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Treatment of Capecitabine-Induced Hand-Foot Syndrome Using MEBO: A Case Report

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Authors' contributions

This work was carried out in collaboration both all authors. Author HSR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AIBBS and HSR managed the analyses of the study. Author AIBB managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Handfoot syndrome is a side effect of Capecitabine chemotherapy. It highly effects the quality of patients' life due to the pain and swelling of the hand and foot. Previous studies had proven Moist Exposed Burn Ointment (MEBO) as an ideal regiment for several skin pathologies. Here, we report 8 cases of grade II and III hand foot syndrome treated with topical MEBO.
Case Report: Eight **(**8) cases of grade II and III hand foot syndrome have been reported. On these patients, symptoms generally occurred after 2 until 3 months after capecitabine administration. Topical MEBOs were used twice a day for 3 months, pain reduction was achieved with no capicetabine dose interruption and reduction during chemotherapy period. The patients had grade III of HFS during capecitabine therapy on the 3rd month after the initial treatment, with the usage of topical MEBOs, capecitabine doses and chemotherapy cycle could be maintained.
Discussion: Despite the strategies to prevent HFS, the appearance of the symptoms was still consistent in patients who achieved Capecitabine. The goal of HFS treatment due to chemotherapy is toreduce the symptoms, maintaining the life quality of chemotherapy patients without reducing the dose or changing/stopping the regiments. MEBO had shown a promising result on several meta-analysis studies.

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Conclussion: Regarding the treatment of chemotherapy related toHFS, MEBO is one of the main treatments of choice due to its cooling, moisturizing, and healing effects. It had been proved in a a meta-analysis study regarding the treatment of skin burn. MEBO had shown to reduce severe pruritus and local skin pain due to its antibacterial, analgesic, and anti-inflammatory effect.

Keywords: Hand and foot syndrome; moist exposed burn ointment; topical; capecitabine.

1. INTRODUCTION

Although it is not a life-threatening condition, hand-foot syndrome would highly affect the quality of the patients' life. Hand-foot syndrome ischaracterized by complaints of burning sensation on hands and feet, with swelling and redness. As the disease advanced, more blisters, desquamation, edema, and hyperkeratocys appear [1]. Hand foot syndrome is a common complication of a patient treated with Capecitabine. Capecitabine is an anticancer drugs and effective in fluoropyrimidine-sensitive diseases. It is currently being used as an adjuvant therapy of colorectal cancer and a first-line treatment for metastatic colorectal cancer [2]. The mechanism for fluoropyrimidine-induced HFS appears to be related to the accumulation of 5-FU metabolites in the skin[1].

Capecitabine's side effect is one of the main reasons why patients did not continue chemotherapy regiments [3]. Putra [4] had reported that throughout 2010-2012, there were 10 patients with colorectal cancer treated with Capecitabine, and all of them complained of HFS. 48.7% patients did not finish the chemotherapy regiments, and the main reason was due to their side effects [4]. The goal of HFS treatment due to chemotherapy is toreduce the symptoms, maintaining the life quality of chemotherapy patients without reducing the dose or changing/stopping the regiments [1].

Here, we report 8 cases of grade II and III hand foot syndrome treated with topical Moist Exposed Burn Ointment (MEBO). Confirmed by several studies, MEBO had showed several advantages in treating burn injuries. It has higher effectivity in reducing pain, has lower cost compared to other topical treatments, better ability in reducing transepidermal water loss, and isreported to show faster histological wound healing compared to honey ointment [5]. In this case report, the patients showed improvement both in symptoms and appearance after MEBO therapy.

2. CASE REPORT

Eight (8) cases of grade II and III hand foot syndrome have been reported, 2 patients were grade III HFS, and the others were grade II. These symptoms occurred after 2 until 3 months after capecitabine administration for locally advanced (stage III) colonic adenocarcinoma. Topical MEBOs were used twice a day for 3 months, pain reduction was achieved with no capicetabine dose interruption and reduction during chemotherapy period. As seen on Fig.1. Below, the patients had grade III of HFS during capecitabine therapy on the 3rd month after the initial treatment, with the usage of topical MEBOs, capecitabine doses and chemotherapy cycle could be maintained (as seen on Fig. 2).

3. DISCUSSION

The incidence of hand foot syndrome in chemotherapy treatment is reported to occur in 43% -71% in patients treated with Capecitabine [6]. Itis characterized as palmoplantar erythrodysthesia – one of the adverse effects of fluoropyrimidine [6]. Capecitabine is a novel oral fluoropyrimidine prodrug with broad spectrum of anticancer activity and effective in fluoropyrimidine-sensitive diseases. It is currently being used as an adjuvant therapy of colorectal cancer and a first-line treatment for metastatic colorectal cancer. Capecitabine alone or plus docetaxel combination therapy was used in patients with metastatic breast cancer [7].Clinical studies indicated that capecitabine-based therapy in colorectal cancer showed a 24% response rate. In a phase II study, in patients with paclitaxelrefractory metastatic breast cancer, therapy with capecitabine alone can elicit a response rate of 20% [2].

The mechanism for fluoropyrimidine-induced HFS appears to be related to the accumulation of 5-FU metabolites in the skin [2]. For capecitabine, it is hypothesized that high skin concentrations of one of the enzymes that breaks it down to the active 5-FU, thymidine phosphorylase, causes high localized toxic concentrations of 5-FU to be generated. Consistent with this idea, thymidine phosphorylase has been found to be more highly concentrated in the palms than in other skin areas. For both 5-FU and capecitabine, breakdown of 5-FU through the action of

dihydropyrimidine dehydrogenase (DPD) has been implicated. However, while patients with DPD deficiency experience much more fluorouracil toxicity, particularly gastrointestinal and hematologic, they do not have higher rates of HFS. On the other hand, S-1, which contains a DPD inhibitor and thus produces fewer metabolites, is associated with lower rates of HFS.For capecitabine, it has been hypothesized that the drug and its breakdown products either directly or indirectly activate cyclooxygenase-2 (COX-2) inflammatory pathways to cause white blood cell infiltration, dilated blood vessels, and edema in tissues [1].

The grading of HFS was determined by The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) as well as the World Health Organization. The classification was as follows(1):

In most of our case, the syndrome occurred about two to three months after the administration of Capecitabine. HFS usually appears from days up to 10 months after the administration of Capecitabine. It is highly affected by the total cumulative dose of Capecitabine [8]. The patients usually complain of burning sensation on hands and feet, with swelling and redness. As the disease advanced, more blisters, desquamation, edema, and hyperkeratocys appear. It would affect the life quality of the patients.

Several researches' goal was to find an effective therapy to prevent HFS. Corrie et al.randomized 106 patients with breast or colorectal cancer receiving single-agent capecitabine to 50 mg pyridoxine 3 times daily or placebo [9]. There was no statistically significant difference in the incidence of severe HFS-related adverse events and the need for capecitabine dose reduction. Moreover, Braik et al. randomized 77 patients treated with capecitabine-containing chemotherapy regiments to supplemental pyridoxine 100 mg daily or placebo and observed no difference in the incidence of HFS (all grades) [6]. Several strategies suggested to prevent the HFS were as follows (1):

The goal of HFS treatment due to chemotherapy is toreduce the symptoms(as seen on Table 2), maintaining the life quality of chemotherapy patients without reducing the dose or changing/stopping the regiments. Colorectal cancer cells have rapid growth rate. If possible, chemotherapy regiments were expected to work extra miles to kill the growth of cancer cells [10]. Putra [4] had reported 48.7% patients did not finish the chemotherapy regiments, and the main reason was due to their side effect.

Banjarnahor and Silaen [10] had reported the effectivity of immerson and the application of mixture VCO and olive oil to overcome the side effects of HFS. The regiments' main purpose is to maintain the hand and foot moisture. The result shows that these mixtures were effective in treating HFS on more than 80% colorectal cancer patients with HFS [10]. However, regarding the patients with HFS, the regiments had not been reported to reduce any of the symptoms such as burning or blistering.

Fig. 1. HFS grade III

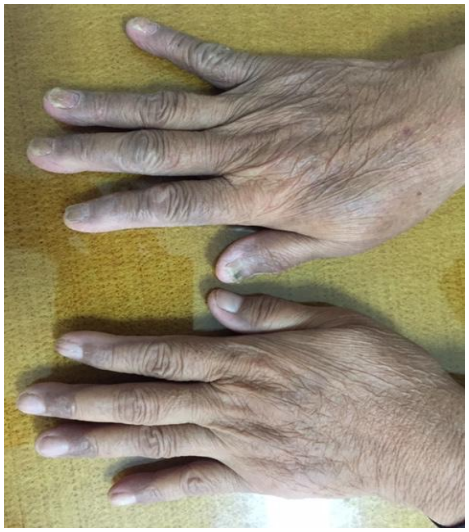

Fig. 2. After MEBO administration

Table 1. The garding of HFS according to WHO and NCI

Grade	WHO	NCI
1	Dysesthesia/paresthesia, tingling in hands and feet	Minimal skin changes or dermatitis (e.g. erythema, edema, or hyperkeratosis) without pain
2	Discomfort in holding objects and upon walking, painless swelling, and erythema	Skin changes (e.g. peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental activities of daily life
3	Painful erythema and swelling of palms and soles, periungual erythema, and swelling	Severe skin changes (e.g. peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care activities of daily life
4	Desquamation, ulceration, blistering, severe pain	

Table 2. Preventive and symptomatic treatment options for HFS

Preventive Measures
Avoid mechanical stress/trauma (i.e. friction, pressure, tight footwear)
Avoid exposure to high temperatures around administration (e.g. bathing with hot water, vigorous exercise, wearing tight clothing and shoes)
Maintenance of good hygiene with regular visits to the podiatrist in case of corns and calluses. Referral to dermatologist for treatment of pre-existing dermatologic conditions
Moisturizing with urea-based cream three times per day (avoid excessive rubbing)
Local hypothermia (regional cooling) at time of administration (only for short-term infusions of PLD and docetaxel)
Symptomatic Treatment
Pain: analgesics or topical anesthetics (lidocaine patches)
Inflammation: topical high-potency corticosteroids
Hyperkeratosis: topical keratolytics
Erosions: petroleum/lanolin-based ointments
NCI-CTC grade 2 or higher: oral celecoxib
Other°: oral vitamin B6 (Pyridoxine) 400 mg, oral vitamin E, topical 99% dimethylsulfoxide (DSMU), topical sildenafil, oral corticosteroids

Hapsari et al. [11] reported the use of Aloe Vera gel in treating HFS. The result showed an improvement on HFS scoring on patients who were treated with Aloe Vera gel. Aloe Vera had known to consist 99.5% water that could maintain the skin moisture and *mannose-6-phosphate* as the main polysaccharide that isresponsible for the collagen heal in tissue healing. Besides, the salycilic acid in Aloe Vera could reduce the inflammation. However, this study has limitations due to the small sample size and the lack of control regarding the Aloe Vera use on patients[11]. On further studies in management of acute radiation dermatitis, it also showed that despite the its promising characteristics, aloe vera has not been shown to reduce severe symptoms, and in a large random control trial, it was less effective in managing patients' symptoms compared to aqueous lotion[12].

In this case, patients used MEBOs twice a day for 3 months. Pain reduction was achieved with no capicetabine dose interruption. Moist Exposed Burn Ointment (MEBO) is a pure herbal formulation originated from China. The ingredients of MEBO® herbal formulation are phellodendron amurense, scutellaria baicalensis, coptis chinensi, pheretima aspergillum, beeswax, and sesame oil. The pharmacological effects are derived from β-sitosterol (isolated from Phellodendron amurense), flavonoids (particularly baicalin, which is isolated from Scutellaria baicalensis), alkaloids (especially berberine, which is isolated from Coptis chinensis) and vehiculum, which is a mixture of beeswax and sesame oil. The exact mechanism of action of MEBO® has not been confirmed. It is thought that the oil-based content has the most essential role in wound healing, i.e. for cooling the wound, maintaining moisture, and reducing pain[5].

Confirmed by several studies, MEBO had showed several advantages in treating burn injuries. It has higher effectivity in reducing pain, has lower cost compared to other topical treatment, better ability in reducing transepidermal water loss, and reported to show faster histological wound healing compared to honey ointment [5]. In this case, MEBO showed a good improvement on all patients. The dry and blistered skin showed improvement three months after treated with MEBO.

MEBO also has another advantage. Itsconsistency prevents any adhesion with the gauze due to its oil droplet structure. This prevents the newly grown skin layer from damage. This advantage was one of the reasons that MEBO was used as treatment of choice in treating skin burn [5]. And in a meta-analysis regarding the treatment of skin burn, MEBO had shown to reduce severe pruritus and local skin pain due its antibacterial, analgesic, and anti-inflammatory effect [12].

In patients treated with Capecitabine, the incidence of hand foot syndrome was high. Capecitabine is a novel oral fluoropyrimidine prodrug with broad spectrum of anticancer activity and effective in fluoropyrimidine-sensitive diseases. It is currently being used as an adjuvant therapy of colorectal cancer and a first-line treatment for metastatic colorectal cancer. The mechanism for fluoropyrimidine-induced HFS appears to be related to the accumulation of 5-FU metabolites in the skin. Even though it is not life-threatening, HFS highly affects the patients' quality of life.

4. CONCLUSSION

The side effects of chemotherapy is the highest reason patients chose not to continue the regiments. The goal of HFS treatment is to reduce the symptoms without having to stop nor change the chemotherapy regiments. Regarding the treatment of chemotherapy relatedto HFS, MEBO is one of the main treatments of choice due to its cooling, moisturizing, and healing effects. It had been proved in a a meta-analysis study regarding the treatment of skin burn. MEBO had shown to reduce severe pruritus and local skin pain due its antibacterial, analgesic, and anti-inflammatory effect.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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