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Capecitabine-induced hand foot syndrome: a brief look at possible pathways that may be associated with inflammation

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Abstract

Hand foot syndrome is a toxic reaction related to certain chemotherapy agents. Capecitabine is a prodrug used in the treatment of many cancers, such as gastrointestinal, biliary tract and breast cancers. It is associated with hand and foot syndrome (HFS), which preferentially affects palms and soles. There is still no consensus on effective international standard therapeutic strategies for the treatment and prevention of HFS because the underlying physiological and pharmacological mechanisms leading to the development of HFS have not been adequately explained. HFS is rarely life-threatening, but it may deteriorate the patient's quality of life. Quitting or a reduction in the dose of the causative drug mostly provide the amelioration of the symptoms. The aim of this review is to briefly evaluate the possible inflammatory mechanisms that may be associated with capecitabine- induced HFS.

Keywords: Capecitabine, Hand foot syndrome, Cyclooxygenase 2

Kapesitabine bağlı el ayak sendromu: enflamasyonla ilişkili olabilecek olası yolaklara kısa bir bakış

Özet

El ayak sendromu, belirli bazı kemoterapi ajanlarıyla ilişkili toksik bir reaksiyondur. Kapesitabin, gastrointestinal sistem, safra yolları ve meme kanserleri gibi birçok kanserin tedavisinde kullanılan bir ön ilaçtır. Tercihen avuç içi ve ayak tabanlarını etkileyen el ve ayak sendromu (HFS) ile ilişkilidir. HFS gelişimine yol açan altta yatan fizyolojik ve farmakolojik mekanizmalar yeterince açıklanamadığından, HFS'nin tedavisi ve önlenmesi için etkili uluslararası standart tedavi edici stratejiler üzerinde hala bir görüş birliği yoktur. HFS nadiren yaşamı tehdit eder, ancak hastanın yaşam kalitesini bozabilir. Sebep olan ilacın bırakılması veya dozunun azaltılması çoğunlukla semptomların düzelmesini sağlar. Bu derlemenin amacı, kapesitabin ile indüklenen HFS ile ilişkili olabilecek olası enflamatuvar mekanizmaları kısaca değerlendirmektir.

Anahtar Kelimeler: Kapesitabin, El ayak sendromu, siklooksijenaz-2

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INTRODUCTION

Achievements in cancer therapy and chemotherapeutics provide more treatment options and more exposure to adverse effects associated with them. A large number of mucocutaneous side effects, the exact mechanism of which is still unknown, can be induced by chemotherapeutic agents. 'Palmar plantar erythrodysesthesia (PPE)' is a cutaneous drug reaction. It is mostly developed by chemotherapeutic agents (1). 'Chemotherapy-induced acral erythema' is also termed 'palmar-plantar erythrodysesthesia', 'hand-foot syndrome (HFS)', 'Burgdorf reaction' and 'toxic erythema of palms and soles' (1,2). Hand-foot syndrome was first reported by Zuehlke et al. in 1974 as 'erythematous eruption of the palms and soles' due to mitotane therapy (3).

Most patients present with erythema, swelling, and sensory abnormalities, such as a tingling sensation and dysesthesia in the palms or soles. In severe cases, the affected skin tissue exhibits desquamation or turns into an ulcerated or blistered formation (1,4-12). HFS is rarely life-threatening, but daily activities of the patient, such as walking or holding objects, may be restricted (1,5,10). It has been shown that it can deteriorate the quality of life (5,6,8,13,14).

Different classifications for grading the degree of severity of HFS have been developed by; the 'National Cancer Institute (NCI) of the United States of America', the 'World Health Organization', and Blum et al. (1,15,16). The severity of HFS is mostly graded according to the 'National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)' or the 'World Health Organization (WHO) HFS grading scale' (1,7,12,15,17).

Although many conventional or novel agents may cause HFS, the most frequently implicated agents are 'PEGylated liposomal doxorubicin (PLD), capecitabine, 5-fluorouracil (5-FU), cytarabine, docetaxel, and tyrosine kinase inhibitors. Of these, the incidence of HFS is higher with capecitabine (between 50% and 60%) (4,8,10). Chemotherapy-induced erythrodysesthesia is termed as classic hand foot syndrome (HFS). Capecitabine-induced HFS is also involved in this group. However, 'multikinase-associated skin toxicities' are commonly termed as 'hand foot skin reaction (HFSR)' (12). Capecitabine was developed as a prodrug of 5-FU in the class known as fluoropyrimidines, including 5-FU and Tegafur. It is taken orally and is converted in vivo to cytotoxic 5-FU, which has antineoplastic activity in many cancers (1,18). Capecitabine has been used in the treatment of numerous malignancies, such as the gastrointestinal tract, pancreas, biliary tract, breast, liver, head and neck, prostate, and genitourinary tracts, due to its high bioavailability, acceptable tolerability, and targeted intratumoral activation, as indicated in its prescribing information: 'for advanced or metastatic colorectal cancer and for advanced or metastatic breast

cancer as a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated or as a regimen with docetaxel after disease progression on prior anthracycline-containing chemotherapy' (18,19). Hyperbilirubinemia, diarrhea, and HFS are the most commonly seen dose-limiting adverse effects related to capecitabine use (18).

Development and the degree of severity of HFS may be affected by multiple factors, such as the type and dose of the chemotherapeutic agent, gender, and genetic variations involved in drug metabolism, and this makes the determination of the incidence of the reaction challenging (7,9,10,20). However, it has been reported that patients treated with antineoplastic drugs develop HFS in a range of 6% to 64% (1,4,10,21-23). The exact cause of HFS remains unknown. The severity and incidence of HFS are associated with the dose administered (4,24,25). The highest incidence rates of HFS have been reported in patients treated with capecitabine and pegylated liposome-encapsulated doxorubicin treatment (7,10,20,26). HFS was found to be present in 22%–77% of patients taking capecitabine in previous studies (10,11,14). In a study of capecitabine using the Blum et al. classification system, the incidence of HFS was reported to be 68.3% (26). The minimum incidence rate of HFS in the prescribing information of capecitabine is even stated as 54% (19). It is a dermatologic toxic reaction that has a dose-dependent manner and rechallenge of patients with the causative drug mostly generates the reaction (4,5,22,26,27). Loss of fingerprints can be detected and may cause identification problems in certain patients (28). Hyperpigmentation may be seen as a consequence of capecitabine-induced HFS in African American patients (10). Quitting or a reduction in the dose of the causative drug generally improves the recovery of the symptoms (5,6,26,27). It may also cause a notable reduction in the patient's quality of life. It may require drug withdrawal or reduction, which may result in a decrease in the effectiveness of treatment and thus a disruption in the chemotherapy plans (5,14,29,30).

Pathogenesis of Capecitabine –Induced Hand Foot Syndrome

There is still no consensus on effective international standard therapeutic strategies for the treatment and prevention of HFS because the underlying physiological and pharmacological mechanisms leading to the development of HFS have not been adequately explained. The pathogenesis of HFS is thought to be different for each class of drug (4,11,29,31). Beard et al. proposed that it might be the host-versus-altered-host response, an immune-mediated response, in patients administered a continuous infusion of 5-FU (32). It is also emphasized that this mechanism may not be generalizable to drugs other than 5-FU and capecitabine (1,7,32). Another explanation for capecitabine-induced HFS has been impaired renal function, as the elimination of the metabolites is

primarily through the kidneys (8). Another theory suggests that, as a consequence of the elimination of capecitabine by the eccrine system (sweat secretion), and since the hands and feet have an increased number of eccrine glands, the accumulation of capecitabine in this specific area may lead to HFS (5,6,8,31,33,34).

Even though, the toxic metabolite/metabolites of capecitabine induced HFS are not clearly understood, one theory regarding HFS mediated by capecitabine implies that it may be related to the accumulation of capecitabine and its metabolites (5,6,31). Thymidine phosphorylase (TP), capecitabine-activating enzyme, is also angiogenic, and its expression is increased in various tumors. Asgari et al. reported that TP is found in high concentrations in keratinocytes on the palms (5,35). They also concluded in their 1999-dated study that its expression and activity show a correlation to the degree of differentiation of normal keratinocytes (35). Expression of the capecitabine-activating enzyme TP was identified as higher in the palmar skin, and it is suggested that this may be associated with the high concentration of active components level in this area. Accumulation of the capecitabine metabolite because of upgraded levels of thymidine phosphorylase in keratinocytes may lead to an increased probability of developing HFS (5,6,35). Complementary to this hypothesis, another study planned on healthy volunteers reported that intrapatient comparison of the evaluation of the difference between the palm and back areas of the hand exhibited significantly higher reactivity of TP (activating enzyme) and dihydropyrimidine dehydrogenase (DPD) (catabolic enzyme) and the proliferation marker Ki67 in the palm when compared to the back area. This higher expression of TP and DPD in the palm area results in local activation of capecitabine and this may be an explanation for the preferential specificity of HFS for the palms (36). It is suggested that the increased level of TP expression in the palm may result in cytotoxic effects related to the locally elevated production of 5-FU during capecitabine treatment, and the increased proliferation rate detected in the palm contributes to this by making these cells more sensitive to the cytotoxic effects of 5-FU that are produced locally (36). The contribution of a higher proliferation rate also supports the explanation for the localized activation of capecitabine and the preferential concentration of HFS in the palms (36). A previous supportive theory came from another study, and it was shown that patients treated with 5-FU and a DPD inhibitor and with an inherited DPD deficiency exhibited a more diminished frequency of HFS (8,37,38). These aforementioned studies make a contribution to the previous theory regarding the possible mechanism of HFS, which is based on the idea that increased vascularization, temperature, and pressure in the hands and feet may be associated with capecitabine-induced HFS (5,6). It is concluded

that this may be related to the angiogenic effects of TP, whose expression is upgraded in keratinocytes, and that angiogenic effect-mediated vascularization is implicated in playing a role in capecitabine-induced HFS (6,35,36).

A recent study also broadened the point of view on this subject and the theory that capecitabine-induced HFS may be related to the accumulation of capecitabine and its metabolites. This study, with metabolomic analysis of HFS-positive and negative cancer patients taking capecitabine, detected nine novel metabolites of capecitabine. It was shown that newly detected acetylation metabolites of capecitabine, M9/M10, formed primarily by N-acetyltransferase 2 (NAT2) and with a minor contribution by N-acetyltransferase 1 (NAT1), exhibited inhibition over the growth of HaCaT cells in a dose-dependent manner. Hydroxylation, methylation, degradation, and acetylation have been demonstrated as novel metabolic pathways of capecitabine in patients with HFS. It has been suggested that the metabolism of capecitabine may be affected by the polymorphic variants of NAT1 and NAT2 (39).

Evaluation of the histopathology of HFS exhibited epidermal changes, such as 'basal layer vacuolar degeneration, full-thickness necrosis, hyperkeratosis or parakeratosis' (1,10). Inflammatory changes, dilatation of the blood vessels, oedema, and infiltration of white blood cells were detected in the tissues affected by HFS (1,5-8,26). Cianchi et al. have shown that up-regulation of cyclooxygenase 2 (COX-2) gene expression may be associated with tumor angiogenesis in human colorectal cancer. COX-2 and vascular endothelial growth factor (VEGF) were significantly correlated with microvessel density, and it is suggested that VEGF is likely one of the most considerable mediators of the COX-2 angiogenic pathway (40). However, the exact pathogenesis of HFS remains poorly understood; its inflammatory basis has been kept in mind from the very beginning as one of the possible underlying mechanisms of HFS. It has previously been hypothesized that HFS may be a type of inflammation related to the overexpression of COX-2 formed extensively in the palm of hand and plantar of the foot that capecitabine or its metabolites may trigger directly or indirectly (6,31,41-43). In regard to this theory, a retrospective study carried out by Lin et al. has indicated that celecoxib, a specific inhibitor of COX-2, diminished the incidence of HFS in 67 metastatic colorectal cancer patients, using capecitabine (41). A prospective study carried out by Zhang et al. has also indicated that celecoxib could decrease the incidence of HFS associated with capecitabine in patients with metastatic colorectal cancer (43). The prevention of moderate to severe HFS with celecoxib was reported in a 2014-dated meta-analysis by Macedo et al (29). The potential prophylactic efficacy of oral celecoxib use for capecitabine-associated HFS was reported in a meta-analysis by Huang et al.,

highlighting the need for long-term studies of celecoxib use in order to evaluate its adverse effects (44). Another meta-analysis by Pandy et al., using only randomized controlled trials to compare the efficacy of prophylactic agents (urea cream, pyridoxine, and celecoxib) versus no prophylaxis in preventing HFS in cancer patients administered systemic cancer treatment, reported that celecoxib may be more effective for HFS associated with capecitabine (for all grades) (12). It is reported in the literature that further studies are needed in this area to provide reliable and relevant information to guide clinical practice.

The investigation of the efficacy of celecoxib in the treatment of HFS still continues, with new studies evaluating the change in its route of administration. To overcome the systemic adverse effect of celecoxib's reported gastrointestinal and cardiovascular toxicity, seen with its long-term use, a topical application form of celecoxib (a topical hydrogel of celecoxib, 1%) was recently evaluated in a pilot trial as a safe alternative for HFS associated with chemotherapy in cancer patients. Its systemic adverse effects and absorption are limited by topical application. It penetrated the stratum corneum and was distributed in the epidermis and dermis. It is emphasized that most of the drug was retained in the epidermis in this hydrogel application, and it ameliorated the HFS (45). Recently, another supportive study evaluating a different member of the family of non-steroidal anti-inflammatory drugs, diclofenac, has also been published. The effectiveness of topical 1% diclofenac gel in the prevention of capecitabine-induced HFS has been reported (46).

An alternative hypothesis for the mechanism of capecitabine-induced HFS concentrated on an inflammatory response associated with abnormal autoimmune regulation instead of previously thought COX-2-mediated inflammation (47). A clinical study was conducted to evaluate the potential diagnostic and capecitabine-related adverse effects biomarkers on urinary endogenous metabolites. It analyzed the metabolic profiles of 139 colorectal patients, 50 non-neoplastic controls, and also colorectal patients with or without capecitabine- related adverse effects. The authors of the study suggested that erroneous cell proliferation, differentiation, potential metabolic pathways, and an excessive immune response may make patients with cancer more sensitive to capecitabine-related adverse effects (47).

Another study that evaluated the contribution of keratinocytes to capecitabine-induced HFS concluded that mitochondria-associated apoptosis is activated in keratinocytes by capecitabine therapy. It has been shown that dysfunction of mitochondria contributes to apoptosis associated with capecitabine, stimulating the cell deaths of keratinocytes, and may cause a direct and irreversible reduction of the corneuos layer (48). This experimental animal study investigated the relationship between alterant keratinocytes and the

development of capecitabine-induced HFS and concluded that keratin and the corneous layer were decreased in HFS associated with capecitabine. The result of the study further implicated that capecitabine and its metabolites increased the cell death of keratinocytes through the activation of apoptosis signaling pathways. It has been shown that capecitabine actuated mitochondrial-associated apoptosis in keratinocytes. Determination of the up-regulation of apoptosis-related proteins and a decline in mitochondrial membrane potential revealed that mitochondrial apoptosis was notably associated with capecitabine- induced HFS. It was reported in the study that capecitabine-induced HFS has been shaped through mithochondrial dysfunction, activated caspase-dependent apoptosis, induced cell death of keratinocytes, and, as a consequence of these reactions, an irreversible and direct reduction of the corneous layer. Differing from the other previous studies, skelemin or ionic channel have been postulated to be more adequate to describe capecitabine-induced HFS rather than inflammatory and immune pathways (48).

Furthermore, another study combining metabolomics with cell RNA sequencing has recently demonstrated that the inflammation mechanism of capecitabine-associated HFS may be related to abnormal expression of interleukin (IL) 6 or IL8 and not solely to overexpression of COX-2. It is reported that the involvements of the P38MAPK, NF-κB, and JAK-STAT3 signaling pathways, which may be associated with overexpression of IL6 or IL8, were detected as potential pathways taking part in hand foot syndrome associated with capecitabine. The exposure of skin cells to capecitabine and its metabolites exhibited much higher expression levels of IL6 or IL8 than those of COX-2, as well (49). Another study, differing from other previous studies hypothesizing the idea that cell death related to fluoropyrimidine may be associated with apoptosis, has suggested that pyroptosis may be involved in the development of HFS associated with capecitabine. The pyroptosis of keratinocytes induced by 5-DFUR, an active metabolite of capecitabine, may be gasderminE (GSDME) dependent, and this pyroptosis may trigger persistent inflammation. In addition, TP is implicated in the pyroptosis of keratinocytes induced by 5-DFUR in vitro. Tipiracil, a TP inhibitor administered topically, exhibited a reversal effect in HFS associated with capecitabine without impacting the antitumor effect (50).

In addition to these aforesaid theories that may interact with inflammatory pathways, enzymes that are responsible for the metabolism, the transporters involved in the absorption of capecitabine, and pharmacogenomics may (‘thymidine phosphorylase, uridine phosphorylase, dihydropyrimidine dehydrogenase, cytidine deaminase, N-acetyltransferase 1, N-acetyltransferase 2, thymidylate synthase methylenetetrahydrofolate

reductase, ATP binding cassette transporters, solute carrier proteins SLC22, SLC28, SLC29 transporters') take part in capecitabine-induced HFS, and it is not discussed in this review. However, it is suggested that there may be an association between dihydropyrimidine dehydrogenase and thymidylate synthase variants and capecitabine toxicity. Variability seen in the activity of dihydropyrimidine dehydrogenase and thymidylate synthase enzymes related to genetic polymorphisms and capecitabine toxicity may interact (31). Transporters involved in the absorption have been suggested to be related to HFS associated with capecitabine. The adverse effects seen in colorectal cancer patients associated with fluoropyrimidine treatment interactions with the polymorphisms of the ATP-binding cassette subfamily B member 1 (ABCB1) gene and interactions between certain members of SLC transporters ['in particular, human Organic Anion Transporter 2 (h OAT2), human Concentrative Nucleoside Transporter (hCNT1), and human Equilibrative Nucleoside Transporter 1 (h ENT1) of the SLC 22, SLC28, and SLC 29 families, respectively'] and 5-FU have also been reported in the literature (31).

CONCLUSION

Hand-foot syndrome is an expected adverse effect of some chemotherapeutic agents, mostly seen with capecitabine. Quitting or dose reduction may disrupt the treatment of patients. It may be further suggested that non- adherence to the treatment may arise. The exact mechanism is poorly understood. However, the evolving literature with new hypotheses is an area that is improving. It is of crucial requirement to investigate the underlying mechanism of HFS in order to establish a standard treatment consensus. Therefore, further evaluations are essential in the prevention and treatment of HFS for the progress and betterment of patient care.

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