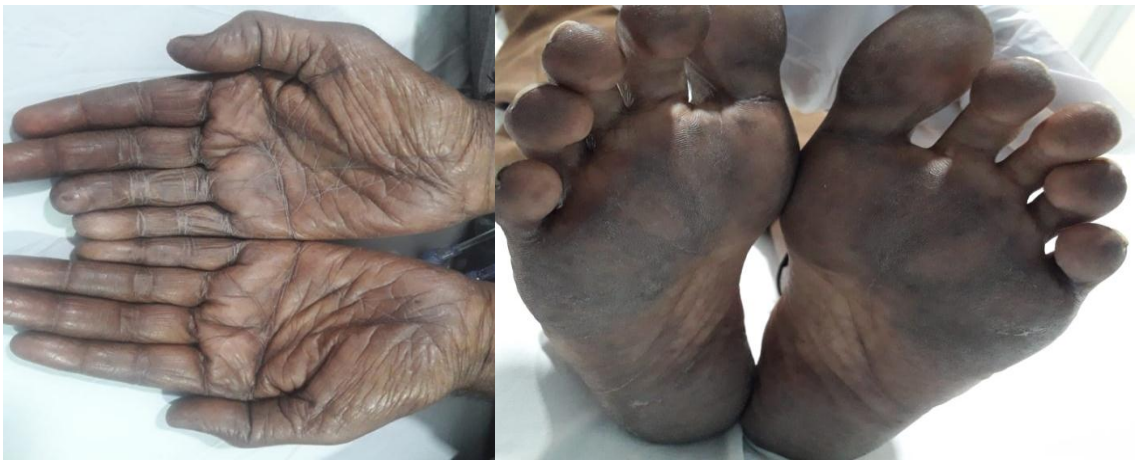

Figure 3: Hyperpigmentation, Dry, Desquamation on palms and soles in patient 2.

The HFS was attributed to capecitabine (Grade-I). Patient was managed with Hafoos cream BD for palms and soles and the dose of capecitabine was reduced to 2-0-3 x 14 days. The Adverse drug reaction assessment was done by using Naranjo's scale which showed 'probable' type of Adverse drug reaction.

DISCUSSION

Hand-Foot Syndrome or Palmar-Plantar Erythrodysesthesia was first reported by Zuelhke in 1974.Since then, there have been numerous reports of the syndrome as an adverse event in many chemotherapeutic regimen, which were mostly associated with capecitabine therapy (≥50% of the patients).[5] Capecitabine is a novel oral fluoropyrimidine carbamate rationally designed to allow selective 5-fluorouracil activation in tumor tissues. About 45-56% of the patients taking chemotherapy with capecitabine which is used as a standard drug in colorectal cancer experience the HFS. Further, due to greater efficacy on tumor bearing cells, it is used in combination with other chemotherapy agents as first line treatment in patients with advanced metastatic gastric cancer and breast cancer.

HFS manifest as various degree of dysesthesia, painful erythema and edema of palms and soles, which may be followed by desquamation of the involved skin. A grading system incorporating both clinical and functional domains have been developed. Grade 1 shows erythema of lateral aspects of fingers, progressing to thenar and hypothenar eminences, with swelling, numbness, dysesthesia, and tingling. Grade 2 shows a progression of grade-1, with the pain, tenderness and discomfort affecting daily activities. In grade-3, along with severe pain, there is also development of blisters, moist desquamation and ulcer formation.[6]

In a case report, Hyun-sook et al has conducted a study entitled "compliance and effective management of the HFS in colon cancer patients receiving capecitabine as adjuvant chemotherapy" shows that the treatment compliance rate was 90.5% (76 out of 84 patients). The HFS developed in 65 patients(77.4%). 33 patients(50.7%) had Grade 1 HF, 22 patients(33.8%) had Grade 2 HFS and 10 patients(15.5%) had grade3 HFS, as their most severe episode.[8]

The exact mechanism of capecitabine induced HFS is unknown, but there are three leading hypothesis explaining its development. The first one proposes the involvement of skin keratocytes resulting in accumulation of capecitabine metabolites and hence a likelihood of developing HFS. The second is that the capecitabinte is eliminated by eccrine system relating

to the increase number of eccrine glands on hand and feet.[7] Finally, the third one suggest that increased vascularization and increased pressure, temperature in hand and foot may lead to manifestation.

We reported two cases of HFS development after capecitabine exposure, of which one patient was in grade-1 and other in grade-2 HFS. In both the cases, the hyperpigmentation of palms and soles ameliorated after the drug was withdrawn. Topical emollients was used as supportive measure. Keratolytics such as 40% urea or salicylic acid, lactic acid (Hafoos cream) decreases the thickness of hyperkeratotic areas and aids in natural exfoliation. Capecitabine was later re-introduced in patient's chemotherapeutic regimen following reduction in its dose.

According to one of the recent study Sarah M Gressett et al, has conducted a study entitled "Management of HFS induced by capecitabine". They concluded that treatment interruption or dose reduction remains the only methods shown to effectively manage HFS, but supportive measures(use of topical emollients and creams, systemic and topical corticosteroids, Vitamin E, pyridoxine and COX-2 inhibitors) to reduce pain and discomfort and prevent secondary infections are also very effective.[9]

The adverse drug reaction assessment was done using "Naranjo's causality assessment scale" which showed 'probable' type of reaction with capecitabine in both the cases. Treatment was restarted with a reduced dose of capecitabine. The patient was advised to continue topical emollients, NSAID's (Naprosyn) and follow-up after every cycle of chemotherapy.

Our study aims to contribute awareness from the drug related toxicities. Prompt identification and management of HFS is essential to facilitate the continuation of chemotherapy because dose reduction can postpone or undermine optimal anticancer treatment efficacy. Since capecitabine as an oral therapy is self administered by the patient, effective patient education about HFS prior to the commencement of therapy, guidance on skincare and protection is another strategy for prevention. Further, scheduling of visits with an oncologist for HFS screening and monitoring after the drug initiation, diagnosing HFS in its mild form and recognizing subsequent dermatologic complications, identifying the most effective treatment strategies are important in optimizing patient quality of life. Therefore, HFS is manageable if both patient and oncology care teams are educated promptly about it.

CONCLUSION

Although Hand-foot syndrome is widely regarded as a non-lifethreatning toxic reaction to cancer treatment, infectious complications of this condition can prove fatal. Prevention, early recognition and implementation of various management strategies for HFS play a vital role in minimizing unfavourable outcomes.

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