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# Assessing the Clinical Impact of Palmar-Plantar Erythrodysesthesia in Patients Receiving Capecitabine Monotherapy

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## Abstract

Capecitabine is an oral fluoropyrimidine with antineoplastic activity indicated for treating colorectal and breast cancer either as monotherapy or in combination with other drugs. Palmar-plantar Erythrodysesthesia (PPE) is one of the most commonly reported side-effects of this treatment however its actual incidence and the subsequent dosing changes that it may lead to in the clinic is poorly reported. To gain more information about the clinical impact of PPE we conducted an audit of all patients treated with capecitabine monotherapy at our centre during 2014. Ninety patients were identified as receiving at least one dose of capecitabine treatment. PPE was the documented reason for dose reduction in 28 (31%) of these individuals. In addition, 7 (20%) of the breast cancer patients were converted from a 3 weekly to a less intense 4 weekly alternate dose regimen. In the colorectal cancer patients, PPE was more likely to lead to a dose reduction in those being treated with curative rather than palliative intent (49% versus 29%). An effective treatment for PPE has the potential to improve quality of life and outcomes in patients being treated with capecitabine chemotherapy.

**Keywords:** Capecitabine; Chemotherapy; Colorectal cancer; Breast cancer; Hand-foot syndrome; Palmar-plantar erythrodysesthesia

## Aim

To establish the incidence of PPE and its effects on dose intensity in patients being treated with capecitabine monotherapy.

## Introduction

Capecitabine is an oral fluoropyrimidine with antineoplastic activity indicated for treating colorectal and breast cancer either as monotherapy or in combination with other drugs (XELODA Prescribing Information). It is absorbed intact in the intestine and converted in the body to 5-fluorouracil (5-FU) by a three step enzymatic cascade. Its mechanism of activation is unique in that it exploits the high activity of Thymidine Phosphorylase (TP) in malignant cells, resulting in the generation of 5-FU preferentially in tumour tissue itself [1].

The recommended dose of capecitabine monotherapy is 1250 mg/m$^2$ administered orally twice daily (morning and evening; equivalent to 2500 mg/m$^2$ total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. In the adjuvant treatment (i.e., given after surgery with curative intent) of Colorectal Cancer (CRC), 8 cycles (24 weeks) of treatment are recommended [2]. In the palliative treatment (i.e., for incurable disease when the intent is to improve symptoms and prolong life) of breast cancer and CRC, the treatment duration may be extended if patients are both tolerating treatment well and clinically benefiting. Capecitabine may also be used concurrently with radiotherapy at the lower dose of 825 mg/m$^2$ for the neoadjuvant treatment of rectal cancer [3].

As with all chemotherapies, its use is limited by toxicities. The most common adverse reactions reported in clinical trials (≥30%) are, Palmar-Plantar Erythrodysesthesia (PPE), diarrhoea, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia [2,4,5].

PPE, also known as hand foot syndrome, Burgdorf's reaction or chemotherapy-induced acral erythema is a dermatological reaction that appears on the palms of the hand and/or the soles of the feet. It is a recognised side-effect of several anticancer agents including: capecitabine, docetaxol, cytarabine, sunitinib and sorafenib [6,7]. The exact pathogenic mechanism has not yet been fully identified and is probably different for the diverse range of agents associated with the condition. Doxorubicin and sorafenib have been postulated to cause PPE due to local delivery of high drug concentrations though eccrine glands which have their highest density in the palms and soles [8,9]. PPE may also develop preferentially due to the increased vascularization, temperature and pressure in the hands and feet in comparison to other areas of the body [10]. It has also been proposed that keratinocytes in the skin of the palms and soles may contain increased levels of TP, which leads to the production and accumulation of 5-FU through local capecitabine metabolic activation [11].

PPE has been reported to be the most common adverse effect of capecitabine containing chemotherapy affecting up to 82% of patients at some point during their course of treatment [12]. It is more likely to develop and occur with greater severity as the number of chemotherapy cycles and thus duration of treatment increases.

PPE typically presents with erythematous plaques of the hands and soles of the feet. In the most commonly used criteria - the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE version 4) [13] it is classified as grades 1-3 with increasing severity as follows:

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