Identification, Prevention and Treatment of Hand-Foot Syndrome Induced by Chemotherapy: Systematic Review

https://doi.org/10.32635/2176-9745.RBC.2019v65n4.363

Identificação, Prevenção e Tratamento da Síndrome Mão-Pé Induzida por Quimioterapia: Revisão Sistemática

Identificación, Prevención y Tratamiento de la Enfermedad Mental por Quimioterapia: Revisión Sistemática

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Abstract

Introduction: Hand-foot syndrome is an adverse reaction experienced by many cancer patients and a predictor of morbidity and mortality. **Objective:** To evaluate the scientific evidence related to the identification, prevention and treatment of chemotherapeutic-induced hand-foot syndrome, to identify the main signs and symptoms that enable the recognition of the syndrome, and to discuss the occurrence of onychomycosis in the context of the hand-foot syndrome. **Method:** This is a systematic review at MEDLINE/PubMed, Virtual Health Library and Scopus, including gray literature and manual search. The 29 studies included in the review were analyzed and graded according to the hierarchy of evidence levels Grading of Recommendations Assessment, Development and Evaluations (GRADE) and reliability among examiners (Kappa coefficient) was calculated. **Results:** It were identified studies that demonstrated efficacy in preventing hand-foot syndrome using cryotherapy and hydrotherapy. Satisfactory results were evidenced with the use of urea cream for prevention and treatment, and the use of pyridoxine showed inconclusive results. Mechanisms for identification of the syndrome and classification of inducing agents were found. The taxane group predominated among hand-foot syndrome inducing drugs. **Conclusion:** There are consistent evidences but do not include all drugs inducing the syndrome and do not explore other manifestations related to onycholysis and onychomycosis. The study presented results that may help prescribers to identify hand-foot syndrome, as well as alternatives for prevention and treatment. However, it is worth highlighting the need for future studies to elucidate the etiology and treatment protocols.
Key words: Hand-Foot Syndrome/drug therapy; Antineoplastic Agents; Onychomycosis; Onycholysis; Taxoids.

Resumo

Introdução: A síndrome mão-pé é uma reação adversa experimentada por vários pacientes em tratamento para o câncer e fator preditor de morbidade e mortalidade. **Objetivo:** Avaliar as evidências científicas relacionadas à identificação, prevenção e tratamento da síndrome mão-pé induzida por agentes quimioterápicos, identificar os principais sinais e sintomas que possibilitam o reconhecimento da síndrome e, ainda, discutir a ocorrência de onicomicoses no contexto da síndrome mão-pé. **Método:** Trata-se de uma revisão sistemática na MEDLINE/PubMed, Biblioteca Virtual da Saúde e *Scopus*, incluindo literatura cinzenta e busca manual. Os 29 estudos incluídos na revisão foram analisados e classificados segundo a hierarquia dos níveis de evidência *Grading of Recommendations Assessment, Development and Evaluations* (GRADE) e a confiabilidade entre os examinadores (coeficiente Kappa) foi calculada. **Resultados:** Foram identificados estudos que demonstraram eficácia na prevenção da síndrome mão-pé com o uso da crioterapia e hidroterapia. Evidenciaram-se resultados satisfatórios com o uso do creme de ureia na prevenção e tratamento, e o uso de piridoxina não apresentou resultados conclusivos. Foram encontrados mecanismos para identificação da síndrome e para classificação dos agentes indutores. O grupo dos taxanos predominou entre os medicamentos indutores da síndrome mão-pé. **Conclusão:** Existem evidências consistentes, porém não contemplam todos os fármacos indutores da síndrome e não exploram outras manifestações relacionadas às onicólises e onicomicoses. O estudo apresentou resultados que poderão auxiliar os prescritores na identificação da síndrome mão-pé, além de alternativas para prevenção e tratamento. Contudo, vale destacar a necessidade de pesquisas futuras para elucidar a etiologia e protocolos de tratamento.
Palavras-chave: Síndrome Mão-Pé/tratamento farmacológico; Antineoplásicos; Onicomicose; Onicólise; Taxoides.

Resumen

Introducción: El síndrome de pies y manos es una reacción adversa experimentada por muchos pacientes con cáncer y un predictor de morbilidad y mortalidad. **Objetivo:** Evaluar la evidencia científica relacionada con la identificación, prevención y tratamiento del síndrome de pies y manos inducido por quimioterapia, identificar los principales signos y síntomas que permiten el reconocimiento del síndrome y analizar la aparición de onicomicosis en el contexto del síndrome mano-pie. **Método:** Esta es una revisión sistemática en MEDLINE/PubMed, Virtual Health Library y Scopus, que incluye literatura gris y búsqueda manual. Los 29 estudios incluidos en la revisión se analizaron y clasificaron de acuerdo con la jerarquía de los niveles de evidencia *Grading of Recommendations Assessment, Development and Evaluations* (GRADE). **Resultados:** Identificamos estudios que demostraron eficacia en la prevención del síndrome mano-pie usando crioterapia e hidroterapia. También mostraron resultados satisfactorios con el uso de crema de urea en la prevención y el tratamiento, y el uso de piridoxina no mostró resultados concluyentes. Se encontraron mecanismos para la identificación del síndrome y la clasificación de los agentes inductores. El grupo de taxanos predominó entre los fármacos inductores del síndrome mano-pie. **Conclusión:** Existe evidencia consistente pero no incluye todas las drogas que inducen el síndrome y no explora otras manifestaciones relacionadas con la onicólisis y la onicomicosis. El estudio presentó resultados que pueden ayudar a los prescriptores a identificar el síndrome de manos y pies, así como alternativas para la prevención y el tratamiento. Sin embargo, vale la pena destacar la necesidad de futuras investigaciones para dilucidar la etiología y los protocolos de tratamiento.
Palabras clave: Síndrome Mano-Pie/tratamiento farmacológico; Antineoplásicos; Onicomicosis; Onicólisis; Taxoides.

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INTRODUCTION

Cancer is a rising disease[1] and demands full care to the patient[2,3]. It requires the increase of the national investment in research and the application of knowledge in prevention, control and management of the disease through all its segments[3].

In Brazil, the National Institute of Cancer José Alencar Gomes da Silva (INCA) estimated a growth of 600 thousand new cases for each year of the biennium 2018-2019, for every type of the disease, except for non-melanoma skin[4]. Further, the survival rate grew with a mean of 92% for prostate and 85% for breast neoplasm[4]. This rise has occurred because of early diagnosis together with the consolidation of neoadjuvant and adjuvant treatments[4]. Nevertheless, the innumerous adverse reactions of these treatments as fatigue, sarcopenia, osteopenia, osteoporosis, cardiovascular dysfunction, overweight, immunosuppression, sleeping disorders and hand-foot syndrome contribute to worsen the health condition and quality of life of the patients[5].

The hand-foot syndrome is also known as palmar plantar erythema, acral erythema or Burgdorf reaction. It is an adverse reaction experienced by several patients in chemotherapy treatment[6] with potential of limiting cutaneous toxicity when using the effective dose for the treatment.

The incidence of that syndrome varies from 20% to 60% for the patients treated according to the drug in use. Among the inducing drugs, are the cytostatic, cytotoxic and/or immunotherapics as: pegylated liposomal doxorubicin, doxorubicin, capecitabine, mitotane, cyclophosphamide, 5-fluorouracil, cytarabine, docetaxel, paclitaxel, sorafenib, sunitinib and gefitinib[5,6]. However, the hand-foot syndrome is a theme yet quite controversial in oncology[6].

This syndrome was documented for the first time in 1974 by Zuehlke[7], emphasizing its manifestation after the use of mitotane[7]. It presents the following symptoms: pruritus, pain, edema and erythema and acral erythema in the palms of the hands and/or sole of the feet in various grades as described in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 of 2017[8], that classify the hand-foot syndrome in three grades based in the severity of the affection. Grade 1 is characterized by minimum alterations of the skin or painless dermatitis; grade 2 is characterized by alterations of the skin, but the pain does not interfere in the daily functions; and grade 3 is characterized by ulcerative dermatitis interfering in the daily functions[8].

Innumerous strategies of prevention and/or treatment have been adopted in the attempt to prevent and/or reduce the incidence of the hand-foot syndrome that are essential for the maintenance of chemotherapy and to achieve the best results[5,6].

In systematic review and meta-analysis[9], whose objective was to evaluate the clinical efficacy of the strategies of prevention of the hand-foot syndrome available in the literature, the authors evaluated oral and topic preventive drugs and report that, with the advent of new drugs, new adverse events appear also and studies that address strategies of prevention of the hand-foot syndrome should be encouraged.

Therefore, there are questions that need to be responded, among them, the main signs and symptoms presented by the patients and that characterize the hand-foot syndrome and the treatment strategies proposed whose mechanisms favor good results either in prevention or treatment and the relation of the hand-foot syndrome with onychomycosis[10].

Therefore, the objective of the present review was to evaluate the scientific evidences related to the identification, prevention and treatment of the chemotherapics agents-induced hand-foot syndrome, identify the main signs and symptoms that allow the recognition of the syndrome and, yet, to discuss the occurrence of onychomycosis in the context of the hand-foot syndrome.

METHOD

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11]. The search was performed in the databases MEDLINE/PubMed, Health Virtual Library (BVS) and Scopus without restriction of data, approaching the hand-foot syndrome associated to the use of chemotherapics drugs. Each database was searched in its fullness and there were no restrictions of language or type of publications. The first search occurred on May 29, 30 and 31, 2017, including gray literature and manual search on August 2018. The present paper was filed at the International Prospective Register of Systematic Reviews (Prospero) and published with number CDR42019114757.

Eligibility criteria, evaluation of the quality and risk of biases

Two investigators identified by the initials PPP and MAR screened the databases to identify the relevant studies based in their titles. When one or both disagreed about the inclusion criteria for a certain study, the discrepancies were resolved by consensus with or without the assistance of a third investigator (RSP). In a second moment, following the recommendations of Cochrane

Effective Practice and Organization of Care[12], the articles compiled in the initial stage were analyzed, having been selected those that met all the eligibility criteria, the evaluation of quality and risk of biases: 1) articles with randomized or non-randomized clinical trials; 2) groups that suffered intervention with control group; 3) articles that evaluated the symptoms of the hand-foot syndrome in relation to onycholysis and suggestions of treatment; 4) observational studies, including case series and case reports that referenced symptoms and proposals of treatment for hand-foot syndrome and onychomycosis, considering the paucity of publications encountered about the theme in study (Table 1).

The search took place with the utilization of the parameters described in the eligibility criteria in the databases mentioned earlier with the support of five research strategies and varying the descriptors MeSH/ DeCs and Boolean operators as described: **Search 1_** "hand-foot syndrome" AND "breast neoplasms" OR "breast" AND "neoplasms" OR "breast neoplasms" AND "therapy" OR "therapy" OR "treatment" OR "therapeutics" OR "therapeutics" OR "taxanes" OR "hand-foot syndrome" OR "hand-foot" AND "syndrome" OR "hand-foot syndrome" OR "hand" AND "foot" AND "syndrome" OR "hand foot syndrome" AND "breast neoplasms" OR "breast" AND "neoplasms" OR "breast neoplasms" AND "therapy" OR "therapy" OR "treatment" OR "therapeutics" OR "therapeutics" AND acral AND "erythema" OR "erythema" "hand-foot syndrome". **Search 2_** "breast neoplasms" OR "breast" AND "neoplasms" OR "breast neoplasms" AND "therapy" OR "therapy" OR "treatment" OR "therapeutics" OR "therapeutics" OR "taxanes" OR "hand-foot syndrome" OR "hand-foot" AND "syndrome" OR "hand-foot syndrome" OR "hand" AND "foot" AND "syndrome" OR "hand foot syndrome" AND "quality of life" OR

Table 1. Description of the articles selected

Author, year	N	Mean age	Design	Quality of the evidence
McCarthy et al., 2014[13]	53	54.8	Randomized controlled trial	High
Scotté et al., 2005[14]	45	65	Case-control	Moderate
von Gruenigen et al., 2010[15]	34	64	Double-blind, randomized, controlled clinical trial	High
Zhao et al., 2014[16]	100	36-78	Double-blind, randomized, controlled clinical trial	High
Hofheinz et al. 2015[17]	152	31-88	Phase III randomized clinical trial	High
Ren et al., 2015[18]	871	51.8-52.0	Randomized controlled trial	High
Yoshimoto et al., 2010[19]	78	55.0 -55.6	Retrospective study	Moderate
Kawaguchi et al. 2011[20]	993	Not informed	Retrospective observational study	Moderate
Dalenc et al., 2018[21]	70	70	Randomized controlled study	High
Bardia et al., 2006[22]	5	54.2	Case series	Low
Farhat et al., 2008[23]	5	60.2	Case series	Low
Kara et al., 2006[24]	5	51.2	Case series	Low
Chew et al., 2009[25]	4	51	Case series	Low
Wang et al., 2016[26]	3	47-85	Case series	Low
Corazza et al., 2014[27]	1	60	Case report	Low
Richards et al., 2012[28]	1	66	Case report	Low
Housholder et al., 2012[29]	1	63	Case report	Low
Ozkol et al., 2016[30]	1	24	Case report	Low
Sauter et al., 2007[31]	1	76	Case report	Low
Akoglu et al., 2014[32]	1	52	Case report	Low
Braghiroli et al., 2017[33]	1	73	Case report	Low
Jung et al., 2015[34]	1	43	Case report	Low
Qiao et al., 2012[35]	1	59	Case report	Low
Katoh et al., 2004[36]	1	70	Case report	Low
Gurumurthi et al., 2013[37]	1	52	Case report	Low
Hoesly et al, 2011[38]	1	61	Case report	Low
Jain et al., 2012[39]	1	45	Case report	Low
Assi et al., 2013[40]	1	72	Case report	Low
Simão et al. 2012[41]	1	37	Case report	Low

"quality" AND "life". **Search 3_** "quality of life" AND "breast neoplasms" OR "breast" AND "neoplasms" OR "breast neoplasms" "hand-foot syndrome" OR "hand-foot" AND "syndrome" OR "hand-foot syndrome" OR "hand" AND "foot" AND "syndrome" OR "hand foot syndrome" AND "quality of life" OR "quality" AND "life" OR "quality of life" AND "breast neoplasms" OR "breast" AND "neoplasms". **Search 4_** "breast neoplasms" "onychomycosis" AND "taxanes" AND "breast neoplasms" AND "onychomycosis" AND "Hand-foot syndrome" AND "mycosis" AND "taxanes" AND "breast neoplasms" AND "mycosis" AND "paclitaxel" AND "breast neoplasms" AND "mycosis" AND "Hand-foot syndrome" AND "mycosis" AND "paclitaxel" AND "Hand-foot syndrome" AND "onychomycosis" AND "taxanes" AND "breast neoplasms" AND "onychomycosis". **Search 5_** "Hand-foot syndrome" AND "mycosis" AND "taxanes" AND "breast neoplasms" AND "mycosis" AND "paclitaxel" AND "breast neoplasms" AND "mycosis" AND "Hand-foot syndrome" AND "mycosis" AND "paclitaxel" AND "Hand-foot syndrome".

Data collection was done through an electronic form elaborated for that purpose containing the following variables: authors of the study and year of publication, country of the study, design of the study, type of drug utilized by the patient, number of patients studied and results. The studies were reviewed and classified according to the hierarchy of the levels of evidence Grading of Recommendations Assessment, Development and Evaluations (GRADE)[42].

The reliability of the reviewers was measured with the function kappa[43]. The calculations resulted in a value of Kappa of 0.9 whose result is considered excellent.

RESULTS

Based in the strategies defined for the search, 483 publications were identified, of which 417 were excluded by the reviewers upon reading the titles and abstracts, remaining only 66 articles.

After duplicates were removed (n=22), the 44 articles left were evaluated in stages, excluding the reviews, articles unrelated to the hand-foot syndrome, studies without access in full (abstracts), those that did not match the objectives proposed for the study and 29 articles were included, reaching 2,433 patients (Figure 1).

The studies were published in innumerous journals as randomized clinical trials (n=6; 20.69%); case-control (n=1; 3.45%); retrospective observational study (n=2; 6.90%); case series (n=5; 17.24%) and case reports (n=15; 51.72%). It were not encountered qualitative studies evaluating the perception of the individuals affected by the hand-foot syndrome or studies that deepened the cause of this adverse reaction. Asia was the continent of origin of the majority of the articles included in the study (n=13; 44.83%), with Japan (n=3; 10.34%), China (n=3; 10.34%), India (n=3; 10.34%), Lebanon (n=2; 6.90%) and Turkey (n=2; 6.90%); followed by Europe (n=7; 24.14%), with Germany (n=3; 10.34%), United Kingdom (n=1; 3.45%), Italy (n=1; 3.45%) and France (n=2; 6.90%); North America, with the United States (n=6; 20.69%); and Oceania and South America, with Australia (n=1; 3.45%) and Brazil (n=2; 6.90%), equivalent to 10.34%. There was no article selected in Africa.

The majority of the studies (24; 82.76%) was published between 2010 and 2017.

Characteristics of the studies included

Table 1 shows the characteristics of the studies included in relation to the design, number of participants and mean age, in addition to the level of evidence of the articles in this review. The classification of the evidence was based in the quality of the study and risk of biases. Among these studies, there are publications related to the prevention and treatment of the hand-foot syndrome with studies well designed and within the criteria established for scientific investigation. The subtitles of these articles and their respective results are presented below.

Cryotherapy for the prevention of the docetaxel-induced toxicity in nails and hands

Two studies compared the effectiveness of cryotherapy in the hands of the patients with docetaxel-induced toxicity in nails. In the first study[13], the investigators demonstrated the use of frozen gelatinous gloves to prevent toxicity of docetaxel-induced toxicity of nails in hands in patients with cancer. Of the 53 study participants, because of the high level of discomfort while wearing gloves, only 21 were able to present enough data for the evaluation. During the analyzes, no differences were encountered in the participants in relation to the toxicity between gloved and ungloved hands. Seemingly, cryotherapy did not reduce the incidence, severity and time for docetaxel-induced cutaneous toxicity.

In the second study[14], the 45 patients who wore frozen gloves were evaluated for onycholysis and cutaneous toxicity. Onycholysis varied from 89% *versus* 49% (grade 0) and from 11% to 51% (grade 1 to 2), respectively. The results encountered were significant in the hand protected by the frozen glove in comparison with the hand control ($p< 0.0001$). One skin toxicity occurred with 73% *versus* 41% (grade 0) and of 27% *versus* 59% (grade 1 to 2), respectively. The median time for the occurrence

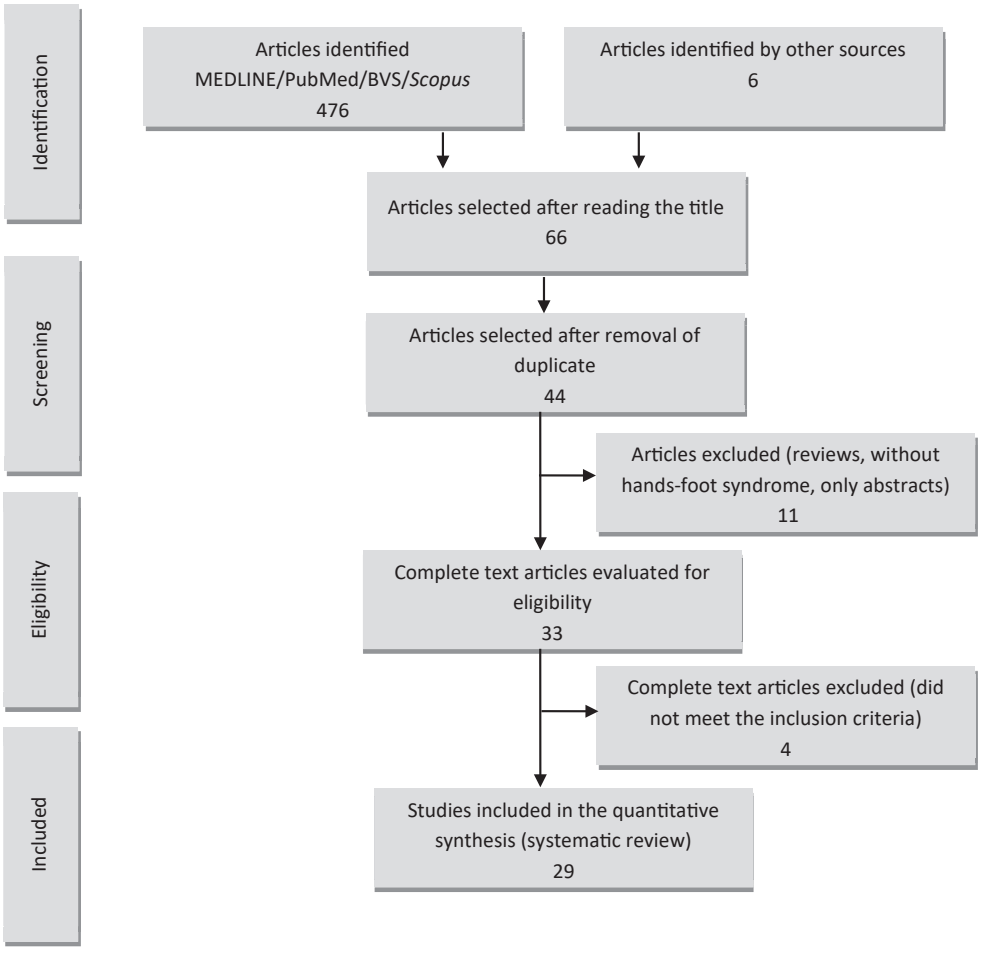

Figure 1. Flowchart of the process of selection of articles in the different phases of the systematic review

of toxicity of nail and skin were not significant in the comparison between the protected hand with frozen glove in relation to control (106 *versus* 58 days for ungual toxicity; 57 *versus* 58 days for cutaneous toxicity).

Prevention of the hand-foot syndrome by chemotherapy with pyridoxine

Two studies evaluated the use of pyridoxine in the prevention of the hand-foot syndrome. In the first double-blind, randomized study[15], the investigators compared pyridoxine with placebo in the prevention of the hand-foot syndrome induced by pegylated liposomal doxorubicin. The study participants were stratified by cancer diagnosis: ovary, breast and endometrium and randomized in group A (n=18) and group B (n=16). The participants of the group A received pyridoxine twice a day and of the group B, placebo every other day associated to education in health related to hand-foot syndrome. The study concluded that the use of pyridoxine 100 mg twice a day every other day did not prevent the appearance of the hand-foot syndrome.

In the second study[16] the objective was to observe the effect of "Tao-hong-si-wu-Tang", a preparation utilized in the traditional Chinese medicine compared with pyridoxine in patients who presented hand-foot syndrome induced by capecitabine, sorafenib and gefitinib, utilized in gastric tumor, lung, breast and rectal cancer. The preparation "Tao-hong-si-wu-Tang" was formed by Taoren (Semen Persicae) 30 g, Honghua (Flos Carthami) 30 g, Shudihuang (Radix Rehmanniae Praepara-ta) 30 g, Danggui (Radix Angélica Sinensis) 30 g, Chuanxiong (Rhizoma Chuanxiong) 15 g, Baishao (Radix Paeoniae Alba) 15 g, Guizhi (Ramulus Cinnamomi) 15g, Chuanniuxi (Radix Cyathulae) 15 g, Gancao (Radix Glycyrrhizae) 6 g and Dazao (Fructus Jujubae) three pieces. The participants were randomly distributed in two groups A and B.

The participants of the group A received the decoction of "Tao-hong-si-wu-Tang", soaking the hands and feet for 30 minutes once a day. The group B received 100 mg of pyridoxine orally, twice a day. After a treatment of two weeks, the therapeutic effect was evaluated by

the investigators based in three main symptoms: pain, ulceration and muscular atrophy. It was encountered significant difference between the two groups in relation to pain relief and improvement of the daily life (p<0.01). After two weeks of treatment the effective rate was 88.3% in the group A and above 50% in group B. It was concluded with this study that the decoction of "Tao-hong-si-wu-Tang" modified is effective in the treatment of patients with hand-foot syndrome.

Use of urea in the prevention of the hand-foot syndrome

Two studies analyzed the use of urea in the prevention of the hand-foot syndrome. One of them compared the use of mapisal cream *versus* urea cream for prophylaxis of the capecitabine-associated hand-foot syndrome[17]. The product mapisal is a cream containing a great variety of antioxidants and nutritive oil extracts. The study justifies the use of antioxidants considering that, during the manifestation of the hand-foot syndrome, occurs a drop of the skin antioxidant capacity[17]. It is a Phase III randomized study where 152 patients were evaluated and, of these, 47 developed hand-foot syndrome; 39.5% were patients in use of the mapisal and 22.4% in use of urea at 10%. The authors concluded that the use of urea cream at 10% to prevent the hand-foot syndrome is better than the mapisal cream.

The randomized open study of Ren et al.[18] evaluated the benefit of the urea-base cream for the prophylaxis of the hand-foot sorafenib-induced cutaneous reaction in patients with advanced hepatocellular carcinoma where 871 patients were treated with urea cream at 10% three times a day associated to the regular care (n=439), or only supporting regular care excluding all the creams (n=432). The evaluation of the hand-foot syndrome was done every two weeks until the 14th. week. Once the syndrome occurred, the patients received any cream, including the urea-base cream.

This study[18] utilized a specific modified classification system for symptoms of the hand-foot syndrome to interpret the results. According to the classification proposed, the scale Grade 1 is described as: numbness, dysesthesia and/or paresthesia, tingling, painless edema or erythema of hands and/or feet and/or discomfort, that does not interrupt the normal activities; Grade 2: painful erythema and edema of hands and/or feet and/or discomfort that affect the daily activities of the patient; and Grade 3: moist desquamation, ulceration, blisters or pain in the hands and/or feet and/or discomfort interfering with labor or living activities. After 12 weeks, the incidence of the hand-foot syndrome in any grade induced by sorafenib was lower, with statistical significance in the group that used the urea-base cream *versus* the group who received only support care (56.0% *versus* 73.6%, respectively; *odds ratio* [OR], 0.457, 95% CI, 0.344-0.608; p<0.001); similar to the incidence of grade ≥2 hand-foot skin reaction (20.7% *versus* 29.2%, respectively; OR, 0.635; 95% CI, 0.466 to 0.866; p=0.004).

Pyridoxine and urea: prevention and treatment

One study evaluated the use of pyridoxine for prophylaxis of the hand-foot syndrome in 38 patients with metastatic breast cancer in use of capecitabine[19] and compared with historical data of 40 patients treated with capecitabine and without pyridoxine.

The authors showed that the use of pyridoxine can reduce the risk of developing high grade (p<0.01) hand-foot syndrome. The investigators evaluated also the use of urea cream applied in the first manifestation of the hand-foot syndrome and demonstrated that the urea cream appears to reduce the probability of developing the hand-foot syndrome and prevents the escalation to a higher grade.

Use of H2 blockers associated to taxoids and incidence of the hand-foot syndrome

Kawaguchi et al.[20] included 993 patients of 20 institutions in order to evaluate the use of H2 (ranitidine, lafutidine) blockers in patients in use of docetaxel, evaluating the hand-foot syndrome. The inhibitor effect of the antagonists of the H2 receptors associated with docetaxel increased the incidence of the cutaneous toxicity of the hand-foot syndrome grade 2 and facial erythema. This was demonstrated by two analyzes of multivariate logistic regression. Lafutidine influenced more the incidence of the hand-foot syndrome and facial erythema. Ranitidine had lower influence, although with significant result over the incidence of the hand-foot syndrome and facial erythema (OR 2.58; p=0.029). This is explained because the depuration of docetaxel is mediated by the isoenzyme CYP3A4 whose active site is inhibited by H2 inhibitors of the type of ranitidine, thus increasing the incidence of the hand-foot syndrome.

Hydrotherapy: treatment of the hand-foot syndrome persistent after chemotherapy

Controlled, multicenter, randomized, prospective study conducted by Dalenc et al.[21], applied hydrotherapy after the treatment of non-metastatic breast cancer. The study investigated the efficacy of hydrotherapy as support treatment for management of neoadjuvant therapy-induced persistent and lasting adverse reactions.

Two groups of patients were randomized. The inclusion criteria were women ≥18 years, in complete remission after

combined treatment with neoadjuvant chemotherapy (paclitaxel and docetaxel), surgery (including conservative surgery or mastectomy with axillary or sentinel lymph node dissection) and radiotherapy for treatment of progesterone and estrogen receptor invasive breast carcinoma HER2 positive and negative. The women must also be in adjuvant hormone therapy as an inhibitor of aromatase or tamoxifen with or without antagonist of the liberating hormone of the luteinizing hormone. The patients should also present at least two dermatologic adverse events graded ≥1 using NCI-CTCAE version 4.02: dry skin, loss of nail, pain, pruritus, hyperpigmentation of the skin, dermatitis of radiation and lymphedema. All were included within a 1-5 weeks window after the conclusion of the radiotherapy.

The group control (n=33) received support and routine care and the group treatment (n=35) received three weeks of specific hydrotherapy. The treatment with hydrotherapy consisted in an alternative regimen of daily care including: (1) baths during 20 minutes at the most at 34º C to grant emollient and anti-inflammatory effect; (2) shower bath during 5 minutes to facilitate the removal of scales softened during the bath followed by pulverization with thermal water and mist, in order to improve the antipruritic and calming effects of the thermic treatment; (3) oral intake of thermal water and associated to all thermic treatments; (4) coat the skin with thick and occlusive layer of emollient to improve skin moisturizing; (5) specific massages applied by a physiotherapist to soften the skin and the cicatricial tissue and reduce the edema and postoperative lymphedema; (6) esthetic care at a make-up facility by an expert to learn how to hide body and facial scars and persistent skin spots.

The majority of the items evaluated presented significant results in the intervention group with hydrotherapy *versus* the control group as described: quality of life in relation to breast cancer (p=0.0001); dermatologic quality of life (p=0.0015), adverse reactions (p=0.0044) and body image (p=0.0139).

Below, are described 15 reports and five case series that included the occurrence of the hand-foot syndrome in patients in use of chemotherapy. In table 2, publications with indicators that help the professional to identify the hand-foot syndrome are described and the profile of the inducer agent and in table 3, the publications related to the strategies of treatment.

Case series and case reports

In one of the series[22], the investigators noticed that the effect of the hand-foot syndrome in five patients after the use of doxorubicin and cyclophosphamide followed by a taxoid in dose-dense[22] whose treatment needed the use of pegfilgrastim. Among the cases, it stood out a female patient in treatment for breast cancer. The patient developed hand-foot syndrome after two days of the first dose of paclitaxel. Initiated with a sensation of tingling and burning in the palms of the hands and in the heels in both sides of the body, further evolving with desquamation, skin fissures and blisters in the feet and edema. Most of the lesions recovered after eight weeks. Another patient developed redness, sensitiveness and fissures in hands and feet even with support and use of ice bag in hands and feet during the infusions of chemotherapy.

Farhat et al.[23] reported five cases of patients who developed hand-foot syndrome in treatment with docetaxel. In all the cases, the conduct was the interruption of the treatment with docetaxel.

In other five cases[24] of patients with metastatic breast cancer in treatment with capecitabine and docetaxel who developed hand-foot syndrome, the treatment of choice was vitamin E with resolution of manifestations of the syndrome in all the cases[24].

Chew e Chuen[25] reported four patients who presented cutaneous reactions after weekly treatment with docetaxel. One of the patients received hydrocortisone cream, oral cloxacillin and counseling for cold compresses in the local of the lesions as treatment; another patient treated with oral cloxacillin and mupirocin cream; the third patient treated with propionate of clobetasol oral and the fourth, a combination of dipropionate of betamethasone at 0.05%, clotrimazole at 1% and sulphate of gentamicin at 0.1%. All the patients continued the chemotherapy with improvement of cutaneous reaction.

In the series published by Wang et al.[26], three women developed cutaneous rashes in hands and feet during the chemotherapy treatment. Findings of physical exams suggested infection by tinea, since they spread to palms of the hands and soles of the feet with erythematous, squamous and progressive border, nails thickening and discoloration, suggestive of onychomycosis. These patients were submitted to lab tests for mycological tests of the lesions. In the three cases, in the direct test for fungi, it were observed ramified hyphae and, in the culture of the material of two patients there was growth of *Trichophyton rubrum*. The patients were treated with antifungal: terbinafine, econazole and fluconazole. This conduct allowed the continuation of the chemotherapy treatment. For the authors, it is important to diagnose the cases of fungic infections associated to the hand-foot syndrome in order to guide the proper treatment.

The case reports included 15 patients[27-41] who developed hand-foot syndrome. Ten patients received taxanes-based treatment (docetaxel or paclitaxel); capecitabine was present in the treatment of four of these

Table 2. Description of indicators of hand-foot syndrome

Author, year	Signs and symptoms	Location in the body	Inducing drug
Bardia et al., 2006[22]	Tingling, redness, loss of sensitiveness, fissures and desquamation; edema and blisters	Palms of the hands and heels; blisters in the feet	ACT (paclitaxel); ACT (docetaxel); docetaxel
Farhat et al., 2008[23]	Intense pruritus, burning, edema and facial and neck erythema. Cutaneous erythema and burning with desquamation	Palms of the hands and sole of the feet; face and neck	FEC (fluoruracil, epirubicin and cyclophosphamide) and docetaxel; ACT (docetaxel) and filgrastim
Kara et al., 2006[24]	Desquamative skin lesions	Skin, hand and nails	Docetaxel, capecitabine and zoledronic acid
Chew e Chuen, 2009[25]	Erythematous plaque, pain, burning, and formation of blisters, itching, erythematous lesions with desquamation	Hands back and wrists	Docetaxel; docetaxel+ carboplatine; docetaxel+ capecitabine; liposomal doxorubicine
Wang et al., 2016[26]	Desquamation, pain, pruritus and erythema; fissures, fissures and bleeding of the areas affected; papular erythematosus; ungual lesion	Fingers, hands and feet; ankles and legs; thick, dark and/or yellowish nails	ACT (paclitaxel); capecitabine; liposomal doxorubicin
Corazza et al., 2014[27]	Multiple plaques and spots; pain, burning, edema, erythema, hyperpigmentation	Hands back and palm; back and lateral surface of the feet, armpits and inner thigh	Docetaxel
Richards et al., 2012[28]	Erythema, pain and loss of sensitiveness	Skin of the hands and feet	Paclitaxel
Housholder et al., 2012[29]	Rash, pruritus, pain, edema, telangiectasia and bristly cuticles	Back of hands, proximal hands and cuticles	Paclitaxel
Ozkol et al., 2016[30]	Erythema, pain, edema, hyperpigmentation and desquamation	Palms of the hands, sole of the feet, face and neck	Docetaxel
Sauter et al., 2007[31]	Paresthesia, edema, pain, blisters, ulceration	Tips of the distal fingers of the hand	Capecitabine
Braghiroli et al., 2017[33]	Edema, erythema, desquamation, ulceration, vesicopustules and feeling of burning	Hands, wrists and feet	Trastuzumab and paclitaxel
Jung et al., 2015[34]	Tingling, pruritus, erythema, pain, maculopapular edema and lesions in the infrasternal skin	Tips of the hands fingers and dorsal and medial sole of the right foot; elbows and arms, back and dorsal thigh	Pegylated Doxorubicin
Qiao et al., 2012[35]	Erythema and pain in lesions in the infrasternal skin	Palms of hands and soles of feet	Capecitabin
Katoh et al., 2004[36]	Pain, tingling, erythema, edema	Hand, feet sole and face	Docetaxel
Gurumurthi et al., 2013[37]	Lesions, pain, erythema, tingling, edema	Skin, hands palms, feet sole	Docetaxel

Table 3. Strategies of drugs treatment for hand-foot syndrome

Author, year	Treatment proposed	Outcome
Bardia et al., 2006[22]	Analgesic and wet dressings; ice bags	Skin rash recovered in 8 weeks
Corazza et al., 2014[27]	IV Multivitamin, topic emollient and topic steroid	Symptoms started to disappear four days after the beginning of the treatment
Richards et al., 2012[28]	Topic sulfadiazine of silver for areas of open wound, triamcinolone and emollience	One month after the conclusion of the regimen with paclitaxel occurred the resolution of the plates
Housholder et al., 2012[29]	Clobetasol propionate cream; twice a day in both hands	Rash improved 1 month with the use of the cream
Ozkol et al., 2016[30]	1- Prednisolone 40 mg/day (1-4 days) 2- Pheniramine 22.75 mg/mL/day, 4x day (2-4 days) 3- Mometasone furoate topic, 2x day (3-10 days) 4- Topic urea 2x days (4-10 days)	In the 7th day of the treatment, the edema and the erythema reduced
Sauter et al., 2007[31]	Gauze bandages with fucidin	Complete local cicatrization
Akoglu et al., 2014[32]	Topic steroids, oral pyridoxin (250 mg/day): elevation of extremities during the infusion and application of cold compress	The lesions receded completely after 1 week; dysesthesia symptoms continued
Braghiroli et al., 2017[33]	Suspension of chemotherapy and administration of opioids and prednisone (0.5 mg/kg) in addition to compresses of potassium permanganate and application of occlusive dressing with fludroxycortide	After five days there was significant improvement of the pain and lesions
Jung et al., 2015[34]	Antioxidant (Mapisal®) - 3x day during 3 days	The symptoms passed from grade 3 to grades 1-2. The infrasternal skin lesions disappeared after 1 week of local treatment
Qiao et al., 2012[35]	Topic urea	The symptoms passed from grade 3 to grades 1-2. The infrasternal skin lesions disappeared after 1 week of local treatment
Gurumurthi et al., 2013[37]	Parenteral steroids	The symptoms were resolved after four days and the regimen of chemotherapy
Hoesly et al., 2011[38]	Fluocinonide cream 0.05%; ammonium lactate cream 12%; mupirocin ointment, econazole cream and oral ciprofloxacin. The use of ciprofloxacin was due to a clinical suspicion of cutaneous superinfection and history of paronychia by Pseudomonas aeruginosa	The superinfection by Pseudomonas spp. post hand-feet syndrome was considered the most likely source of sepsis, although the results of hemocultures remain negative. Despite the wide spectrum IV antibiotic therapy and aggressive measures of resuscitation, the patient died in less than 24 hours
Jain et al., 2012[39]	Emollients and analgesic	The symptomatic treatment of the hand-foot syndrome was satisfactory and the additional cycles of docetaxel continued in the usual interval without additional aggravation of the lesions
Assi et al., 2013[40]	Orientation to wear long sleeves and cover the areas exposed to sun as face and neck and application of sun blocker and moisturizers	Improvement after one week and chemotherapic treatment resumed as planned. Skin symptoms stabilized and extension reduced
Simão et al., 2012[41]	*Aloe vera* 3 times/day	Regression of the hand-foot syndrome in 10 days after beginning of the treatment; improvement of the quality of life and resuming of chemotherapy treatment

patients. The predominant conduct was the suspension of the infusion of chemotherapy followed by the use of topic corticosteroids, oral pyridoxine, sulfadiazine of silver, urea and *aloe vera*-base cream. It were also mentioned the use of cold compresses and the elevation of the extremities during the infusion in the attempt to increasing the tolerance of chemotherapy and block the induction of the hand-foot syndrome.

DISCUSSION

The identification of the hand-foot syndrome goes unnoticed by several team caregivers. The patients present signs and symptoms as dysesthesia, tingling sensation, burning, pain, erythema, desquamation of the skin, accompanied of painful blisters and pruritus that, soon after discontinuation, evolve to open wounds. Overall, occur in the hands and feet, however, other parts of the body can be affected as neck, armpits, intra-sternal space, groin, legs, chest and torso[27]. Among the various inducing drugs of the hand-foot syndrome, the taxanes in this review were encountered in 50% of the publications of case reports.

In the 29 studies identified in the systematic review, n=26 (90%) presented alternatives of treatment and/or prevention either pharmacological or non-pharmacological for patients affected with the hand-foot syndrome[15-20,22-32]. The majority of the articles published about the management of the hand-foot syndrome were case reports. Among the options of treatment with drugs, the posology, the duration of the treatment and the outcome varied broadly in the studies.

Cryotherapy, in the study of Scotté at al.[14], was effective to prevent the hand-foot syndrome since when applied in certain target-areas, as the hands, promotes vasoconstriction that favors the reduction of toxic agents in the site treated[44]. It was also presented in the report of case series, although the application in the hand-foot syndrome affected areas was with ice packs[22]. Ice, in addition to promoting vasoconstriction, has anti-inflammatory action and reduces the edema because facilitates the cellular oxygenation contributing for pain reduction[44].

The use of pyridoxine (vitamin B6) in the prevention of the hand-foot syndrome demonstrated controversial results. von Gruenigen et al.[15] demonstrated that the use of pyridoxine was not effective to prevent the hand-foot syndrome, while Yoshimoto et al.[19] affirmed that pyridoxine can be effective for milder grades when associated to capecitabine.

Urea-base cream in the studies evaluated was effective both for prevention[19,20] and treatment of the hand-foot syndrome[21]. Urea is among the assets that allow effective skin hydration, it is a humectant substance. And this propriety grants the capacity of absorbing the water of the tissue[45]. Consequently, it promotes an epidermal barrier with regenerative and protective activity against aggressors that would promote the drying of the skin. It has keratolytic effect in high concentrations (≥20%), through interaction with the epidermal corneocytes. And, in addition, has the characteristic of permeating other active substances[45].

Hydrotherapy was a non-pharmacological strategy that presented good results in the treatment of the hand-foot syndrome[23]. The benefits encountered with hydrotherapy included anti-inflammatory action, emollience and hydration.

Of the publications, n=20 (69%) presented results as series and case reports. In one of the case series[26], the authors presented vitamin E as alternative for treatment with significant outcome. It is believed that its action is related with the antioxidant properties, preventing the peroxidation of lipids, resulting in more stable cellular membranes[26].

The use of analgesics was mentioned for pain relief of the hand-foot syndrome. The analgesics of the anti-inflammatory class are quite utilized in clinical practice. Its analgesic action is related with the inhibition of prostaglandins, substances that sensitize nociceptors whose blocking promotes analgesia[46]. For the severest cases described in the case reports, anti-inflammatory steroids of the class of glycorticoids (prednisolone, mometasone, dexamethasone and triamcinolone) were utilized. These therapeutic agents present great anti-inflammatory potential.

Still in this therapeutic class, the use of clobetasol was mentioned in one of the reports[31] as alternative for treatment with resolution of symptoms after one month of use. Among them, fludroxycortide and clobetasol were administered using the technique of occlusive dressings.

Sulfadiazine of silver was also mentioned in the treatment of the hand-foot syndrome in one of the cases. The patient presented open wounds whose bactericide action was evidenced succesfully[30]. The use of antimicrobials has the intention of preventing complications in the lesions although rare as the infections by staphylococci or gram-negative bacteria, or yet, erysipelas with risk of sepsis[47]. Other antimicrobials as oral cloxacillin and gentamicin at 0.1% were utilized and cited in the report cases.

Dry skin is also quite common in patient in use of chemotherapic. In this review, the use of moisturizing and emollient creams were presented as co-adjuvant of the conducts of treatment[28-30,40,41]. Skin hydration is essential

in any circumstance, therefore, it is indispensable the use of moisturizers either for prevention or treatment of the hand-foot syndrome because the skin drying causes the rupture of the epidermal barrier and reduces the water, increasing the risk of lesions[48] .

In one of the case reports, it was presented the treatment with *aloe vera*-based cream[41]. *Aloe vera* has humectant, emollient, anti-inflammatory, healing and regenerative properties of tissues. It is suggested that mannose-6-phosphate, the main polysaccharide present in *aloe vera* is the responsible for the healing. The cicatrization occurs by direct stimulation of the activity of macrophages and fibroblasts. The activation of fibroblasts increases both the synthesis of the collagen as of the proteoglycans, promoting the tissues repair. The mechanism of action is based in the inhibition of the derivate products of the acid arachidonic metabolism, such as the thromboxane B, which limits the production of prostaglandin F2a, preventing the progressive dermal ischemia[41,49,50].

The hand-foot syndrome is a very common adverse reaction during the treatment with chemotherapic agents and is a predictive factor of morbidity and mortality, since the lesions are the gateway for the installation of microorganisms and, consequently, implies in risk of sepsis[29-47].

It is known that the dose accumulated of chemotherapic associated to low immunity favors the risk of infections. Among the infections observed in the clinical practice, there are the fungic infections in the nails of hands and feet. However, only one case report was found that mentioned onycholysis and a series of cases that approached the case of onychomycosis within the context of hand-foot syndrome[27]. After the confirmation of the fungic infection through mycologic tests performed and based in the scraping of ungual lesions, the treatment adopted was with terbinafine, econazole and fluconazole[27].

This review showed a scenario of what is described in the literature including the hand-foot syndrome, with the approach of the fungic infections manifested as onychomycosis, including aspects of identification, prevention and treatment of the hand-foot syndrome, however, there are limitations about the quality of the evidences available.

It was adopted the approach of critical review of the literature with emphasis in the contribution of each item included. Like other reviews of the same nature[51], the objective was to reach a hypothesis yet unexplored by the scientific community. However, the present review has all the elements of the systematic reviews of the literature as: research question, selection of blinding by more than one reviewer, strategies of search and eligibility criteria to select the articles. Still, it has limitations as the impossibility of conducting a meta-analysis because of the heterogeneity if the studies selected.

Another limitation was the non-availability of the European databases as source of research (paid access), which hampered the access to other articles. Therefore, it is proposed an innovative interpretation of the existing data to widen the researches.

CONCLUSION

The results of this review indicated that the hand-foot syndrome implies in damages for cancer treatment and compromising of the quality of life of the patients. It was also evidenced that, despite being a reaction several patients present, it is still little explored by the scientific community. Because of this, it occurred a significant number of reports of cases in patients in treatment for cancer. Still, the observational studies and case reports help the oncologic care multiprofessional team to identify, prevent and treat chemotherapeutic agents-induced hand-foot syndrome. Another aspect noted was the necessity to consider the superficial mycosis within the context of the hand-foot syndrome like the complementary strategies of treatment. However, new studies are necessary with methodological designs of quality, nearly experimental prospective study and controlled randomized clinical trials in order to establish the stages the patients in treatment with chemotherapeutic agents are more prone to infections caused by fungi. Studies of this type can provide more robust scientific evidence about the theme in study with possibility of elucidating the etiology and define safe treatment protocols. Protocols better defined as personal care and education in health could be compared to allow better diagnosis and management of the hand-foot syndrome.

The appearance of this syndrome affects the quality of life of the patients and most of the times, it limits the routine activities. Qualitative and quantitative studies need to be designed to help the management of the patients, understand the relation of the syndrome and self-esteem with the objective of establishing strategies for the promotion of health in oncologic patients, either through the disclosure of information, education in health, promotion of health and training of the multiprofessional team involved.

CONTRIBUTIONS

Paulina Patente Pereira participated of the project, collection of the data, selection of the articles for review, analysis of the data, wording and critical. Reginaldo dos Santos Pedroso participated of the project, assisted in

the selection of the articles, analysis of the data, wording and critical review. Maria Ângela Ribeiro designed the study, participated of the project, conception and methodological orientation, collection and selection of articles for review, analysis of the data, wording and critical review. All the authors approved the final version to be published.

ACKNOWLEDGMENTS

To the Coordination of Improvement of Higher Education Personnel (Capes) - Financial code 001.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

Program of Health Professional Medical Residency (PRAPS) of the Ministry of Education (MEC).

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Recebido em 25/7/2019
Aprovado em 7/11/2019