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ORIGINAL ARTICLE

Incidence of Hand-Foot Syndrome in Metastatic Breast Cancer Patients Treated with Capecitabine in Middle Euphrates Region of Iraq

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ABSTRACT

Background: Capecitabine is a fluoropyrimidine which is converted to 5-fluorouracil (5-FU) at the tumor site.

Objectives: To evaluate the incidence of hand-foot syndrome (HFS) in metastatic breast cancer patients treated with capecitabine in our region.

Methods: A retrospective descriptive study conducted at Al- Hussein cancer center in Karbala province of Iraq between April 2018 and August 2020.There were 58 female patients with metastatic breast cancer treated with capecitabine as monotherapy included in our study.

Results: About 77.59% of our patients developed HFS , patients > 40 years old were the most affected age group in 84.44%. Majority of our patients were grade 1 in 66.67% and more than half patients (51.11%) developed their first episode of HFS after third cycle.

Conclusion: Capecitabine is a well-tolerated treatment with low toxicity, most of our patients presented in early grades and first symptoms tend to occur after third cycle.

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INTRODUCTION

Hand-foot syndrome (HFS), also called as palmarplantar erythrodysesthesia is a dermatological reaction occurs in hand palms and/or the soles of the feet [1,2]. Chemotherapy-induced HFS is a prevalent complication of both traditional chemotherapeutic agents and the newer targeted molecular drugs. It have a significant impact on patients quality of life and chemotherapy dose adjustment are usually required [3].

Capecitabine which is a systemic oral prodrug of 5-fluorouracil (5-FU) demonstrated a favorable safety profile in the treatment of metastatic breast cancer with avoidable complications of intravenous infusion and response rate in more than 37% of patients [4]. Unfortunately HFS was the most common capecitabine reported adverse effect in ≥ 50% of patients leading to significant morbidity in patients receiving this agent [5]. While HFS pathogenesis is not completely clear , it could be caused by capillaries damage in hand palms & soles of the feet , leading to a COX inflammatory-type reaction or it may be due to capecitabine metabolism enzymes such thymidine phosphorylase and dihydropyrimidine dehydrogenase [6].

HFS manifestations vary among patients , it may present as pain, swelling, desquamation, ulceration, and blistering. If capecitabine is not stopped , skin destruction may happened with desquamation, bullous formation and secondary bacterial infection in advanced conditioins [7].

Since capecitabine is an oral treatment given at home, it is vital that patients must realize the value of adherent to medication , be aware of HFS risk and contact doctor or nurse if symptoms developed. Dose reduction or drug interruption with supportive care with emollients , cold compressors and topical steroids may alleviate the symptoms [6]. Avoidance of sunlight, heat, elevation of hands & feet and oral pyridoxine may relieve symptoms [8]. While several studies have shown ethnic differences in the clinical manifestation of HFS , we try in this study to assess the incidence and determine the severity of HFS in the Middle Euphrates region of Iraq. It can help to develop future treatment strategies among breast cancer patients in this area of our county.

MATERIALS AND METHODS

We conducted a retrospective descriptive study to evaluate capecitabine related HFS in 58 female patients with metastatic breast cancer from April 2018 to August 2020 in Middle Euphrates region of Iraq. Our data were obtained from cancer registry department in Al Hussein cancer center in Karbala. This center was established in November 2011 with oncology & hematology wards. It covers not only Karbala population but other patients from Middle Euphrates region in Iraq are referred to this center for solid & hematological malignancy treatment [9,10].

We included all naive metastatic breast cancer patients with visceral crisis receiving capecitabine (1000-1250 mg/m^2 PO twice daily D1-D14 every 21 days) as monotherapy. Patients who received combined drugs , previously treated , poor performance status, impaired renal function or liver function were excluded from our study. The grading of HFS was regarding to national cancer institute classification system as shown in Table 1.

Table 1. **National cancer institute classification system for HFS** [11].

Grade	National cancer institute classification
Grade 1	Minimal skin changes (erythema , edema, or hyperkeratosis) without pain
Grade 2	Skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental activities of daily living.
Grade 3	Severe skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting self-care activities of daily living.

Data also provided further information about age, performance status, timing of HFS first episode and if dose adjustment was required. Selected topic was accepted by scientific committee; official acceptance was taken from health authorities to conduct this study. Collected information was kept confidential.

RESULTS

There were 58 female patients with naive metastatic breast cancer enrolled in our study , mean age of studied sample was 48.87 years old, range (26-73) years. HFS presented in 45 patients (77.59%) while there was no symptoms in 13 patients (22.41%) as shown in Figure 1.

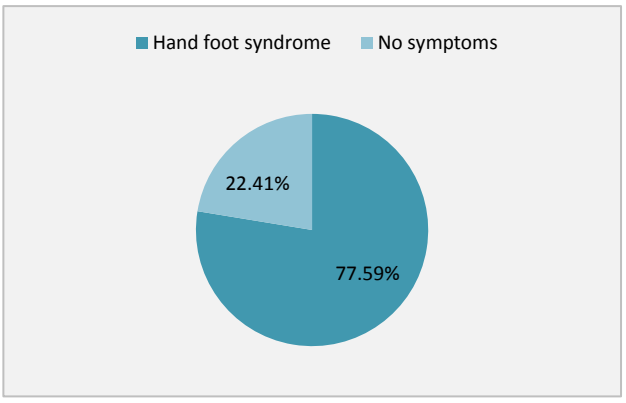

Figure 1. **Incidence of HFS in 58 patients.**

Patients with age group (41-50) years were mostly affected in 15 patients (33.33%) followed by age group (50-60) years in 12 patients (26.66%) as shown in Table 2.

Table 2. **Age distribution of HFS patients.**

Age in years	N (%)
< 30	3 (6.67%)
31-40	4 (8.89%)
41-50	15 (33.33%)
51-60	12 (26.66%)
61-70	8 (17.78%)
>70	3 (6.67%)
Total	45 (100%)

Majority of our patients presented with grade 1 in 30 patients (66.67%) followed by grade 2 in 13 patients (28.89%) and grade 3 in 2 patients (4.44%) as shown in Table 3.

Table 3. **Grades of HFS in our study.**

Grades	N (%)
Grade 1	30 (66.67%)
Grade 2	13 (28.89%)
Grade 3	2 (4.44%)

In our study first episode of HFS developed after third cycle in 23 patients (51.11%) followed by 11 patients (24.44%) after second cycle, 6 patients (13.33%) after forth cycle, 3 patients (6.67%) after fifth cycle, 2 patients (4.44%) after first cycle and none of our patients developed HFS after sixth cycle as shown in Table 4. Dose adjustment was done in 13 patients of which 7 patients received 75% of dose, 4 patients received 50% of dose while drug discontinued in 2 patients.

Table 4. **Timing of first episode.**

Cycles number	N (%)
Cycle 1	2 (4.44%)
Cycle 2	11 (24.44%)
Cycle 3	23 (51.11%)
Cycle 4	6 (13.33%)
Cycle 5	3 (6.67%)
Cycle 6	0 (0.00%)

DISCUSSION

In 2018 there were more than 2 million newly diagnosed patients with breast cancer, accounting about one quarter of cancer cases among women. In the vast majority of the countries , this disease is the most frequently diagnosed cancer [12]. In Iraq breast cancer represents the most common cancer in female presenting more than 40% of newly diagnosed cancer , making treatment of breast cancer as a great challenge to health workers in our country [13,14]. Drugs side effects had poor impact on cancer patients compliance , understanding these side effects and urgent treatment leading to improve treatment outcomes [15,16].

In our study 77.59% of patients taking capecitabine developed HFS, same results in Japan 72.4%, USA 68.3% and Korea 77.4% [7,17,18]. While only 38.9% of German patients developed HFS [19]. Patients > 40 years were the most affected by HFS, this may be explained by that majority of Iraqi breast cancer patients were diagnosed in this age group [20].

Most of our patients were grade 1 in 66.67%, same results in India 60%, USA 89%, Japan 66.7% and Korea 50.7% [7,17,18,21,22]. But studies in Singapore showed that grade 2 was the most frequent in 31.42% of patients [23].

Majority of our patients developed their first episodes of HFS after third cycle , while in studies in USA & Korea most of patients developed their first episodes within the first two cycles of treatment [7,18].

CONCLUSIONS

Our study revealed that HFS incidence is common in metastatic breast cancer patients treated with capecitabine . Cases older than 40 years were the most affected, grade 1 was the most frequent grades and majority of our patients developed HFS after third cycle. These results highlights the need for future studies in other parts of Iraq with larger number of patients to understand this side effect and decrease its significant influence on quality of life in our patients.

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