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ORIGINAL RESEARCH PAPER

A study on the incidence and severity of hand-foot syndrome in cancer patients treated with capecitabine

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ABSTRACT

***Introduction**: Hand-Foot Syndrome is a localised dermatologic reaction and is one of the most common adverse effects of capecitabine containing chemotherapy in cancer patients. Although it is not life-threatening toxicity, it can be quite serious, leading to a delay in or discontinuation of anticancer therapy. **Objectives**: To estimate the incidence of Hand-Foot Syndrome receiving treatment with capecitabine containing chemotherapy at State Cancer Institute and to determine the severity of Hand-Foot Syndrome. **Materials and methods**: The study was a hospital-based retrospective study conducted at a State Cancer Institute in Assam, for a period of six months from August 2019 to January 2020. A total of fifty-one cancer patients were included, out of which thirty-three had Hand-Foot Syndrome. **Results**: Overall incidence of Hand-Foot Syndrome was 64.7% cases, 39.4% of cases in males and 60.6% cases in females. As per NCI-CTCAE grading, 60.6% of cases had grade 1 HFS, 36.4% of cases had grade 2 and 3% of cases had grade 3 HFS. The first episode of HFS occurred in 12.1% cases after cycle 1, 60.6% cases after cycle 2 and 27.3% cases after cycle 3. **Conclusion**: The incidence of HFS is common in patients treated with capecitabine and is usually starts within the first two cycles of therapy. It has a significant influence on patients quality of life and abilities.*

***Keywords:** NCI-CTCAE; monotherapy; combination therapy.*

INTRODUCTION

Hand-foot syndrome(HFS), which is also known as palmoplantar erythrodysesthesia is a localized dermatologic reaction associated with the initiation of therapy with certain chemotherapeutic agents and is the most frequently reported side effect of oral capecitabine.[1] Hand-foot syndrome (HFS) has been previously reported as a side effect in 45-56% of patients treated with capecitabine.[2]

Although the exact pathogenesis of HFS is not clear, it may be due to damaged deep capillaries in the soles of the feet and palms of the hands, leading to a COX inflammatory-type reaction, or related to enzymes involved in the metabolism of capecitabine, namely, thymidine phosphorylase and dihydro pyrimidine dehydrogenase.[3]

The pathological changes which occurred include the vacuolar degeneration of the basal keratinocytes, dermal perivascular lymphocytic infiltration, apoptotic keratinocytes and dermal edema.[4] The clinical features of HFS are characterized by a prodrome of dysesthesia, painful oedema and erythema of the palms, digits, and soles which may evolve into blisters and erosions.[1] Although not a life-threatening toxicity, it can be quite serious, leading to a delay in or discontinuation of anticancer therapy and affecting normal daily activities and the quality of life. If not promptly managed, HFS can progress to an extremely painful and

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debilitating condition, causing significant discomfort and impairment of function, potentially leading to worsened quality of life in patients receiving capecitabine.[5]

However, treatment interruption and or dose reduction usually leads to rapid reversal of the signs and symptoms of HFS along with supportive treatments can help alleviate it.[6] This study aims to estimate the incidence of Hand-Foot Syndrome among cancer patients receiving treatment with capecitabine containing chemotherapy at state cancer institute and to determine the severity of Hand-Foot Syndrome.

METHODS AND MATERIALS

The study was a hospital-based retrospective study conducted at State Cancer Institute (SCI) in Assam, who attended the Department of Medical Oncology for a period of six months from August 2019 to January 2020. A total of Fifty-one cancer patients were included, who attended for the capecitabine therapy. Out of these fifty-one patients, thirty-three had Hand-foot syndrome. The data were collected from the Medical Records Department and patient's records were taken according to criteria as below: **Inclusion criteria:** 1) Above 18 years age group; 2) Patients who were on treatment with capecitabine containing chemotherapy. **Exclusion criteria:** 1) Less than 18 years age group; 2) Pregnancy; 3) Lactating mother. We retrieved the data regarding patient's characteristics (age, sex, performance status, the severity of HFS, first episode of HFS from which cycle of chemotherapy, dose adjustment requirement, capecitabine therapy as either monotherapy or combination therapy and chemotherapy settings as either adjuvant or palliative) by reviewing the patient's file from Medical Records Department.

Patients who were on capecitabine were assessed clinically/physically in every cycle receiving capecitabine chemotherapy.

As per NCI CTCAE grading, the severity of Hand-Foot Syndrome was graded who were on capecitabine therapy as shown in **Table 1**.

Table 1 National cancer institute common terminology criteria for adverse events[1]

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

Performance status is assessed using Eastern Cooperative Oncology Group (ECOG) performance status grading as shown in **Table 2**.

Table 2 ECOG Performance Status[7]

Grade 0	Fully active, able to carry on all pre-disease performance without restriction
Grade 1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of light and sedentary nature
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of working hours
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of working hours
Grade 4	Completely disabled. Cannot carry on any self-care. Confined to a bed or chair
Grade 5	Dead

RESULTS

In this study, out of 33 cases of HFS, 13 were males (39.4% cases) and 20 were females (60.6%) with male-female ratio were 1:1.5. As per NCI CTCAE grading, 60.6% of cases had grade 1 HFS, 36.4% of cases had grade 2HFS and 3% of cases had grade 3 HFS. The first episode of HFS occurred in 12.10% cases after cycle 1, 60.60% cases after cycle 2, 27.30% cases after cycle 3 and none occurred after cycle 4. Dose adjustment was done among 33 cases of HFS, of which 12 cases had received 75% of the total dose, 5 cases had received 50% of total dose and other 2 cases were discontinued. Capecitabine induced HFS to include primary diseases like CA stomach, CA colon, CA breast, CA rectum etc. About 19 cases (57.60%) received capecitabine as monotherapy and 14 cases (42.4%) as combination therapy. Some 12 cases (36.4%) was on adjuvant setting and 21 cases (63.6%) were on the palliative setting.

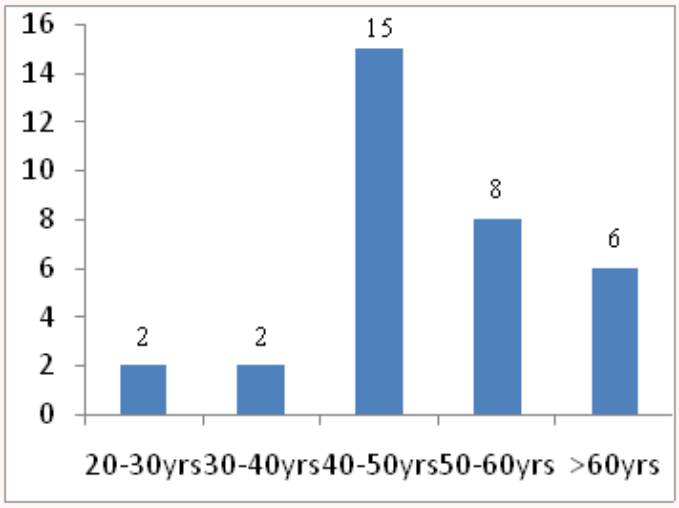

Figure 1 Age distribution

Among 33 HFS patients, 2 cases were in 20-30 yrs age group, 2 cases were in 30-40 yrs age group, 15 cases were in 40-50 yrs age group, 8 cases were in 50-60 yrs age group and 6 cases were in >60 yrs age group.

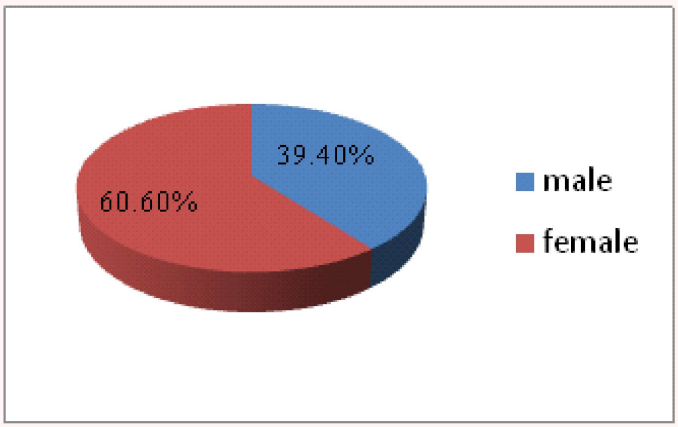

Figure 2 Gender distribution

Out of 33 HFS patients, 13 cases were males (39.4% cases) and 20 cases were females (60.6%) with male-female ratio was 1:1.5.

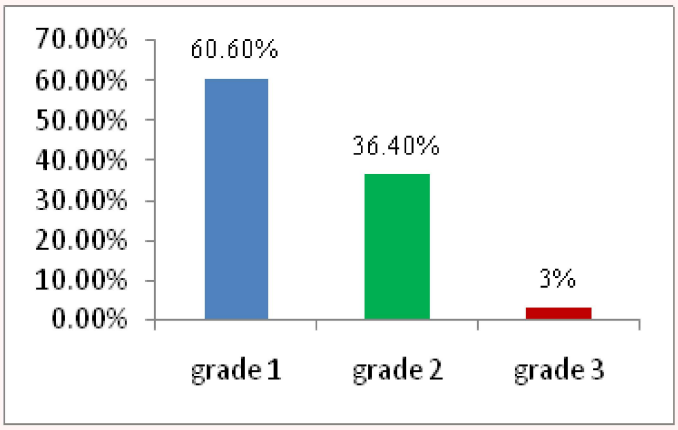

Figure 3 Severity of HFS

As per NCI CTCAE grading, 60.60% of cases had grade 1 HFS, 36.40% of cases had grade 2HFS and 3% of cases had grade 3 HFS.

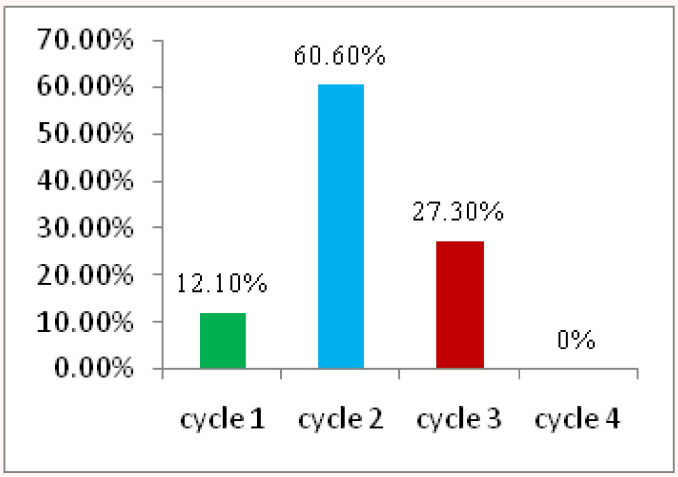

Figure 4 First episode of HFS

The first episode of HFS occurred in 12.10% cases after cycle 1, 60.60% cases after cycle 2, 27.30% cases after cycle 3 and none occurred after cycle 4.

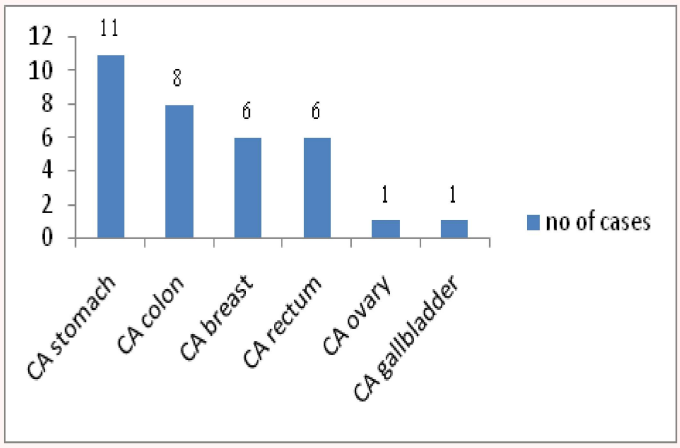

Figure 5 Primary diseases

Patients those who were on Capecitabine induced HFS includes primary diseases like CA stomach (11cases), CA colon (8 cases), CA breast (6 cases), CA rectum (6 cases), CA Ovary (1 case) and CA Gall bladder (1 case).

DISCUSSION

In this study, the overall incidence of HFS was found to be 64.7%, with a slight predominance among females with male-female ratio was 1:1.5 (13 males and 20 females).

In this study, 60.6% of cases experienced grade 1 HFS. A study done by Matsuoka Hiroshi et al had 66.7% cases of grade 1 HFS, 10% cases of grade 2 and none had grade 3 HFS.[8] The Study of Azuma Yuichiro et al showed 37.8% cases of grade 1 HFS, 31.6% cases of grade 2 and 3.1% cases of grade 3.[9] A Study done by Yap Yoon Sim et al found 28.6% of grade 1 HFS, 31.42% of grade 2 and 2.9% of grade 3 HFS.[6] Son Hyun Sook et al study showed that 50.7% had grade 1, 33.8% had grade 2 and 15.5% had grade 3.[10]

Among the 33 patients who had HFS, 20 patients (60.6%) had their first episode after cycle 2. The Study done by Son Hyun Sook et al showed that 26.1% had the first episode of HFS after cycle 1 and 73.9% had after cycle 2.[9]

In this study, 12 cases (36.4%) of HFS was on adjuvant setting and 21 cases (63.6%) of HFS was on the palliative setting. A Study done by Yap Yoon Sim et al found that those who had HFS had 21% cases were on adjuvant and 79% cases were on palliative.[6]

In the present study, about 19 (57.60%) cases, received capecitabine as monotherapy and 14 (42.4%) cases as combination therapy. A study done by Muller Volkmaret al showed that those who had HFS received capecitabine as monotherapy in 38.8% cases and 61.2% cases received as combination therapy.[11]

CONCLUSION

The incidence of HFS is common in patients treated with capecitabine and is usually starts within the first two cycles of therapy. Although the incidence of a severe grade of HFS is low, it can have a significant influence on patient's quality of life and abilities. Prevention, early recognition, and

implementation of various management strategies for HFS are important in optimizing patient's quality of life and minimizing unfavourable outcomes. The study comprises of relatively a small sample size for a short period. Hence, a larger prospective study with a large sample size for long duration is required to arrive at a definite conclusion. Whether the results of the present study can be reproduced in other multicentre studies has yet to be determined. Further studies are therefore necessary.

Limitations: Varying doses of capecitabine used in this study and relatively small sample size and short duration of the study.

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REFERENCES

1. Hoesly FJ, Baker SG, Gunawardane ND, Cotliar JA. Capecitabine-induced hand-foot syndrome complicated by pseudomonal super infection resulting in bacterial sepsis and death: case report and review of the literature. Arch Dermatol 2011;147(12):1418-23.
2. Abushullaih S, Saad ED, Munsell M, Hoff PM. Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. Cancer Invest 2002;20(1):3-10.
3. Saif MW. Capecitabine and hand-foot syndrome, Expert Opinion on Drug Safety 2011;10(2):159-69.
4. Lee SD, Kim HJ, Hwang SJ, Kim YJ, Nam SH, Kim BS. Hand-foot syndrome with scleroderma-like change induced by the oral capecitabine: a case report. Korean J Intern Med 2007;22(2):109-12.
5. Kang YK, LeeSS, Yoon DH, LeeSY, YoungJC, Kim MS, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study. J of clinical oncology 2010;28(24):3824-9.
6. Yap YS, Kwok LL, Syn N. Predictors of hand-foot syndrome and pyridoxine for prevention of capecitabine-induced hand-foot syndrome: a randomized clinical trial. JAMA Oncol 2017;3(11):1538-45.
7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55
8. Hiroshi Matsuoka, Yoko Katagata, Hideki Ohta, Koutarou Maeda. Multidisciplinary approach to the management of capecitabine associated hand foot syndrome in cancer patients receiving capecitabine plus oxaliplatin and bevacizumab for advanced colorectal cancer. Fujita Medical Journal 2017;3(1):1-5.
9. Yuichiro Azuma, Kojiro Hata, Kimie Sai, Ryoko Udagawa. Significant association between hand-foot syndrome and efficacy of capecitabine in patients with metastatic breast cancer. Biological and pharmaceutical bulletin June 2012;35(5):717-24.
10. Son HS, Lee WY, Lee WS, Yun SH, Chun HK. Compliance and effective management of the hand-foot syndrome in colon cancer patients receiving capecitabine as adjuvant chemotherapy. Yonsei Med J 2009;50(6):796-802.
11. Muller V, Fuxius S, Steffens CC, Lerchenmüller C, Luhn B. Quality of life under capecitabine (Xeloda®) in patients with metastatic breast cancer: data from a german non-interventional surveillance study. Oncology research and treatment 2014;37(12):748-55.