THE EFFECT OF TOPICAL STEROID AND ORAL GABAPENTIN IN THE TREATMENT OF CAPECITABINE INDUCE HAND FOOT SYNDROME AMONG CANCER PATIENTS

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Submitted: 14/9/2020; Accepted: 3/2/2021; Published: 21/9/2021

ABSTRACT

Background

Cancer patients facing many complications during treatments, such as oral Mucositis, neuropathy, and chemotherapy-induced diarrhoea. Unique toxicities can accompany Specific routes of administration of colon cancer drugs such as hand-foot syndrome.

Objectives

To study the effects of topical steroids and oral gabapentin in treating capecitabine induce hand-foot syndrome among cancer patients.

Patients and Methods

A total of 50 patients diagnosed with hand-foot syndrome attended in Hiwa cancer hospital in Sulaimani-Iraq, who met the inclusion criteria, were enrolled in the current study from august 2019-February 2020. patient's characteristics, concomitant drugs Used, any other diseases were recorded in a questionnaire designed for the study. Grading of the hand-foot syndrome and its severity of presentation is done by Using NCI-CTCAE (National Cancer Institute - Common Terminology Criteria for Adverse Events) and WHO (World Health Organization) and associated histologic findings. In addition, the quality of Life of the Patients was evaluated by using RAND 36-item short forming survey (SF36); The DN4 scale measured the neuropathy of Patients.

Results

The grades of the hand-foot syndrome after treatment were significantly improved compared to pretreatment (p-value; ≥0.001). Moreover, it changed the frequency of hand-foot syndrome by using topical steroids (clobetasol 0.05%), gabapentin, or both.

Conclusion

The study showed a statistically significant improvement in grades of the hand-foot syndrome of participants and increasing quality of life through using topical Steroids and gabapentin.

Keywords:*Capecitabine, Hand-foot syndrome, clobetasol, gabapentin, Quality of life SF36.*

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https://doi.org/10.17656/jsmc.10312

INTRODUCTION

Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia (PPE), was initially expressed in the literature in 1974 by Zuehlke in patients receiving mitotane therapy for hypernephroma; in the early 1980s, it was introduced to as chemotherapy-induced acral erythema and appeared to be related to continuous exposure to many chemotherapies[1].

Capecitabine showed to be a more selective alternative to 5-FU, as it is changed into the active form, especially in the tumour cell and decreasing the adverse effects related to 5-FU [2] (nearly 80%) of patients display less severe grades of HFS[1 and 2 of WHO criteria and 1 of the National Cancer Institute (NCI) criteria [3]. HFS is generally self-limiting, and rarely patients admitted to the hospital or need life-threatening manifestations, despite its effects on quality of life and their particular treatment [4]. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v4.0) grading system for dermatologic toxicities and the World Health Organization (WHO) classification is the most generally used method of grading HFS (Table 1) NCI classification shows three levels of toxicity while WHO identifies four different grades. Grade 1 toxicity is described in both classifications by fewer skin changes, including painless swelling or erythema, numbness, dysesthesia/paresthesia, and tingling not changing normal activities.

Since severe reactions (grade 3 in NCI and 4 in WHO) include severe pain, ulceration, and inhibition of everyday activities [5] when WHO grade 3 or 4 or NCI grade 3 toxicity first appears, or WHO grade2 toxicity shows up repeatedly, the dosage should be lowered to50 or 75% of the initial dosage, or the drug stopped. Drug withdrawal is desirable if the toxicity of these grades recurs even after the dosage is decreased [6].

A major tool in the treatment of HFS is changing of the tumour therapy; lowering or stopping the drug often leads to rapid change, chemotherapy like capecitabine in drug manufacture leaflet was written and recommended dose modification [7]. Treatment is to help symptom control.

Supportive measures such as high-potency topical corticosteroids to reduce inflammation wound and blister care for erosions and ulcerations to avoid infection, topical keratolytic to decrease hyperkeratosis, emollient use, and pain control [4]. Patients should, therefore, be careful of the appearance of the first signs and symptoms of HFS and advised, upon the development of grade 2 or 3 symptoms, to stop treatment until they recover to grade 0 or 1 [1]. Recently, the first stage of the management of HFS is discontinuing therapy and, if needed, dose reduction [2] interruption of capecitabine mainly leads to recovery and healing through several days/weeks, depending on severity [1]. In addition, recent research shows that HFS in patients receiving chemotherapy can be prevented by lifestyle changes that withdraw irritation to the hands and feet [2].

Table 1. Grades of severity for hand-foot syndromes [7].

GRADE	WHO	WHO correlation histology	National Cancer Institute(NCI-CTCAE*version 3.0)	National Cancer Institute (NCI-CTCAE*version 4.02)
I	(Decent) Erythema, dysesthesia, regular activity possible	Dilated capillaries.	Minimal skin changes (e.g. erythema), no pain.	Minimal skin changes (e.g., erythema, swelling, or hyperkeratosis), no pain.
II	Erythematous swelling, palmoplantar pain under mechanical stress	Isolated keratinocyte necrosis in higher epidermal layers	Skin lesions(e.g. ,blistering,bleeding,swelling) or pain , no impairment of functioning	Skin lesions(e.g., blistering, bleeding, swelling, or hyper-keratosis) with pain, and restricted daily activities
III	Painful erythematous swelling, fissures, restricted daily activities	Necrosis of the basal cell layer keratinocyte	Ulcerating dermatitis or skin lesions with pain and restricted function	Severe skin lesions (e.g., blistering, bleeding, swelling, or hyperkeratocyte) with pain and limited autonomy
IV	Excruciating pain, erythematous swelling, possible blistering and ulcers, impossible to perform usual daily activities	Necrosis throughout the epidermis	-------	------

***National Cancer Institute Common Terminology Criteria for Adverse Events.**

Aim of the study

To evaluate the effect of topical steroids (clobetasol 0.05%) and oral gabapentin on the grades of hand-foot syndrome.

PATIENTS AND METHODS

This is a cross-sectional study conducted among the cancer patients receiving capecitabine and who developed the hand-foot syndrome in Hiwa cancer hospital in Sulaimani, over six months from August 2019 –February 2020. Fifty adult cancer patients who met the inclusion criteria were enrolled in the current study, all have gone through an interview process, and all demographic data, including patient's characteristics, concomitant drugs used, any other diseases, were recorded in a questionnaire specially designed for the study

In Hiwa hospital, every month, we have nearly 200 patients receiving capecitabine for different types of cancers; from these patients, 50 patients were have developed the hand-foot syndrome, and we grade them according to National Cancer Institute (NCI-CTCAE*version 4.02).

These patients are receiving capecitabine at different doses, and different protocols depend on the type and stage of cancer. However, most of them received it for 14 days then 7-day rest, and most of them developed hand-foot syndrome after three cycles of treatment. Grading of the hand-foot syndrome and its severity of presentation is done by using NCI-CTCAE (National Cancer Institute - Common Terminology Criteria for Adverse Events) and WHO (World Health Organization) and associated histologic findings [8] for management and treating of the hand-foot syndrome; we used the most useful managements available on a list of treatments according to previous researches [9-12], the quality of life of the patients was evaluated by using the RAND 36-item short forming survey (SF36), which consists of 36 items that measure eight dimensions of health from the viewpoint of the patient. Such measures assess physical functioning, job limitations due to physical or emotional issues, social functioning, mental health, strength and vitality, Body discomfort, and general perception of wellbeing. The rating scale ranges from 0 - 100, with high scores showing high functioning and better QoL.[13-15] for management and treating of hand-foot syndrome, each patient follow up for three cycles each cycle were 14 days on treatment and seven days

on rest, depending on grade and neuropathy patients taking either clobetasol or gabapentin as treatment, in every cycle patients were seen in Hiwa hospital and asked about side effects, and QOL in that week were recorded, and dose modification if they need and see their oncologist reduce or stop their drug if grades were severed or their investigations went wrong[16].

RESULTS

A total of 50 patients of hand-foot syndromes were included in the present study with mean age as (52.58 ± 15.32) years, 8% of them were ageing (19-29) years and 12% of the ageing (30-39),20% were ageing (40-49), (60-69),24% were ageing (50-59), and and16% were ageing>70. Depending on NCI-CTCAE (National Cancer Institute - Common Terminology Criteria for Adverse Events) and WHO (World Health Organization) and associated histologic findings(8),For management and treating of the hand-foot syndrome, we graded hand & foot,31(62%) of them were in grade 1, 7(14%) of them were having grade 2, and 12 (24%) were in grade 3. after grading and depending on their grade patients were received drugs and used them for 14 days and followed up for three cycles, these figures (1 A & B) show improvement in changing grades and increasing quality of life of the participants' p-value of the grade changes was <0.05 (=0.001) which is highly significant: depending on the scale of grading, if grade 1 without neuropathy patients received clobetasol for 14 days, if grade 2 and 3 with or without neuropathy patients received either alone or in combination. Details, Fgures (2,3,4) A & B:

Table.1.2. Demographic characteristics of the participants.

	Frequency	Per cent
Age group(year)		
19 – 29	4	8.0
30 – 39	6	12.0
40 – 49	10	20.0
50 – 59	12	24.0
60 – 69	10	20.0
≥ 70	8	16.0
Total	50	100.0
Gender		
Female	26	52.0
Male	24	48.0
Total	50	100.0
Address		
Inside the city	23	46.0
Outside the city	27	54.0
Total	50	100.0
Education level		
Illiterate	25	50.0
Primary School	9	18.0
Secondary School	5	10.0
High School	11	22.0
Total	50	100.0

Table 1. Continued ..

Occupation		
Governmental	10	20.0
Non-Governmental	12	24.0
Un-employ	1	2.0
Housewife	19	38.0
Student	3	6.0
Retired	5	10.0
Total	50	100.0
Marital status		
Single	5	10.0
Married	45	90.0
Total	50	100.0
BMI Group		
<18.5 Underweight	7	14.0
18.5 - 24.9 Healthy weight	20	40.0
25 - 29.9 Overweight	11	22.0
≥ 30 Obese	12	24.0
Total	50	100.0
Smoker		
Yes	5	10.0
No	45	90.0
Total	50	100.0
Alcoholic		
No	50	100.0
PMH		
None	25	50.0
HTN	5	10.0
D.M	14	28.0
HTN, D.M	6	12.0
Total	50	100.0
PSH		
Yes	39	78.0
No	11	22.0
Total	50	100.0
Allergy		
Yes	3	6.0
No	47	94.0
Total	50	100.0

Table 13 Assessment of hand-foot syndrome

	Frequency	Percent
Pain of HF		
Hand	4	8.0
Foot	16	32.0
Both	17	34.0
No pain	13	26.0
Total	50	100.0
Previous skin condition		
Yes	3	6.0
No	47	94.0
Total	50	100.0
Grades of Hand-foot at diagnosis		
1	31	62.0
2	7	14.0
3	12	24.0
Total	50	100.0
Nature HF		
H = F	15	30.0
H > F	21	42.0
H < F	14	28.0
Total	50	100.0
using Herbal		
Yes	8	16.0
No	42	84.0
Total	50	100.0
Using Cold		
No	50	100.0
Season		
Yes	1	2.0
No	49	98.0
Total	50	100.0
Taking Analgesic		
Yes	17	34.0
No	33	66.0
Total	50	100.0

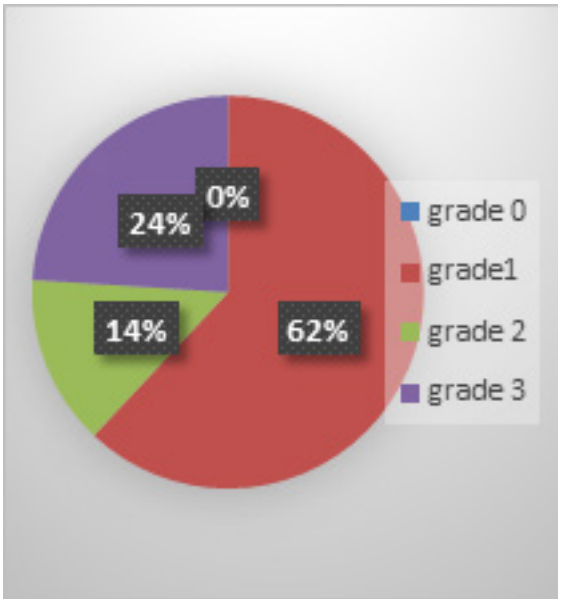


Figure.1.1.A Grade before treatment.

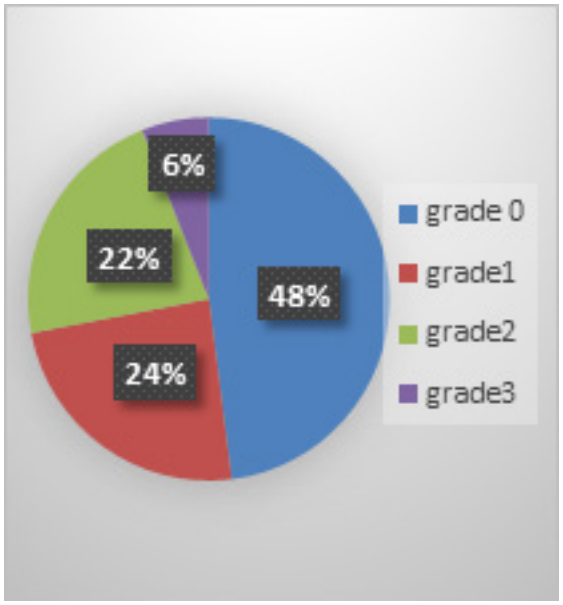


Figure1.1.B Grade after treatment.

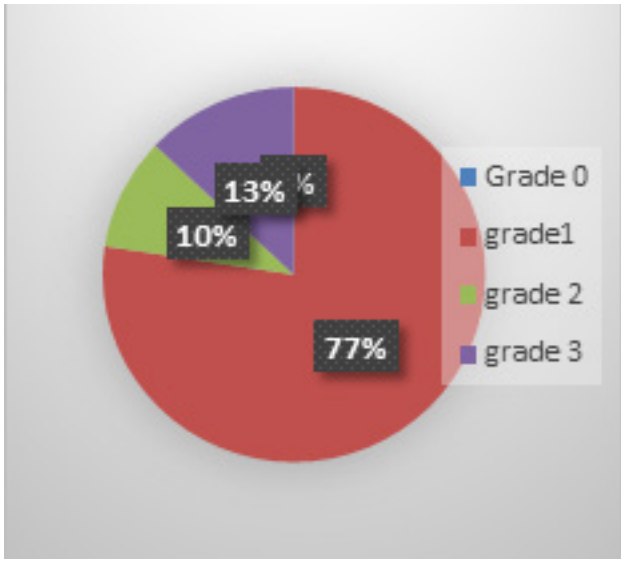


Figure.1.2.A Before treatment with clobetasol.

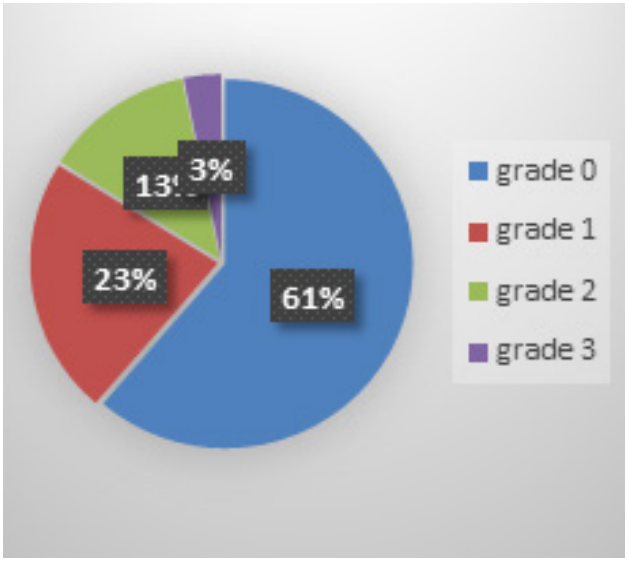
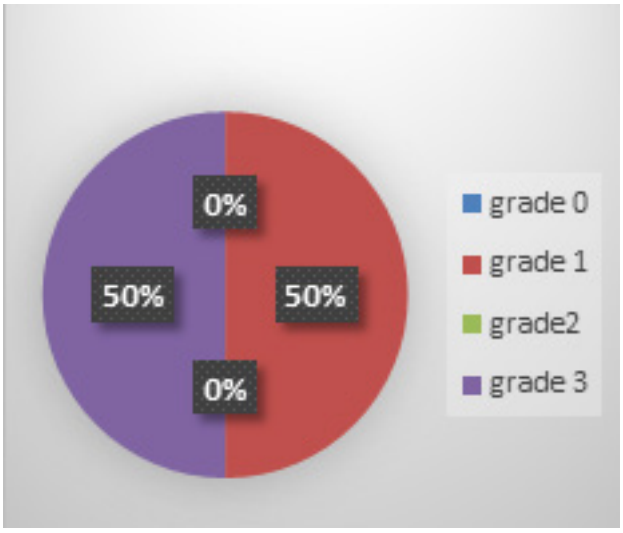


Figure.1.2.B After treatment with clobetasol.



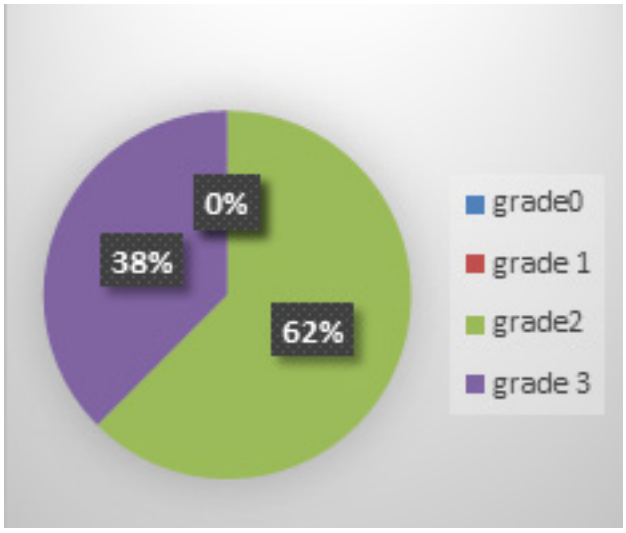
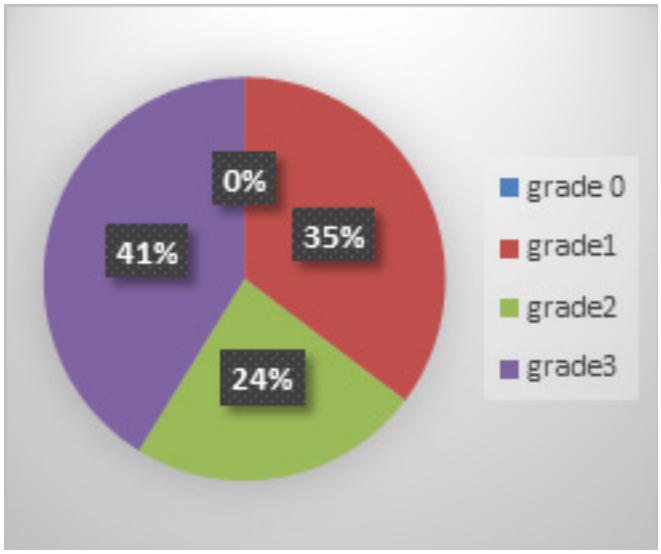


Figure.1.3.A Before treatment with gabapentin. **Figure.1.3.B After treatment with gabapentin.**



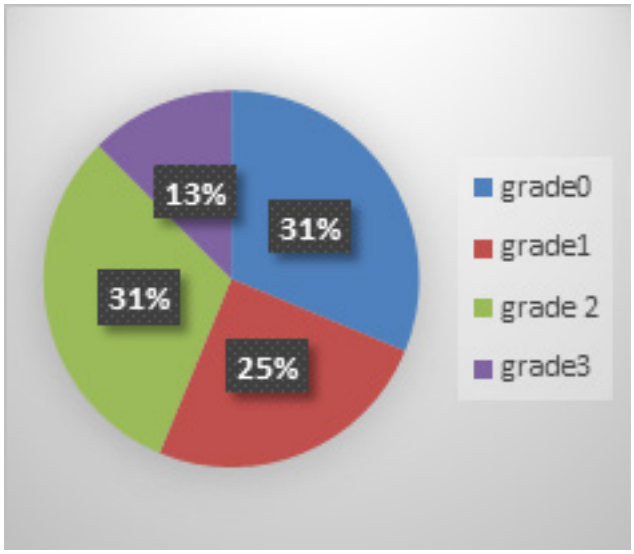


Figure1.4.A Before treatment (clobetasol & gabapentin). **Figure .1.4.B After treatment with (clobetaso&gabapentin).**

DISCUSSION

There are no significant differences in demographic data, including age, the median age of participants was (52.50); this was close to MEVLUT et al. (2006), the median age of participants was (53) [17] more than half of the enrolled patients were female 26 (52%), which is similar to Hyun et al. (2009), female patients were 33(39.3) and [18] . Also similar to VINCENT et al. (2011) which was female participants were more than male participants (74%, 26%) [19].

Regarding the tumour site in this study, colorectal cancer was 25 (50%) patients; the breast was 15 (30%) close to Samer et al. (2002)[20] also close to Kazuyoshi et al. (2017) [21].

In the current study, moderately differentiated patients were 16(32%), well-differentiated was 5 (10%), poorly differentiated was 4 (8%). Undifferentiated was 9(18%) compared to Rong et al. (2010) study was contrasted these changes may be related to stages and type of cancers of participants [22], regarding this study, grade 1 was 31 (62%), grade 2 was 7 (14%), grade 3 was 12(24%) compared to other studies, Yoon et al. (2017), grade 1 was 60(29%), grade 2 was 66 (31%), grade 3 was 6(3%) [23], and another study by Samer et al. (2002), grade 1 was5(17.9%), grade 2 was 20 (71.4%), grade 3 was 3(10.7%). (20) also, a study done by YiYuan et al. (2012), the incidence of grade 1 was 80(46), grade 2 was 32 (18%), grade 3 was 5(3%)[24], these changes in grades may be related to a change in dose of capecitabine and protocol used for chemotherapy.

Regarding localization of hand-foot syndrome in the current study, the hand was 14 (28%), feet was 21(42%), both in hand and feet was 15 (30%), results compared to VINCENT et al. (2011) study was resembled, a hand was 15%, feet 24%, both hand and feet 61%[19].

In conclusion, the study showed a statistically significant improvement in changing grades of the hand-foot syndrome of participants and increasing quality of life by using topical steroids and oral gabapentin. Also, the pharmacist's role is significantly seen in educating patients and advising them for a better prognosis.

Conflict of interest

None.

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