Chemotherapy-Induced Hand-Foot Syndrome: Clinical and Epidemiological Approach to Cancer Patients

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Síndrome Mão-Pé Induzida por Quimioterapia: Abordagem Clínica e Epidemiológica de Pacientes com Câncer

Síndrome Mano-Pie Inducida por Quimioterapia: Enfoque Cínico y Epidemiológico de Pacientes con Cáncer

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Abstract

Introduction: Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia is a toxic skin reaction resulting from antineoplastic chemotherapy, which occurs frequently and is an important clinical problem for individuals with malignant neoplasm. The development of HFS may lead to treatment discontinuation and, often, a reduction of the chemotherapy dose. **Objective:** To analyze the clinical and epidemiological data of patients with HFS treated with chemotherapy. **Method:** A descriptive and retrospective study, with data collected from January 2013 to January 2014 in medical charts using the register of antineoplastic toxicities and the *Eastern Cooperative Oncology Group Performance Status* scale. **Results:** It were analyzed 250 charts. Of these, 70 underwent chemotherapy treatment, and 15 (21.4%) presented HFS, with grade 1 toxicity after 2 cycles of capecitabine (13.3%); grade 2 after two, four and up to 12 treatment cycles (40%); grade 3, after five and 11 cycles of capecitabine (20%) and with grade 4, one patient presented such toxicity after two cycles of capecitabine and another patient presented HFS after two cycles of liposomal doxorubicin (13.3%). **Conclusion:** Chemotherapy treatment causes high risk of presenting HFS. However, this syndrome showed low incidence in cancer patients receiving treatment with capecitabine, doxorubicin and cytarabine.

Key words: Hand-foot Syndrome/epidemiology; Drug Therapy; Neoplasms.

Resumo

Introdução: A síndrome mão-pé (SMP) ou eritrodisestesia palmopalmar é uma reação cutânea tóxica decorrente da quimioterapia antineoplásica, que ocorre com frequência e constitui importante problema clínico ao indivíduo com neoplasia maligna. O desenvolvimento da SMP pode levar à interrupção do tratamento e, com frequência, à redução da dose do quimioterápico. **Objetivo:** Analisar os dados clínicos e epidemiológicos de pacientes com SMP tratados com quimioterapia. **Método**: Estudo descritivo e retrospectivo, com coleta de dados realizada entre janeiro de 2013 e janeiro de 2014 em prontuários utilizando-se do registro de toxicidades dos antineoplásicos e da Escala de *Performance Status do Eastern Cooperative Oncology Group*. **Resultados:** Foram analisados 250 prontuários. Destes, 70 realizaram tratamento quimioterápicos e 15 (21,4%) apresentaram SMP, com toxicidade grau 1 após uso de dois ciclos de capecitabina (13,3%); grau 2 após dois, quatro e até 12 ciclos de tratamento (40%); grau 3 após cinco e 11 ciclos de capecitabina (20%); e, em grau 4, um paciente apresentou toxicidade após dois ciclos de capecitabina e outro, apresentou SMP após dois ciclos de doxorrubicina lipossomal (13,3%). **Conclusão:** O tratamento com quimioterapia causa alto risco de apresentar SMP. No entanto, mostrou baixa incidência dessa síndrome em pacientes com câncer que fazem tratamento com capecitabina, doxorrubicina e citarabina.

Palavras-chave: Síndrome Mão-Pé/epidemiologia; Tratamento Farmacológico; Neoplasias.

Resumen

Introducción: El síndrome de manos y pies (SMP) o la eritrodistesia palmopalmar es una reacción cutánea tóxica resultante de la quimioterapia antineoplásica, que ocurre con frecuencia y es un problema clínico importante para las personas con neoplasia maligna. El desarrollo del SMP puede conducir a la interrupción del tratamiento y, a menudo, a una reducción de la dosis de quimioterapia. **Objetivo:** Analizar los datos clínicos y epidemiológicos de pacientes con SPM tratados con quimioterapia. **Método:** Estudio descriptivo y retrospectivo, con recopilación de datos realizada entre enero de 2013 y enero de 2014 en registros médicos utilizando el registro de toxicidad antineoplásica y la Escala de estado de rendimiento del Grupo de Oncología Cooperativa del Este. **Resultados:** Se analizaron 250 registros médicos. De estos, 70 se sometieron a tratamiento de quimioterapia y 15 (21,4%) presentaron SMP. Con toxicidad de grado 1 después del uso de 2 ciclos de capecitabina (13,3%); grado 2 después de dos, cuatro y hasta doce ciclos de tratamiento (40%); grado 3 después de cinco y 11 ciclos de capecitabina (20%); grado 4, y un paciente presentó dicha toxicidad después de dos ciclos de capecitabina y otro paciente presentó SMP después de dos ciclos de doxorrubicina liposomal (13,3%). **Conclusión:** El tratamiento con quimioterapia causa un alto riesgo de presentar SMP. Sin embargo, ha mostrado una baja incidencia de este síndrome en pacientes con cáncer que reciben capecitabina, doxorrubicina y citarabina.

Palabras clave: Síndrome Mano-Pie/epidemiología; Tratamiento Farmacológico; Neoplasias.

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INTRODUCTION

The use of antineoplastic drugs extends the survival of the patients with diversified neoplasms. It is known, nevertheless, that the most prolonged exposure to the substances increases the risk of side effects in different organs and tissues[1]. The antineoplastic chemotherapics act on normal and neoplastic cells in different proportions within the organism because of differences in the metabolic processes of these two cellular populations. One of the characteristics of the tumoral cells is its high rate of cellular division. The bone marrow cells, of the hair follicles and of the mucosal lining have a high rate of proliferation as well, like for instance, the hand-foot syndrome (HFS) [2].

HFS or palmar-plantar erythrodysesthesia is a toxic cutaneous reaction resulting from antineoplastic chemotherapy that occurs frequently and is an important clinical problem of the individual with malignant neoplasm[3].

The development of HFS may lead to the interruption of the treatment and, frequently, reduction of the chemotherapics dose. Even when it does not represent limiting-dose factor of the antineoplastic drugs may cause chronic discomfort and limitation of the daily activities [3]. It results from the high vulnerability of the cutaneous tissues to the action of the antineoplastic drugs and it characterizes by edema, pain, erythema and desquamation of hand and feet after the administration of drugs as capecitabine, fluorouracil, cytarabine and doxorubicin[4].

The accurate mechanisms that lead to the onset of HFS are yet unknown. In theory, only hand and feet are involved in differences of temperature, differentiated microvascularization, elevated rate of keratinocytes, high frequency of eccrine glands and epidermal cells dividing quickly[5,6]. Cyclooxygenase-2 (COX-2) overexpression can be a potential mediator for the development of HFS. It is possible that the cytostatic therapy can mediate a toxic effect over the basal keratinocytes. Apparently, the rate of reproduction of these cells become more susceptible to the toxic effects of chemotherapy. This hypothesis is supported by histological and structural investigations where it were found a basal compensatory hyperproliferation of the epidermal, in addition to a premature and irregular keratinization and increase of mastocytes[7]. It is suspected, still, the potential existence of a genetic base[8].

It is a syndrome that can involve the following nursing diagnosis, according to *Nanda International Nursing Diagnoses*[9]: ineffective peripheral tissue protection (000204), ineffective self-control of health (00078), ineffective protection (00043), impaired housekeeping, impaired home maintenance (00098), risk of low situational self-esteem (00153), anxiety (00146), risk of feeling of helplessness (00152), risk for impaired skin integrity (00047), impaired physical mobility (00214), acute pain (00132), low situational self-esteem (00120), ineffective role performance (00055), impaired social interaction (00052) and self-care deficit for feeding (00102), bathing (00108), intimate hygiene (00110) and dressing (00109).

The most utilized classification of HFS is the Common Terminology Criteria for Adverse Events (CTCAE, v. 4.0)[10]. There are three grades of this syndrome: the first, grade, 1, presents numbness, dysesthesia, paresthesia, edema, erythema or discomfort of hands or feet, but there is no interference in the performance of activities of daily living (ADL), actions executed by patients in their daily life as self-care and ambulate; or instrumental ADL (IADL), actions where objects are handled, as how to cook and dress[9]. Next, grade 2 has manifestations of painful erythema and edema in hands and/or feet that already affected the performance of ADL and IADLs. The wet desquamation, ulcerations, appearance of vesicles and intense pain in the members affected by the disease are presentations of grade 3, and discomfort is aggravated to the point of impairing labor activities, ADL and IADLs[10,11].

Overall, the complaints are related to feeling of stress in hands and feet, tingling, burn or twinges in the palms of the hands, fingers, soles of the feet or plantar regions of the feet fingers[12]. Most of the times, there are large symmetrical areas of grayish erythema that can be accompanied, in acute cases, of intense lamellar desquamation, edema, blisters, erosions, or rarely, ulcerations. The presence of dysesthesia is common, which constitutes a differential symptom between this syndrome and other erythematosus diseases. In addition, it is common the presence of pruritus in hand or sole. The severity of the symptoms is related to the cumulative-dosage, worsening at each new cycle of the antineoplastic drug, but can recess spontaneously during the intervals [13].

Basically, the treatment consists of topic procedures. Some proposals have been established such as the use of urea or lanoline-based protective ointments followed by reduction of the dose or even interruption of the chemotherapic[4,14]. The use of soft emollient creams is advisable[13]. Based in a case report, the authors Simão et al.[13] describe in their study the utilization of a neutral aqueous Aloe Vera cream with positive results and improvement. It is known that this medicinal plant has humectant, emollient, anti-inflammatory, healing and regenerative properties of tissues, with the inhibition of products derived from the metabolism of the arachidonic acid [13]. Other proposals of HFS control and treatment are

been explored, such as topic therapy with corticosteroids, still under investigation[4]. For grade 1 affections, it is suggested that the patients avoid mechanic friction of the skin of palms of hands and feet. An interesting approach is the prophylactic use of topic adhesives of nicotine to promote local vasoconstriction to reduce the action of capecitabine in hands and feet[11].

After the first episode of HFS, since the symptoms have reduced or receded to grade 1, chemotherapy may return to the initial scheme. For grade 2 or 3 conditions, when it is not considered the suspension of the treatment, the doses of the drugs must be modified according to the CTCAE-based individual regimens of dose change. In the cases, however, of HFS grade 3 recurrence, it may be necessary the definitive suspension of the chemotherapic[11]. The complete cure of HFS after the antineoplastic treatment is possible when no localized ulcerations existed. The main complications observed, although rare, are the infections with staphylococcus or gram-negative bacteria or the occurrence of erysipela[11].

Other supporting measures include the use of high potency topic corticosteroids and topic keratolytic aimed to reduce the inflammation, pain and hyperkeratosis, respectively. In addition, the application of antiperspirant in the feet's soles o and in the hands' palms demonstrated a reduction of the incidence of HFS in patients using pegylated liposomal doxorubicin. The regional cooling was also demonstrated effective to prevent HFS, but this is not viable for orally administered drugs or via continuous infusion[15].

Studies of low incidence level indicate that topic sulfoxide dimethyl, nicotine patch, oral vitamin E and cytoprotective amifosfotin agent can be useful for the treatment and prevention of HFS. Topic heparin can also be beneficial in the management to reduce the skin inflammation and diminish the interruptions and discontinuation of the chemotherapy treatment with multikinase inhibitor[15].

The use of urea-based creams in low friction bandage with change and application of cream twice a day has shown to be effective in the prevention of HFS multikinase inhibitor-related[15].

It is seen, therefore, that the impact of this syndrome in the quality of life of the individual with cancer deserves special attention by the healthcare team. Because of this and while considering the importance of systematized nursing care, this study has the objective to analyze epidemiologic and clinical data of oncologic patients with HFS under the perspective of the nursing professional, further to describe one of the main diagnosis of nursing related to HFS in patients treated in a chemotherapy ward at a private clinic in Brazil's northeast region.

METHOD

Descriptive and retrospective study. The data were obtained from patient's charts who were treated in a private chemotherapy ward in the city of Aracaju, Sergipe, Brazil between January 2013 and January 2014 twice a week, according to the availability of the investigators through a complete evaluation of the adverse reactions found in the charts focused to HFS.

During the period data were collected, there were 560 patients in oncologic treatment, from this total, 250 had information collected and 70 charts were selected according to the eligibility criteria. These criteria were: patients older than 18 years, with confirmed diagnosis of cancer by anatomopathological or cytological tests with charts correctly filled where it were obtained essential information as sociodemographic data, risk factors, location of the tumor, treatment performed with chemotherapics capecitabine, fluorouracil, cytarabine and doxorubicin, vemurafenib and dabrafenib, adverse reactions, nursing evolution report and respective diagnosis.

Therefore, the nursing diagnosis, an important mechanism to conduct the procedures of care to the patient and quality of the assistance, were selected according to the grade of toxicity of the referenced syndrome and recognition of risk factors as age, gender, race, tobacco and alcohol addiction that can allow the identification of modifiable factors, which increase the incidence.

The data were collected through a form for reporting antineoplastic toxicities that includes the evaluation of the medullar, gastrointestinal, dermatological, neurological toxicities, ototoxicity and metabolic, functional and cardiac alteration[16].

In addition, it was used the *Performance Status* of the *Eastern Cooperative Oncology Group* (PS-ECOG)[17], that evaluates to what extent the disease affects the capacity to develop the patient's daily activities skills. In the charts, it was considered the grades according to CTCAE[10] for the patients with HFS, commonly used in the facilities where the data were gathered.

The results obtained were analyzed with the software *Statistical Package for Social Sciences* (SPSS) 17.0. Descriptive and inferential statistics with calculations of frequency were performed. In the descriptive analysis, it was used the mean, standard-deviation (SD) and, when necessary, the median for quantitative variables and absolute values and percent for categorical variables.

The Institutional Review Board of the "University Federal de Sergipe" approved this study, report number 560.065. The informed consent form signature was waived

because it is a retrospective study involving data collected from charts.

RESULTS

It were analyzed 250 charts in the period of data collection; of these, 70 (28%) utilized the following drugs as treatment: capecitabine, fluorouracil, cytarabine and doxorubicin, the main responsible for the onset of HFS, resulting from chemotherapic treatment[4]. Amidst the 70 patients, 15 had diagnosis of HFS, and of these, 14 used all the drugs mentioned and only one used fludarabine, gemcitabine and mitoxantrona. Other drugs claimed in the literature as causal agents of HFS were included in the study, representing the other patients such as vemurafenib and dabrafenib. These, however, did not present results of development of the syndrome discussed, therefore, were unrelated.

Of the 70 patients under HFS-associated chemotherapics management, 61.4% were Caucasian, 35.7%, brown and 2.9%, Afro-descendants, being 40 women (57.1%) and 30 men (42.9%). Of the 15 patients who presented HFS, females predominated, with eight women (53.3%) and seven men (46.6%), mean age of 57 years (SD ± 14.6). Still among the 15.73, 3% were Caucasian and 26.6%, brown and 33.3%, retired. Sixty percent were administrative assistants and 40% did not inform, 13.4% were computer analysts, 13.3%, autonomous, 13.3%, public officers and 13.3%, physicians; 73.3% were married and 26.6%, divorced. As for tobacco and alcohol addiction, 0% and 12.5% respectively.

The incidence of HFS among Caucasian patients was 23.2%, among browns, 20%; among Afro-descendants, (0%) the non-incidence of HFS must likely be related to the limited sample of this population in the study and, therefore, it has no statistical and epidemiological value.

Regarding the location of the primary tumor, 26.6% were in the breast, 20%, colon, 13.3%, esophageal, 13.3% in the stomach. 13.3%, ovary and 13.3%, peritoneum.

About the staging of the disease, 100% presented stage IV, therefore, it is possible to conclude that 100% had metastasis. The metastatic sites of bigger incidence were liver (29.1%), peritoneum (20.8%), lymph nodes (16.6%), uterine tuba (8.3%), suprarenal gland (8.3%), ovary (8.3%) and bones (8.3%).

As for PS, the majority presented PS 1 (73.3%) followed by PS 2 (26.6%). The principal comorbidity presented were cardiopathy (25%). No patient presented systemic arterial hypertension, *diabetes mellitus*, nephropathy or autoimmune disease.

The reduction of the dose was utilized in four patients (26.6%) as a result of the dermatologic toxicity provoked by the chemotherapy used. The cycle of treatment, the antineoplastic drug and the level of toxicity of HFS and the treatment adopted are presented in Table 1.

The impaired comfort (00214) and the ineffective peripheral tissue perfusion (000204) are the prevalent nursing diagnosis related to HFS. The first is defined as the perceived lack of comfort, relief and transcendence in the physical, psycho-spiritual, environmental, cultural and social context; and the last, a decrease in oxygen resulting in failure to nourish the tissues at capillary level capable of compromising health [9].

Because of being the most predominant diagnosis, it is worth mentioning that some of the defining characteristics of the impaired comfort and the ineffective peripheral tissue perfusion as anxiety, moaning, pruritus, feeling of heat, cold and/or discomfort, disturbed sleep patterns, crying and inability to rest; and also, impaired skin integrity, delayed peripheral wound healing, pain in the extremities, edema, paresthesia, absent or reduced pulsation and capillary refill time >3 seconds, respectively. For the same reason, the factors related are important to be mentioned: for the first, there are treatment-related secondary effects, lack of control of the environment, lack of privacy and insufficient resources; for the other, poor knowledge of the process of the disease and of the aggravating factors as well as of habits of life, *diabetes mellitus* and hypertension are considerable determinants [9].

Additionally, acute pain (001322) defined as an unpleasant sensorial and emotional experience caused by the existing tissue injury, with sudden or gradual onset, of diverse intensity and anticipated or predictable termination, with duration of nearly 180 days; the deficit of self-care in general (00102, 00108, 00109 and 001010) or domestic actions (00098), which is the impairment of performing feeding actions, total hygiene, clothing and domestic tasks or complementary to these; and the ineffective role performance (00055) when behavioral or self-expressive patterns are atypical to the context, norms or expectations of the environment, are other more frequent nursing diagnosis of patients with HFS [9].

DISCUSSION

HFS is the most common and limiting adverse reaction to capecitabine[4]. Capecitabine (N4-pentyloxycarbonyl-5-deoxy-5-fluorocytidine) is an oral antineoplastic drug with cytotoxic action prescribed for breast, colon, rectum and stomach cancer. It is a prodrug (carbamate of luoropyrimidine) for oral administration of 5'-deoxy-5-fluorouridine (5'-DFUR) converted enzymatically *in vivo* to 5-fluorouracil (5- FU)[18].

Table 1. Cycle of treatment. Chemotherapic agent, grade of toxicity and treatment of the hands and foot syndrome. Aracaju/SE, 2014

Chart	Cycle	Chemotherapic Agent	Grade of toxicity	Treatment of the symptoms of hand-foot-syndrome
01	2	Capecitabine	2	Hydration
02	2	Capecitabine	1	Observation
03	4	Capecitabine	2	Observation
04	12	Capecitabine	2	Not informed
05	11	Capecitabine	3	Not informed
06	3	Capecitabine	Not informed	Reduction of 25% of the dose
07	2	Capecitabine	4	Reduction of dose, hydration, rest
08	2	Capecitabine	2	Hydration
09	2	Capecitabine	1	Observation
10	4	Capecitabine	2	Observation
11	5	Capecitabine	3	Observation
12	12	Capecitabine	2	Not informed
13	11	Capecitabine	3	Not informed
14	3	Capecitabine	Not informed	Reduction of 25% of the dose
15	2	Lipossomal doxorubicin	4	Reduction of dose, hydration, rest

The incidence of this syndrome can vary, affecting 60% of the patients, considering any degree of severity[4]. In this study, the incidence of this adverse reaction was 20.2% of the total of the patients who utilized capecitabine, fluorouracil, citrabine and doxorubicin as treatment.

In a study conducted by Olinto et al.[19], about the attention of the pharmacist to oncologic patients in use of capecitabine, the prevalence of the adverse reaction was 42.2% (n=101). It is worth mentioning that 87% of the patients presented HFS in at least one cycle of follow up. Hoff et al.[20] observed that capecitabine was more well tolerated because the adverse effects most common reported in the study occurred at a lower frequency in patients who utilized this drug than in patients who utilized 5-FU.

About the diagnosis criteria, the tissue integrity is the main factor to be observed during the diagnosis of HFS, and basically this is the result of the interaction among some chemotherapics as inhibitors of multikinase and the factors of vascular growth that reduce the cellular response to capillary micro traumas mainly in sites submitted to great frictions as palms of hands, feet, axillary, causing injuries and diminishing the capacity of cicatrization. The vascular alterations usually precede the alterations of the skin and nails, hairs and furs and, therefore, can favor the early diagnosis of HFS[15].

The great concentration of eccrine ducts in the hands palms and feet soles promotes a bigger accumulation of drugs in these areas, mainly in the thick corneous extract of those who act as reservoir and, because of the toxicity of the chemotherapics, produce oxidative damages and toxic free radicals that cause skin injuries and apoptosis of keratinocytes. Therefore, the frequent inspection of the skin and phaneria of the extremities is of essence during the patient management under the administration of chemotherapics, favoring the prevention of the evolution of HFS and the quality of life of the patients [15].

It is suspected that there is a genetic base as one of the possible causes. A study found a bigger frequency of HFS among African-American treated with capecitabine than in Caucasian patients under the same therapeutic regimen[8]. Another study associated bigger incidence of HFS in Eastern patients in comparison with Western patients under the administration of inhibitors of multikinasis[15]. In this study, it was encountered a similar incidence for Caucasians and Browns, 23.2% and 20%, respectively among patients under chemotherapics associated to HFS; however, in the study, the sample was not sufficient to produce data related to the incidence of HFS in Afro-descendants and Asians.

Effective methods to prevent or cure the syndrome are not yet well established, except for the temporary discontinuation of the treatment, resuming with a reduced dose after partial or total recovery or just with the reduction of the dose for the subsequent cycles for more advanced stages. To prevent and relief the symptoms, it is also indicated moisturizers, cold and wet compresses and general care with the skin[21].

The topic treatment with Aloe Vera was well-succeeded with significant improvement of the tissue integrity, bringing complete relief of the symptoms, basic improvement of the quality of life, further to allowing a fast return of the patient to the chemotherapy treatment, reducing the risks of progression of the oncologic disease. This result suggests that such treatment can be an important adjuvant to the nursing care in patients submitted to antineoplastic treatment with HFS.

The most effective treatment of HFS, suggested by the best scientific evidences, must be focused to the control of the symptoms and to diminish the interruptions of the chemotherapy treatment; for such, preventive measures must be implemented for all the patients at risk of developing this syndrome, using drugs that lessen the inflammation, the hyperkeratosis and the pain, further to the use of strategies that minimize the effect of chemotherapics over the extremities and ointments that favor healing and tissue integrity[3,4,7,15].

Clinical studies have demonstrated that there is a better result in relation to the control of the tumor when the total dose of the chemotherapic is administered in the programmed time, overall, in 21-days intervals between the cycles. This is explained because of the proportion of the tumoral cells that survive or are affected after chemotherapy characterized by the phase of the cellular cycle[22]. However, the delay between the cycles has been the strategy most commonly used to cope with the occurrence of adverse events as neutropenia and anemia in the attempt to avoid the reduction of the dose of the chemotherapic [23].

Recently, it was observed a significant reduction of HFS when combining 5-FU with inhibitor of dihydropyrimidine dehydrogenase. This finding evidenced that toxicity could result from a coproduct of the catabolic degradation of 5-FU, initiated by this enzyme [3].

Although this reaction is dose-limiting and drastically affects the quality of life of the patients, Azuma et al.[24] demonstrated that the outcomes of efficacy as time of failure of the treatment are better in the patients who develop HFS grade ≥2 (HR 0.42, CI95% 0.19-0.90). These findings demonstrate that the development of HFS can be a marker of the efficacy of the therapy, needing additional studies to explore the biomarkers of HSP *versus* the efficacy of capecitabine, in order to match the dosages to the patient response[24].

The limiting factors of this study are related to the reduced number of the sample that failed to allow epidemiological calculations with very relevant level of evidence to estimate the incidence of HFS per chemotherapic administered. The summation of the incidence of HFS in Afro-descendants and Asians was also impaired because of the low number of individuals of these populations in the study sample. Nonetheless, the description of the main diagnosis of HFS and of the treatments for prevention and management of the syndrome can contribute to the practice of nursing in healthcare units in relation to diagnosis, management and reduction of the interruption of the chemotherapic treatment making it more effective, further to improving the quality of life of the patients.

During the study, it was noticed the necessity of more clinical trials about the efficacy of the treatment with emollients, mainly those Aloe Vera-based to manage HFS. There is here also a huge gap in the scientific literature for HFS preventive methods that do not involve the reduction and/or interruption of the chemotherapic treatment, which is in itself a vast segment for oncology-related research.

CONCLUSION

The patient who submits to chemotherapy treatment has high risk of presenting HFS. However, this study demonstrated the low incidence of this syndrome in patients with cancer who are treated with capecitabine, doxorubicin and cytarabine. The patients must be followed up and monitored frequently to minimize or avoid the toxic effects. The action of a multidisciplinary team can bring great benefits to the patient, helping to avoid possible complications caused along the treatment. Other parameters can be further analyzed to corroborate this idea.

To that end, the relevance of the nursing consultation stands out as process of interaction and integration of the relation nurse-patient permeated by education in health. It is important that the nurse monitors its patients for early identification of signs of toxicity, contributing to the control of chemotherapic dosages and prevention of major complications with damages to the patients. It is essential to be aware of the possible diagnosis of nurses and only then provide proper guidance, evaluation and interventions for prevention and relief of HFS; this collaborates to the continuity of the therapy, more adherence to the treatment and improvement of the patient's quality of life.

Furthermore, with the extended use of oral antineoplastic these professionals should focus more in the education of the patients and families, creating strategies to monitor the adverse effects and implement effective interventions.

CONTRIBUTIONS

All the authors participated of the conception and design of the study, analysis and interpretation of data,

wording and review of the manuscript and approved the final version.

DECLARATION OF CONFLICT OF INTERESTS

There are no declaration of conflicts to declare.

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REFERENCES

1. Loprinzi CL, Foote RL, Michalak J. Alleviation of cytotoxic therapy-induced normal tissue damage. Semin Oncol. 1995;22(2 Suppl 3):95-7.
2. Chaves AP, Gomes JAP, Höfling-Lima AL. Alterações oculares induzidas pela quimioterapia. Arq Bras Oftalmol. 2007;70(4):718-25. doi: http://dx.doi.org/10.1590/S0004-27492007000400028
3. Yen-Revollo JL, Goldberg RM, McLeod HL. Can inhibiting dihydropyrimidine dehydrogenase limit hand-foot syndrome caused by fluoropyrimidines?. Clin Cancer Res. 2008;14(1):8-13. doi: http://dx.doi.org/10.1158/1078-0432.CCR-07-1225
4. Lorusso D, Di Stefano A, Carone V, et al. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). Ann Oncol. 2007;18(7):1159-64. doi: http://dx.doi.org/10.1093/annonc/mdl477
5. Jacobi U, Waibler E, Schulze P, et al. Release of doxorubicin in sweat: first step to induce the palmar-plantar erythrodysesthesia syndrome?. Ann Oncol. 2005;16(7):1210-1. doi: https://doi.org/10.1093/annonc/mdi204
6. Zuehlke RL. Erythematous eruption of the palms and soles associated with mitotane therapy. Dermatologica. 1974;148(2):90-2. doi: https://doi.org/10.1159/000251603
7. Latif S, Fraga G, Gadzia J. Increased mast cell density in capecitabine-induced hand-foot syndrome: a new pathologic finding. J Drugs Dermatol. 2010;9(3):268-70.
8. Narasimhan P, Narasimhan S, Hitti IF, et al. Serious hand-and-foot syndrome in black patients treated with capecitabine: report of 3 cases and review of the literature. Cutis. 2004;73(2):101-6.
9. Garcez RM, tradutora. Diagnósticos de enfermagem da NANDA: definições e classificação 2012-2014 [Nursing diagnoses: definitions & classification, 2012-2014]. Porto Alegre: Artmed; 2013.
10. Department of Health and Human Services (US). Common terminology criteria for adverse events (CTCAE) [Internet]. Version 4.0. Rockville (MD): NIH; 2009 May 28. [acesso 2019 Apr. 03]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf
11. Janusch M, Fischer M, Marsch WChH, et al. The hand-foot syndrome - a frequent secondary manifestation in antineoplastic chemotherapy. Eur J Dermatol. 2006 Sep-Oct;16(5):494-9. doi: 10.1684 /ejd .2006.0041
12. Surjushe A, Vasani R, Medhekar S, et al. Hand-foot syndrome due to capecitabine. Indian J Dermatol. 2009;54(3):301-2. doi: https://doi.org/10.4103/0019-5154.55651
13. Simão, DAS, Lima EDRP, Souza RS, et al. Síndrome mão-pé induzida por quimioterapia: relato de um caso. Rev Bras Enferm. 2012;65(2):374-8. doi: http://dx.doi.org/10.1590/S0034-71672012000200026
14. Son HS, Lee WY, Lee WS, et al. 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. doi: http://dx.doi.org10.3349/ymj.2009.50.6.796
15. Miller KK, Gorcey L, McLellan BN. Chemotherapy-induced hand-foot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management. J Am Acad Dermatol. 2014;71(4):787-794. doi: https://doi.org/10.1016/j.jaad.2014.03.019
16. Sociedade Brasileira de Farmacêuticos em Oncologia; Agência Nacional de Vigilância Sanitária. Guia para notificação de reações adversas em oncologia. 2.ed. São Paulo: Conectfarma Publicações Científicas; 2011.
17. 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.
18. Kadoyama K, Miki I, Tamura T, et al. Adverse event profiles of 5-fluorouracil and capecitabine: data mining of the public version of the FDA Adverse Event Reporting System, AERS, and Reproducibility of Clinical Observations. Int J Med Sci. 2012;9(1): 33-9. doi: https://doi.org/10.7150/ijms.9.33
19. Olinto GL, Petry RD, Lindenmeyer L, et al. Implantação de serviço de atenção farmacêutico à pacientes oncológicas em uso de capecitabina. Rev Bras Farm Hosp Serv Saúde. 2013;4(4):46-50.
20. Hoff PM, Cassidy J, Schmoll HJ. The evolution of fluoropyrimidine therapy: from intravenous to oral. Oncologist. 2001;6(Suppl 4):3-11. doi: https://doi.org/10.1634/theoncologist.6-suppl_4-3
21. Nagore E, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. Ann J Clin Dermatol. 2000;1(4):225-34. doi: https://doi.org/10.2165/00128071-200001040-00004
22. Gillespie TW. Chemotherapy dose and dose intensity: analyzing data to guide therapeutic decisions. Oncol Nurs Forum. 2001;28(2 Suppl):5-10.

23. Leonard RCF, Miles D, Thomas R, et al. Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. Br J Cancer. 2003;89(11):2062-2068. doi: https://doi.org/10.1038/sj.bjc.6601279

24. Azuma Y, Hata K, Sai K, et al. Significant association between hand-foot syndrome and efficacy of capecitabine in patients with metastatic breast cancer. Biol Pharm Bull. 2012;35(5):717-24. doi: https://doi.org/10.1248/bpb.35.717

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