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Capecitabine-Induced Hand-Foot Syndrome With Genital Involvement

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Abstract

Palmar-plantar erythrodysesthesia, also known as hand-foot syndrome (HFS), is a common dermatologic toxicity of capecitabine. In this report, the case of a 59-year-old man with metastatic pancreatic ductal adenocarcinoma who developed grade 2 HFS with rare genital involvement is described. This case underscores the importance of recognizing atypical genital involvement in HFS to support timely management.

CASE STUDY

A 59-year-old Caucasian male was diagnosed with pancreatic ductal adenocarcinoma with metastasis to the peritoneum in December 2023. He completed modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) from January 2024 to September 2024, and tolerated chemotherapy without significant adverse events. In September 2024, he was enrolled in a clinical trial (CG-745-2-08, NCT05249101) in which he was assigned to receive capecitabine at 1,000 mg/m^2 orally twice daily on days 1 to 14 of every 21-day cycle in combination with an investigational histone deacetylase (HDAC) inhibitor, ivaltinostat (CG-200745), at 250 mg/m^2 intravenously over 60 minutes on days 1 and 8 of every 21-day cycle. After completing two cycles of treatment, the patient developed skin dryness, skin cracking, and redness on his palms and soles. The patient also developed skin excoriation/desquamation, bleeding, and ulceration at the glans penis, causing severe pain and discomfort with urination and movement. His pain was rated as 10/10. He reported no sexual contact while on treatment and had no history of sexually transmitted diseases. A provider evaluation determined that this was grade 2 hand-foot syndrome (HFS) defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and associated with capecitabine (National Cancer Institute, 2017; Figure 1).

On cycle 3 day 1, the ivaltinostat infusion was deferred and capecitabine was held for 1 week. Lidocaine 4% gel was prescribed to be applied topically every 6 hours on the penis for pain control and to

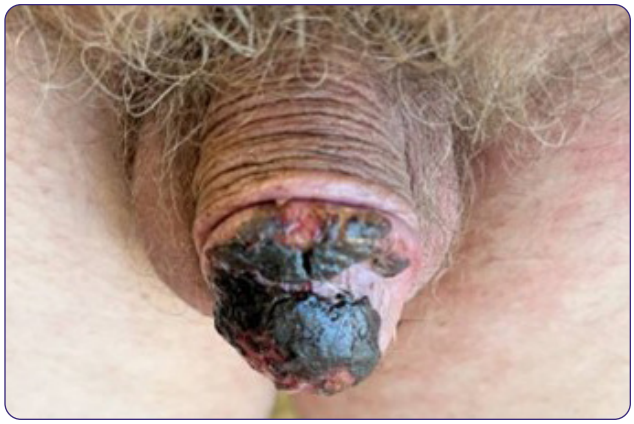

Figure 1. Grade 2 hand-foot syndrome.

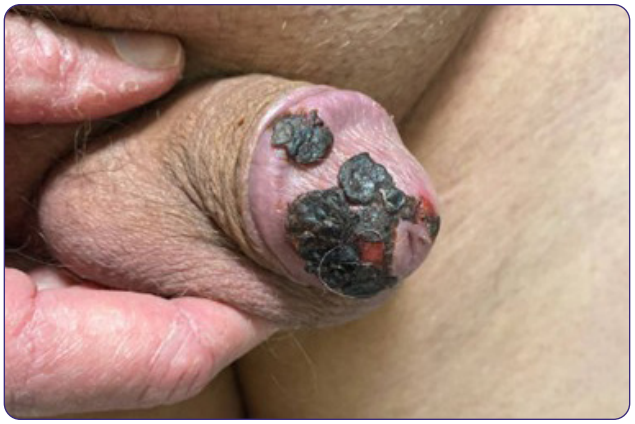

Figure 2. Grade 2 hand-foot syndrome.

alleviate discomfort. Upon reassessment after 1 week of treatment interruption, the patient reported improvement in pain to 5/10 and resolution of bleeding. Thin, dark crusts with skin ulcers formed on the glans penis (Figure 2). Therefore, ivaltinostat treatment was resumed in accordance with the clinical trial protocol, but capecitabine continued to be held for an additional week. Silver sulfadiazine 1% was prescribed to be applied topically on the penis as needed. The patient reportedly used it for 2 days. Following 1 week, the genital HFS resolved completely upon the provider's assessment. The numbness and peeling of skin on his hands and soles remained at grade 1 and had not returned to baseline at that point.

Palmar-plantar erythrodysesthesia (PPE), also known as hand-foot syndrome (HFS), is a dermatological toxicity that is commonly seen with fluoropyrimidines. The proposed pathogenesis involves a direct toxic effect of chemotherapy being absorbed by the skin cells. Symptom onset is variable and may range from 11 days to up to 1 year after therapy initiation (Gressett et al., 2006). The initial symptom is paresthesia followed by symmetrical painful erythema and edema of the palms and soles. If left untreated, the lesions may blister, desquamate, form crusts, ulcerate, or progress to epidermal necrosis (Nikolaou et al., 2016).

A prodrug is a pharmacologically inactive compound that is metabolized in the body into an active drug. Capecitabine is a prodrug that undergoes hydrolysis in the liver and tissues to form fluorouracil (5-FU), which is the active ingredient (Figure 3). Capecitabine used as a single agent or as part of a combination regimen is a maintenance option for patients with pancreatic cancer (NCCN, 2021). The risk of dermatitis is 27% to 37%, and the risk of HFS is 54% to 60% (FDA, 2015a). This case report discusses the incidence and management of capecitabine-induced HFS with a unique presentation of genital skin involvement in a patient with pancreatic cancer participating in a clinical trial.

TREATMENT OF METASTATIC PANCREATIC ADENOCARCINOMA

According to the National Comprehensive Cancer Network Guidelines, the standard first-line treatment for metastatic pancreatic adenocarcinoma typically involves fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX; category 1 recommendation) or a modified version of FOLFIRINOX (Table 1). This chemotherapy is generally continued until disease progression occurs or intolerable side effects develop, with most patients reaching a response plateau after 4 to 6 months (Walker & Ko, 2023). The NCCN Guidelines recommend that patients with stable or responsive disease after first-line therapy may either take a chemotherapy break or transition to maintenance therapy based on tolerance and the magnitude of adverse events on quality of life.

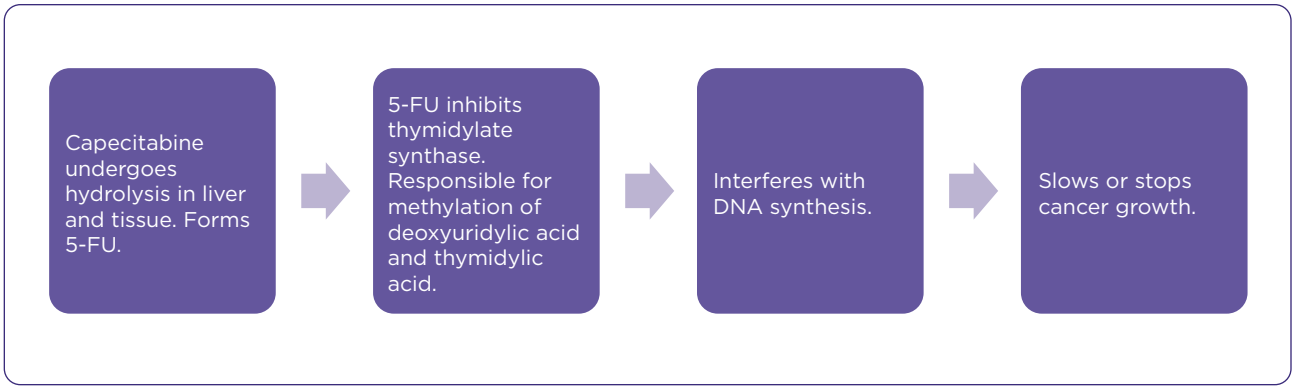

Figure 3. Mechanism of action of capecitabine.

However, the optimal maintenance therapy is not yet defined. In the absence of conclusive data, the NCCN guidelines propose several maintenance options after FOLFIRINOX, including fluorouracil, leucovorin, and irinotecan (FOLFIRI), fluorouracil, leucovorin, and oxaliplatin (FOLFOX), or capecitabine. Participation in clinical trials is also encouraged as an alternative (NCCN, 2021).

Ivaltinostat

Ivaltinostat is a histone deacetylase (HDAC) inhibitor. Histone deacetylases are enzymes that remove acetyl groups from histones, leading to chromatin condensation and decreased gene expression. Histone deacetylase enzymes are overexpressed in pancreatic ductal adenocarcinoma cells and are implicated in oncogenesis as well as tumor progression (Sim et al., 2022). By inhibiting HDACs, this drug class promotes the acetylation of histones, which neutralizes the positive charge on histones, unwrapping DNA from the nucleosome, opening chromatin, and potentially leading to increased gene transcription for genes that can suppress tumor growth. Other therapeutic effects of HDAC inhibition include inhibition of cancer cell proliferation through induced cell cycle arrest, promotion of apoptosis in cancer cells, and increase of cancer cell differentiation to a less malignant phenotype (Marks, 2010). The US Food and Drug Administration has granted ivaltinostat orphan drug designation for pancreatic adenocarcinoma (August 26, 2019), as well as hepatocellular carcinoma (August 18, 2020), and acute myeloid leukemia (January 8, 2021).

Similar drugs from the same class of medications (HDAC inhibitors) include vorinostat (Zolinza) and panobinostat (Farydak). Vorinostat is FDA approved for the treatment of cutaneous T-cell lymphoma, while panobinostat is FDA approved for the treatment of relapsed/refractory multiple myeloma (note: in December 2021, the manufacturer voluntarily withdrew the approval of panobinostat for the treatment of relapsed or refractory multiple myeloma in combination with bortezomib and dexamethasone from the US market; FDA, 2015b; FDA, 2018). Vorinostat's risk of dermatologic toxicity is 19% for alopecia and 12% for pruritus. Panobinostat's risk for cheilitis, erythema, skin lesion, or skin rash are less than < 10%. Notably, hand–foot syndrome (HFS) is not listed as an anticipated toxicity for either agent in their respective product labels (FDA, 2015b; FDA, 2018).

Common adverse events for ivaltinostat are anorexia, abdominal pain, malaise, and decreased neutrophil count (Fountzilas et al., 2024). Ivaltinostat's investigator's brochure (which was provided by the sponsor of this clinical trial, dated December 10, 2021) reports the following on the risk of dermatologic adverse effects: 5.6% (n = 1) of healthy volunteers experienced a mild drug eruption rash, and 11% (n = 2) of patients with advanced solid tumors experienced a skin rash. When given in combination with gemcitabine and erlotinib, 20% (n = 2) experienced grade 1 pruritus, and 50% (n = 5) experienced grade 1 rash. Therefore, based on the low risk and severity found in the investigator's brochure, it was determined that the patient's HFS with genital involvement was not related to ivaltinostat.

Table 1. NCCN Guidelines for Maintenance Therapy of Metastatic Pancreatic Adenocarcinoma

Preferred regimens	Other recommended regimens	Useful in certain circumstances
If previous platinum-based chemotherapy: • Olaparib (only for germline *BRCA1/2* mutations)	Clinical trial Or If previous first-line FOLFIRINOX: • Capecitabine Or If previous first-line gemcitabine + albumin-bound paclitaxel: • Gemcitabine single agent (category 2B) • Gemcitabine + albumin-bound paclitaxel modified schedule (category 2B)	If previous first-line FOLFIRINOX: • 5-FU + leucovorin • FOLFIRI • FOLFOX (category 2B) Prior platinum-based therapy • Rucaparib (for germline or somatic *BRCA1/2* or *PALB2* mutations)

Note. Patients who have response or stable disease after 4–6 months of chemotherapy may undergo a chemotherapy holiday or maintenance therapy. Adapted from NCCN (2021).

Capecitabine

Capecitabine, once converted into 5-FU, inhibits thymidylate synthase, leading to disruption of DNA replication in rapidly dividing cells (Figure 3). This effect is seen in cancer cells but can also affect healthy cells, particularly in tissues with high cell turnover. The skin on the palms of the hands and the soles of the feet is made up of rapidly dividing cells. These areas are particularly sensitive to the effects of 5-FU. The damage results in inflammation, erythema, swelling, pain, and peeling, which are characteristic symptoms of HFS. It is also proposed that 5-FU can cause changes in the microvasculature of the skin. This results in increased vascular permeability, leading to fluid accumulation and swelling in the palms and soles. The increased fluid retention in these areas contributes to the development of painful erythema, blistering, and peeling of the skin (FDA, 2015a; Cytotoxics and Antimetabolites, n.d.; Lou et al., 2016). Upon initiating therapy with capecitabine, patients are counseled on the potential side effects, including strategies to reduce the risk of HFS, such as keeping the skin clean and dry, avoiding friction and hot water, and moisturizing the skin liberally with an alcohol- and fragrance-free emollient.

CASE DISCUSSION

In this case, the genital lesion initially raised concern for necrosis due to its black, crusted appearance. However, the clinical presentation and course were more consistent with HFS involving genital skin rather than true necrosis, as there was no rapid progression, severe pain, ulceration, purulence, malodor, systemic symptoms, or laboratory evidence of infection or ischemia. Fluoropyrimidine-associated HFS may manifest with a broad spectrum of cutaneous findings, and in sensitive areas such as the genital skin, severe xerosis and desquamation may result in dark crusting, potentially exacerbated by friction, moisture, or concomitant investigational therapy. Resolution of the lesion following discontinuation of capecitabine further supports the diagnosis of HFS. A dermatology consultation was not obtained. Instead, silver sulfadiazine 1% was employed for local wound care and prophylaxis rather than as a specific HFS therapy. This case underscores the importance of recognizing atypical presentations of genital HFS to avoid misclassification as necrosis and unnecessary invasive intervention.

There are two published case reports that discuss a similar finding of HFS with genital involvement in patients receiving capecitabine. The first reported reaction by Hu et al. (2018) demonstrates HFS with scrotal and penile involvement occurred during the fifth week of neoadjuvant chemoradiotherapy with capecitabine for low rectal adenocarcinoma. Symptoms were self-limiting and improved 11 days after capecitabine discontinuation and local supportive care using petroleum jelly and non-stick gauze pads applied to the affected area. The second published case report discusses HFS with penile involvement during cycle 2 of neoadjuvant chemotherapy with capecitabine for a patient with proximal rectal adenocarcinoma (Chan & Wang, 2024). This patient, on the other

hand, was treated with nitrofurantoin as empirical management of a urinary tract infection, followed by a prescription for a topical antifungal cream and topical steroids; however, his symptoms continued to worsen. This patient was eventually evaluated by a dermatologist, who prescribed topical tacrolimus along with mupirocin, which led to prompt improvement.

Palmar-plantar erythrodysesthesia is a common dermatologic toxicity associated with certain chemotherapeutic agents, particularly capecitabine. This case highlights the essential role of advanced practitioners (APs) in managing chemotherapy-induced PPE through proactive assessment, patient-centered care, and timely interventions. By integrating preventive strategies, symptom management, and patient education, APs help bridge the gap between complex treatment regimens and optimal quality of life for cancer patients. In addition, this case exemplifies APs' increased involvement in oncology research and clinical trials, contributing to the advancement of practice as well as increased multidisciplinary collaboration with principal investigators and pharmacists to ensure comprehensive patient care.

CONCLUSION

Hand-foot syndrome is a common adverse event associated with capecitabine. However, this case report presents a severe and rare capecitabine-induced HFS with genital involvement. The patient's symptoms resolved gradually within 2 weeks using supportive care and treatment interruption.

Disclosure

The authors have no conflicts of interest to disclose.

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