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Incidence and Grading of Hand –Foot Syndrome in Mostly Used Chemotherapy Protocol at Oncology Teaching Hospital in Baghdad –Iraq

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Original Article

ABSTRACT

***Background**: The chemotherapies are accompanied with high rates of co-morbidities. The hand foot syndrome is a common adverse event of chemotherapy but with high recovery rate after discontinuation.*

***Objective**: To observe the incidence of hand-foot syndrome and its grade in patients treated with chemotherapy protocols that contain capicitabine , liposomal doxorubicin , 5 florouracil , sunitinib ,that caused handfoot syndrome.*

***Patients and methods**: A clinical prospective study conducted in Oncology Teaching Hospital- in Baghdad city during the period from 1st of November, 2018 till 31st of July, 2019 included 100 cancer patients treated with different chemotherapy protocol that contain capicitabine , 5-flurouracil , liposomal doxorubicin , sunitinib. Investigations were performed accordingly.*

***Results**: Hand foot syndrome reported in 56% of patients . Grading of hand foot syndrome for cancer patients treated with these chemotherapy protocols was grade 1 (66.1%), grade 2 (19.6%), grade 3 (10.7%) and grade 4 (3.6%). Hand foot syndrome was significantly related to breast cancer treated with capecitabine in addition to long duration of chemotherapy use.*

***Conclusions**: The incidence rate of hand foot syndrome and its grading in cancer patients treated with chemotherapy were within acceptable international range reported internationally.*

***Keywords:** Chemotherapy, Hand Foot Syndrome, capecitabine.*

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1. INTRODUCTION

The hand-foot syndrome (HFS) is a main adverse effect of specific chemotherapies presented with incidence rates 43-71% in patients indicated for Capecitabine chemotherapy[1]. The HFS is as an adverse effect resulted from different classical chemotherapy agents and novel molecular treatments which is presented clinically by sharp painful erythema affecting both palms and soles could be progressed to develop vesicles or bullae [2].Despite non-lethal outcomes of HFS, it has poor outcomes regarding the quality of life (QoL) and daily physical activity of patients, in addition, to negative impact on treatment course and outcome of chemotherapy due to chemotherapy stop or dose [1, 3].

The etiology of HFS is mainly due to treatment by doxorubicin, cytarabine, docetaxel, infusion with 5-fluorouracil [2]. The HFS is also attributed to treatment by bleomycin, cisplatin, cyclophosphamide, etc.[4]. The capecitabine (5-fluorouracil) overdosemight be accompanied by genetic polymorphisms of the enzymes (dihydropyrimidine dehydrogenase and thymidylate synthase)that participated in capecitabine metabolism [5]. Additionally, multi-targeted tyrosine kinase inhibitors like Sunitinib, Regorafenib and others which is targeting the angiogenesis are also accompanied by HFS, but different clinically and histologically from classical HFS[5]. The hand foot syndrome is commonly reported after treatment by the Anthracyclines (Doxorubicin, Docetaxel and Capecitabine). [2] The HFS is also reported in less incidence rates after treatment by other agents like Cyclophosphamide, Cisplatin, Daunorubicin, etc.[6]. It is shown that the HFS is dose dependant adverse effect of Cytarabine and Capecitabine chemotherapies. Moreover, chemotherapy formula and schedule of administration are also responsible in etiology of HFS as they maintain higher levels of drugs cytotoxitcity [7]. However, the exact pathogenesis is not completely known. Some authors that accumulation of cytotoxic agents in eccrine glands located at palms and soleslead to eccrine squamous syringometaplasia (ESS). The ESS causes metaplasia and focal necrosis of the epithelium of the eccrine duct. In spite of ESS relationship with hand foot syndrome, but this relation is rare[8].

Histopathology examination of HFS revealed moderate spongiosis, necrosis and dyskeratosis of keratinocytes and vascular degenerations of the basal layer. The dermal changes of HFS composed of blood vessels dilation, papillary edema and epidermal infiltration with superficial perivascular lymphohistiocytes[4]. The diagnosis of HFS is depending on history

and physical examination by assessing the clinical dermatological adverse effects of chemotherapy and differentiating from other dermatological disorders. The hand foot syndrome must be differentiated from Graft-versus-Host Disease, erythema multiform and toxic epidermal necrolysis [8].

Severity of HFS is graded into three levels grade I (minimum skin changes), grade II (skin changes) and grade III (severe skin changes [9]. The treatment of hand foot syndrome is mainly concentrated on modifying the chemotherapy by either stopping the treatment or reducing the dose [10]. Sometimes, stopping the treatment or reducing the dose of chemotherapy lead to diminishing the HFS or reducing it to lower severity grades, then the treatment re-continued. Many topical dermatological preparations are also prescribed to relieveHFS symptoms [11].Earlier diagnosis, patients' well awareness in adverse effects and supportive measures are considered as cornerstone in the treatment of hand foot syndrome. Numerous topical agents and systemic treatments mixed with COX-2 inhibitors are helpful in HFS treatment[12].

In Iraq, the trend of all cancer types especially lung and gastrointestinal cancers is increased in last two decades[13]. Age standardized rates of cancer among Iraqi males was 89.8 per 100,000 and among Iraqi females was 83.9 per 100,000[14]. Poor health infrastructure in Iraq due to frequent wars, disasters and sanction obscured the real cancer rates in previous decades which affect the cancer control programs[15]. The incidence of hand foot syndrome in Iraqi patients treated by Capecitabine reached to about 78% with higher predominance among older age patients, however, most of patients were at lower severity grade[16]. Frequent chemotherapy types are used nowadays in treatment of different cancer for patients presented to cancer centers distributed allover Iraqi country which might be accompanied with adverse effects. For that present study aimed to observe the incidence of hand-foot syndrome and its grade and in patients treated with mostly used chemotherapy protocols that contain capecitabine, pyglated liposomal doxorubicin and 5-fluorouracil.

2. PATIENTS and METHODS

This was a clinical prospective follow up study conducted at Oncology Teaching Hospital-Medical City Complex in Baghdad city during the period from 1st of November, 2018 till 31st of July, 2019. The study population composed of patients treated with chemotherapy that caused hand – foot syndrome.

Inclusion criteria

1. Cancer adults patients aged 18 years or older of both genders.
2. Received chemotherapy as adjuvant, neoadjuvant or palliative therapy
3. Receive at least 3 cycles of treatment.

Exclusion criteria

1. Patients with skin diseases like psoriasis, dermatitis, and others
2. Pregnant women.
3. Terminal cases and
4. Refusal to participate in the study.

A convenient sample of 100cancer patients treated with chemotherapywas selected after eligibility to inclusion and exclusion criteria.

The data was collected by researcher from directly or from patients' records and filled in a prepared questionnaire. The questionnaire was designed by the researchers. The following information was checked in every participant: demographic characteristics of cancer patients treated with chemotherapy(age and gender), diagnosis of cancer, clinical history of cancer patients treated with chemotherapy (past medical history, renal function test, liver function test and complete blood picture, therapy protocol of cancer patients treated with chemotherapy, chemotherapy drugs doses (mg), incidence of HFS among cancer patients treated with chemotherapy, grading of HFS among cancer patients treated with chemotherapy and onset of HFS among cancer patients treated with chemotherapy.

After selection of patients, we checked the chemotherapy protocol of each patient and the characteristics of each protocol. The hand foot syndrome was diagnosed by the oncologist depending on who and NCICTCAE V 5.0 criteria for diagnosis and grading of hand – foot syndrome . The investigations including renal function test, liver function test, complete

blood count were done in the Laboratory of Oncology Teaching Hospital-Medical City Complex. The grading of hand foot syndrome was done according to National cancer institute-Common terminology criteria for adverse event v5.0 hand – foot syndrome. The patients were followed for at least 6^{th} cycle of chemotherapy looking for development of hand foot syndrome.

The data collected were analyzed statistically by Statistical Package of Social Sciences software version 22. Chi square test was used for categorical variables (Fishers exact test was used when expected variable was less than 20% of total variable). Independent sample t-test was used to compare between two means and one way ANOVA analysis was used to compare between more than two means.Level of significance (p value) was regarded statistically significant if it was 0.05 or less.

3. RESULTS

This study included 100 cancer patients treated with chemotherapy with mean age of 54.2±13.4 years; 2% of patients were in age group less than 20 years, 1% of them were in age group 20-29 years, 8% of them were in age group 30-39 years, 23% of them were in age group 40-49 years, 31% of them were in age group 50-59 years and 35% of them were in age 60 years and more. Female cancer patients were more than male patients with female to male ratio as 1.9:1. Past medical history was HT and DM in 15% of cancer patients. RFT was impaired in 5% of cancer patients and LFT was impaired in 3% of cancer patients, while CBC detected anemia and neutropenia in 17% of cancer patients (**Table 1**). The common diagnosis of cancer was breast cancer (33%); followed by colon cancer (27%), gastric cancer (14%), rectal cancer (6%), pancreatic cancer (5%), renal cancer (4%), etc.Chemotherapy protocols of cancer patients were commonly included Capecitabin (64%), followed by; 5 fluorouracil (19%), Doxorubicin (8%), Sunitinib (5%) andCisplatin (4%), (**Table 2**). The hand foot syndrome (HFS) was present among 56% of cancer patients treated with chemotherapy. NCI grading of HFS for cancer patients treated with chemotherapy was grade 1 (66.1%), grade 2 (19.6%), grade 3 (10.7%) and grade 4 (3.6%). The onset of HFS was at 2nd cycle (1.8%), at 3rd cycle (41.1%), at 4th cycle (32.1%), at 5th cycle (7.1%) and at 6th cycle (17.9%), (**Table 3**). A significant association was observed between breast cancer and

higher frequency of HFS (p=0.05). There was a significant association between chemotherapy treatment using Capecitabinand higher incidence of hand foot syndrome (p=0.004), (**Table 4**). No significant differences were observed between cancer patients with positive HFS and cancer patients with negative HFS regarding Capecitabin dose (p=0.8) and Doxurubicin dose (p=0.9). Mean 5FU dose was significantly higher among cancer patients with positive HFS (p=0.04), (**Table 5**).

Table 1. General characteristics of cancer patients treated with chemotherapy.

Variable		**No.**	**%**
Age (year)*	<20	2	2.0
	20-29	1	1.0
	30-39	8	8.0
	40-49	23	23.0
	50-59	31	31.0
	≥60	35	35.0
Gender	Male	34	34.0
	Female	66	66.0
Past medical history	HT and DM	15	15.0
	Negative	85	85.0
Renal system	Normal	95	95.0
	Impaired	5	5.0
Liver	Normal	97	97.0
	Impaired	3	3.0
Blood	Normal	83	83.0
	Anemia and neutropenia	17	17.0
Total		**100**	**100.0**
*Mean age ±standard deviation: 54.2±13.4 years			

Table 2. Tumors and treatment characteristics.

Variable		**No.**	**%**
Tumors	Breast cancer	33	33.0
	Pancreatic cancer	5	5.0
	Rectal cancer	6	6.0
	Gall bladder cancer	2	2.0
	Cholangio cancer	1	1.0
	Hepatic cancer	1	1.0
	Gastric cancer	14	14.0
	Colon cancer	27	27.0
	Renal cancer	4	4.0
	Ovarian cancer	2	2.0
	Kaposi sarcoma	1	1.0
	Nasopharyngeal cancer	2	2.0
	Malignant apendel cell	1	1.0
	Squamous cell	1	1.0
Chemotherapy agents	Doxorubicin	8	8.0
	5FU	19	19.0
	Cisplatin	4	4.0
	Capecitabin	64	64.0
	Sunitinib	5	5.0
Total		**100**	**100.0**

Table 3. Incidence and characteristics of HFS among cancer patients treated with chemotherapy.

Variable	**No.**	**%**
HFS		
Positive	56	56.0
Negative	44	44.0
Total	**100**	**100.0**
NCI grading		
Grade 1 HFS	37	66.1
Grade 2 HFS	11	19.6
Grade 3 HFS	6	10.7
Grade 4 HFS	2	3.6
Total	**56**	**100.0**
Onset		
2^{nd} cycle	1	1.8
3^{rd} cycle	23	41.1
4^{th} cycle	18	32.1
5^{th} cycle	4	7.1
6^{th} cycle	10	17.9
Total	**56**	**100.0**

Table 4. Distribution of tumor and treatment characteristics according to HFS prevalence.

Variable		Positive		Negative		P
		No.	%	No.	%	
Diagnosis	Breast cancer	24	42.9	9	20.5	**0.05**^{S}
	Pancreatic cancer	2	3.6	3	6.8	
	Rectal cancer	4	7.1	2	4.5	
	Gall bladder cancer	0	-	2	4.5	
	Cholangio cancer	1	1.8	0	-	
	Hepatic cancer	0	-	1	2.3	
	Gastric cancer	5	8.9	9	20.5	
	Colon cancer	13	23.2	14	31.8	
	Renal cancer	4	7.1	0	-	
	Ovarian cancer	1	1.8	1	2.3	
	Kaposi sarcoma	1	1.8	0	.0	
	Nasopharyngeal cancer	0	.0	2	4.5	
	Malignant apendel cell	1	1.8	0	-	
	Breast cancer	0	-	1	2.3	
Chemotherapy agents	Doxorubicin	1	1.8	7	15.9	**0.004**^{S}
	5FU	10	17.8	9	20.4	
	Cisplatin	0	-	4	9.1	
	Capecitabin	43	76.8	21	4.7	
	Sunitinib	2	3.6	3	6.9	

S: Significant.

Table 5. Distribution of chemotherapy doses according to HFS prevalence.

Variable	Positive	Negative	P
	Mean ±SD	Mean ±SD	
Capecetabin dose (mg)	2539.5 ± 691.5	2500 ± 824.6	0.8^{NS}
Doxurubicin dose (mg)	83.3 ± 28.9	85 ± 21.2	0.9^{NS}
5FU dose (mg)	1501.5 ±1108.4	642.5 ± 67.7	**0.04**^{S}

NS: Not significant, S:Significant, SD: standard deviation of mean

4. DISCUSSION

Treatment of cancer with chemotherapy is accompanied with many benefits especially for some cancer types like breast cancer, colorectal cancer, ovarian cancer, etc [17]. The advantages of chemotherapy are related to malignant cells killing, which unfortunately associated with normal cell damage that lead to much physical harm. Regarding skin, the reaction of cells at the roots and follicles lead to fall of hair and other toxic effects of chemotherapy lead to many complications like hand foot syndrome (HFS) [18]. Present study showed that hand foot syndrome was present among 56% of cancer patients treated with chemotherapy. Our findings are similar to results of Zielinski et al [19] study in different European countries which revealed that 56% of patients with negative HER2 breast cancer treated with Capecitabine plus Bevacizumab developed hand foot syndrome. However, this incidence rate of 56% is higher than results of Gómez-Martin et al [20] study in Spain which stated that incidence of HFS was 19.6% among patients with advanced gastric cancer treated with chemotherapy (Capecitabine). In Iraq, a study conducted by Al-hussein and Hameed found that hand foot syndrome had a moderate adverse effect for cancer patients treated with chemotherapy [21]. The hand foot syndrome is regarded as the main skin complication of chemotherapy after alopecia and mucositis. The reported incidence rates of HFS is ranging between 3% to 64%; higher for Doxorubicin (40-50%) and highest for Capecitabine (50-60%). In spite of these findings, the incidence of HFS is dose-dependent and related to formulas and concentrations of chemotherapy used in addition to effect of duration of cancer and chemotherapy [22]. Exact etiology of hand foot syndrome is not fully understood till now, however, it was shown that damage to capillaries in cancer patients treated with chemotherapy lead to drug extravasation specifically for liposomal doxorubicin and drug accrual in the eccrine sweat ducts of the hands and feet [23]. Current study showed that NCI grading of HFS for cancer patients treated with chemotherapy was grade 1 (66.1%), grade 2 (19.6%), grade 3 (10.7%) and grade 4 (3.6%). These findings are close to results of Gressett et al [24] study in USA which reported that 17% of cancer patients treated with Capecitabine had NCI grades 3 and 4 hand foot syndrome. Increased grading of HFS is accompanied with increased risk of chemotherapy or higher dose. In general, our study findings regarding HFS incidence and grading are consistent with reports of Degen et al [9] study in Germany which stated that incidence of HFS among cancer patients treated mainly with Capecitabine was

raging from 50-60% and incidence of ≥grade 3 HFS was ranging from 10-17%. Wang et al [23]documented that accurate diagnosis of HFS syndrome is essential to avoid useless interruptions to chemotherapy. In Japan, a study carried out by Inokuchi et al [25] found that topical retinoid is the best treatment of HFS developed from Capecitabine chemotherapy. Zhang et al [26] study in China revealed that Celecoxib can be used effectively and safely to prevent capecitabine-related HFS. Another Chinese study carried out by Liu et al [27]found that integrative herbal therapy had been reduced the incidence of hand foot syndrome among patients with colorectal carcinoma treated with chemotherapy. Despite these reports, Mikoshiba et al [28] study in Japan found that adherence of cancer patients on chemotherapy to self-care reduced the incidence of hand foot syndrome. In present study, a significant association was observed between breast cancer and higher frequency of HFS (p=0.05). This finding is similar to results of Azuma et al [29] study in Japan which found that a significantly higher correlation between patients with breast cancer treated with Capecitabine and high incidence of hand foot syndrome. Another study conducted in USA by Patel et al [30] found that hand foot syndrome accompanied Docetaxel therapy was also highly related to breast cancer. Toyama et al [31] evaluated the pyridoxine in prevention of hand foot syndrome associated with breast cancer, but they failed in proving its effectiveness. Our study showed also a significant association was observed between cancer patients treated with Capecitabin and higher frequency of HFS (p=0.004). This finding is consistent with many literatures such as Sanghi et al [32] study in India and Kamil et al [33] study in Malaysia which all documented higher incidence of hand foot syndrome in relation to Capecitabine chemotherapy for cancer patients. The Capecitabine is considered as fluoropyrimidine a systemic prodrug of 5-FU that are administered orally. Nowadays, it is indicated for colorectal cancer and as monotherapy or in combination with Docetaxel in metastatic breast cancer [34]. Milano et al [35] study in France stated that increased epidermal basal cells proliferation rates of the palm make them more vulnerable for skin changes caused by chemotherapy. For Capecitabine, the thymidine phosphorylase enzyme-facilitated local production of 5FU in palm might be the mechanism of hand foot syndrome [35].

5. CONCLUSIONS

The incidence rate of hand foot syndrome for cancer patients is within acceptable international range. Severity distribution of hand foot syndrome for cancer patients is within acceptable international range. Hand foot syndrome tends to be highly related to breast cancer treated with Capecitabine in addition to long duration of chemotherapy use. This study recommended the physicians to prevent hand foot syndrome during chemotherapy treatment of cancer by different methods like reduction of dose, shorter duration use and use of preventive drugs or self-care.

Ethical Clearance

Ethical approval was taken from the Scientific Council of Iraqi Board for Clinical Pharmacy

Data collection was in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches involving humans, verbal informed consent obtained from all participants. Data and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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