



MUCOSITIS, PERIPHERAL NEUROPATHY AND HAND-FOOT SYNDROME: OCCURENCES AND REFLECTION FOR NURSING CARE

MUCOSITE, NEUROPATIA PERIFÉRICA E SÍNDROME MÃO-PÉ: OCORRÊNCIAS E REFLEXÕES PARA O CUIDADO DE ENFERMAGEM

MUCOSITIS, NEUROPATÍA PERIFÉRICA Y SÍNDROME MANO-PIE: HECHOS Y REFLEXIONES PARA EL CUIDADO DE ENFERMERÍA

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ABSTRACT

Objective: to verify the occurrence of the following drug adverse reactions mucositis, hand-foot syndrome and peripheral neuropathy in patients treated with chemotherapy. **Method:** a descriptive, retrospective study, with data collection from medical records of patients diagnosed with cancer. The project was approved by the Ethics Committee, under the protocol 560,065. **Results:** we have analyzed 244 medical records; of these, 28 have shown alterations in the oral mucosa, ranging from grades 1 to 3; 10 patients have shown symptoms of the hand-foot syndrome, ranging from grades 1 to 4 and 14 have presented peripheral neuropathy, grades 1-3. **Conclusion:** the three drug adverse reactions, although below the statistics presented in the literature are relevant and it is up to nursing staff to identify them. These reactions characterize complex concepts that require nursing interventions for the measurement, prevention and restoration of such events. **Descriptors:** Oncology Nursing; Chemotherapy; Adverse Reaction.

RESUMO

Objetivo: verificar ocorrência das reações adversas da mucosite, síndrome mão-pé e neuropatia periférica em pacientes tratados com quimioterapia. **Método:** estudo descritivo, retrospectivo, com coleta de dados em prontuários de adultos com câncer. O projeto obteve aprovação do Comitê de Ética em Pesquisa, protocolo n. 560.065. **Resultados:** foram analisados 244 prontuários; destes, 28 apresentaram alteração na mucosa oral, variando de Grau 1 a 3; 10 pacientes apresentaram sintomas de síndrome mão-pé, variando de Grau 1 a 4 e 14 neuropatia periférica, Graus 1 a 3. **Conclusão:** as três reações, embora abaixo da estatística apresentada na literatura, são relevantes e cabe à enfermagem identificá-las. Essas reações caracterizam conceitos complexos, que exigem intervenções de enfermagem voltadas para a mensuração, prevenção e restauração destas manifestações. **Descritores:** Enfermagem Oncológica; Quimioterapia; Reação Adversa.

RESUMEN

Objetivo: verificar la aparición de reacciones adversas mucositis, síndrome mano-pie y neuropatía periférica en los pacientes tratados con quimioterapia. **Método:** estudio descriptivo, retrospectivo, con la recogida de datos en los registros de adultos con cáncer. El proyecto fue aprobado por el Comité Ético de Investigación, Protocolo. 560.065. **Resultados:** se analizaron 244 historias clínicas; de éstos, 28 mostraron alteraciones en la mucosa oral, que van desde grado 1 a 3; 10 pacientes mostraron síntomas del síndrome mano-pie, que van desde el grado 1 a 4; 14 neuropatía periférica, los grados 1 a 3. **Conclusión:** las tres reacciones, aunque ellos por debajo de las estadísticas presentadas en la literatura son relevantes y corresponde a la enfermería de identificar. Estas reacciones se caracterizan conceptos complejos que requieren intervenciones de enfermería para la medición, la prevención y restauración de dichos eventos. **Descriptores:** Enfermería Oncológica; La Quimioterapia; Reacción Adversa.

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INTRODUCTION

Cancer, within the National Agenda of Priorities in Health Research (NAPHR) ⁽¹⁾, is allocated in the sub-agenda of non-communicable diseases. However, it is also present in other sub-agendas, regarding the bioethics and ethics in research, oral health, the complex of productive health and health technology and economics, among others. All of that occur given its impact on the health / disease, not only as for the restoring but also the maintenance of health.

High technology is needed both in the diagnosis as well as in the treatment of its various types and staging. Conventionally, most treatments used to its cure or control aim at the removal of tumors (surgery) and the destruction of cancer cells when exposed to chemical, biological or ionizing radiation agents. Chemotherapy itself or in combination with other treatments, interfere in the process of repair, cell replication and proliferation, in non specific ways. Therefore, they after normal cells such as the hair follicles, the epithelium of the gastrointestinal tract and the immune system which presents a more rapid renewal profile, thus being more susceptible. ²

It is understood that chemotherapy is a treatment the is potentially subject to provide different drug adverse reactions, including those related to the suppression of the bone marrow, such as anemia, neutropenia and thrombocytopenia; those that comprise nausea and vomiting, besides those that are related to changes in the structures and functions of peripheral CNS, such as neuropathy³. It can also be added to them the tegumental reactions, with unique clinical occurrences and requiring specialized approaches for its identification, assessment and correct intervention. It's relevant to highlight the mucositis, alopecia and acral erythema, commonly known as hand-foot syndromes. ⁴

Some of these adverse reactions, such as mucositis, peripheral neuropathy, and hand-foot syndrome, evolve complex concepts and require different nursing interventions. Mucositis is defined as an inflammatory response of the mucous membrane to the action of anticancer drugs. It mostly affects the oral cavity, where it is estimated to occur in approximately 40% of patients who receive chemotherapy in conventional dosages for solid tumors and 60% to 70% of patients who treat hematological malignancies. ⁵

Chemotherapy induced peripheral neuropathy (CIPN) is considered a condition

caused by the degeneration or dysfunction of the peripheral nerves, which can promote motor, sensory or autonomic disorders. It presents variable incidence according to the type of the chemotherapeutic agent used, the dose and administration schedule. ⁶

The hand foot syndrome is a skin reaction resulted from the direct toxicity of anticancer chemotherapy and is an important clinical problem in individuals with malignant neoplasm. ⁷ It can be understood as a complaint of feeling of tension, tingling, burning or stinging in the palmar and plantar regions, ⁸ where one can observe edema and erythema, which may progress to severe lamellar peeling, blisters, erosions or, rarely, ulceration, as seen in the clinic. ⁹ It's more frequent in patients treated with cytarabine and fluoropyrimidine, especially with capecitabine. According Abdalla e Silva, ¹⁰ more than 50% of patients receiving capecitabine have this syndrome.

Considering the incidence and relevance of these adverse reactions related to chemotherapy, it is the Nursing duty not only identify them but also plan differentiated patient care. ¹¹

OBJECTIVES

- To check the occurrence of mucositis, peripheral neuropathy, and hand-foot syndrome in patients treated with chemotherapy, on an outpatient basis
- To contribute to a reflection on the occurrence of such events and the evidence available in the literature for their care.

METHOD

It's a descriptive and retrospective study, whose data were obtained from medical records of patients who had outpatient chemotherapy in a city in the Northeast of Brazil, from January 2013 to January 2014. Data were collected through the form records of toxicities of anticancer. ¹²

The eligibility criteria were patients older than 18 years old diagnosed with cancer, confirmed by pathological or cytological examination, in chemotherapy treatment. Data were analyzed through descriptive and inferential statistics, with frequency calculations, either by clinical manifestation and association with the disease and the treatment provided. These data were analyzed using the *Statistical Package o for Social Sciences* - SPSS 17.0 (SPSS Inc., Chicago, USA).

This project was approved by the Research Ethics Committee of the Federal University of Sergipe, with protocol number 560 065. The

Kameo SY, Sawada NO, Zamarioli CM et al.

Informed Consent wasn't necessary as it's a retrospective study, which involved data collection from medical records.

RESULTS

244 medical records were analyzed and the most types of incidents were breast cancers (23.7%) and lung cancer (11.0%). As for the clinical staging of neoplasms, 63.9% were locally advanced or metastatic tumor.

Comorbidities presented by the patients were obese (25.4%), hypertension (22.1%), nephropaties (13.5%), diabetes mellitus (10.2%), heart disease (10.2%), neurological illness (4.5%) and autoimmune diseases (1.2%); 12.9% of these showed no comorbidities.

Other factors observed were smoking and drinking, and 17.6% were smoking and 2.8% were former smokers; 12.7% alcoholic and 0.8% had abandoned this habit.

In this study, 28 (11.5%) patients had oral mucositis, which ranged between grades 1 and 3, with 25.0% of Grade 1, 42.8% grade 2, and 25.0% grade 3. There have been cases (7.1%) where the graduation was not present in the medical record and were not observed mucositis reports of other sites in the gastrointestinal tract.

These patients have used different therapeutic plans. Among the platinum derivatives, cisplatin was used in six (10.5%) plans of treatment(1.7%); alkaloids such as vincristine in two (3.5%); taxanes such as docetaxel in five (8.7%) and paclitaxel in one (1.7%), alkilants such as carboplatin in three (5.2%), cyclophosphamide in six (10.5%) and in a ifosfamide in one (1.7%).

It was also observed concomitant changes in the mucosa due to the use of topoisomerase inhibitors such as etoposide (1.7%) and two with irinotecan (3,5%); four with antimetabolites(7.0%); two related to methotrexate and fluouracil (3.5%); one with cytarabine (1.7%); one with fludarabine, capecitabine and pemetrexed. As for the antitumor antibiotics, four (7.0%) with doxorubicin and one (1.7%) with bleomycin, daunoblastina, epirubicin, mitoxantrone and liposomal doxorubicin. The Monoclonal antibodies have also taken part in some therapeutic plans, two (3.5%) due to the two rituximab and two to cetuximab.

The peripheral neuropathy was identified in 20 (8.2%) of the study participants, ranging from Grade 1 to 3, being more prevalent in 3 (36.3%).The main therapeutic plans to those patients included paclitaxel (8; 40%), 5-FU (2; 10%), cetuximab, docetaxel, doxorubicin, fludarabine, gemcitabine, mitoxantrone,

Mucositis, peripheral neuropathy and hand-foot...

irinotecan, liposomal doxorubicin, rituximab and bortezomib, all with one occurrence (1, 5%).

Hand-foot syndrome was identified in 10 (4.0%) of the participants, in all grades, being more prevalent in Grade 2 (50.0%). During this occurrence of this syndrome the plans used in oncological treatment comprised the use of capecitabine (60%) and liposomal doxorubicin (40%).

DISCUSSION

Proportionally, the cancer incidence data reinforce the Brazilian statistics that have pointed the estimate for 2014, that the most incident tumor would be the breast cancer (36.74 / 100 thousand) in the Northeast, excluding skin cancer except the melanoma type. Lung cancer was the third (9.01 / 100,000), according to the National Cancer Institute.¹³ Breast cancer, despite being considered of a good prognosis, has high mortality rates, given the historical profile of being diagnosed in advanced stage. With regard to the lung cancer, is a type that is usually detected in advanced stages, due to the symptoms in the early stages not be a common data.¹⁴

Considering the comorbidities identified in the medical records of the study participants in the study, obesity was the most prevalent. The literature points to a relation of this disease with ovarian, prostate and uterus cancers¹⁴. Hypertension, another comorbidity present in about 22% of the participants, has been highlighted in the morbidity and mortality profile; it presents very variable prevalence due to the criteria of diversity for the diagnosis, involving not only aspects related to blood pressure measurement, as well as the populations studied.¹⁵ The Diabetes mellitus and neurological diseases may be associated with peripheral neuropathy such as autoimmune diseases.¹⁴

Other aspects that are relevant in the oncology are behaviors or risk factors. About 20% of the participants had smoking habits. In the literature, tobacco control remains as the main form of reduction of lung cancer occurrence, and it enhances the chances of larynx cancer when associated with alcohol consumption; This also relates to the risk of developing breast, oral cavity and esophagus cancers.¹⁴

In the occurrence of drug adverse reactions of interest in this study, the mucositis was identified in lower percentages in the literature.¹³ As mentioned above, it is a response to the direct effects of

Kameo SY, Sawada NO, Zamarioli CM et al.

Mucositis, peripheral neuropathy and hand-foot...

chemotherapeutic drugs on cells that divide rapidly in the tissues of oral cavity.¹⁶ Drugs that affect DNA synthesis are the most responsible for the incidence of such diagnosis. The antimetabolite agents (methotrexate, 5-fluorouracil) and the ones analogues to purine (cytarabine) are associated to the incidence rate that ranges from 40 to 60%. Other antineoplastics related to the development of mucositis are etoposide, cyclophosphamide, doxorubicin, daunorubicin, docetaxel and paclitaxel.¹⁷ Such fact has been corroborated in this study, as they are medicines used alone or in combination in the treatment plans of the types of most incident tumors in the population.

The exact mechanisms by which chemotherapy drugs and radiation therapy cause the mucositis have not been fully elucidated. However, researches have shown that in these agents damage the cells from the connective tissue and epithelial mucosa, which exhibit rapid cell division, resulting in inflammation and ulceration of the epithelium.¹⁸

In the nursing field, mucositis is part of a clinical evidence of a nursing diagnosis of damaged oral mucosa (00045) proposed by the NANDA - I.¹⁹ The use of drugs is seen as one of the causal factors of this nursing diagnosis, besides smoking and alcoholism.²⁰ The clinical manifestations of this diagnosis are oral lesions, stomatitis, pain, oral ulcer, discomfort and bleeding, among others. Given its relevance in patients on chemotherapy, it is recommended to employ the concept of mucositis in its broadest form, comprising other segments such as ears, intestines, and vagina, as evidenced in patients undergoing chemotherapy. It is understood that any region of the gastrointestinal mucosa (from the mouth to the anus) may be affected, and for this reason, the term gastrointestinal mucositis has been considered as the most appropriate to describe the process.^{21,22} It is relevant, therefore, to draw the nursing to the search of mucositis at other sites, not the just oral ones.

To promote the evaluation of this phenomenon it must be employed instruments for its characterization. The oral changes have scales for this purpose; among the most used is the World Health Organization (WHO) scale, based on clinical observations and complaints of the patients. Another scale is the Common Toxicity Criteria (CTC) from the National Institute of Cancer of the United States. The amendments evaluated by this one include: changes in the color of the mucous (pallor,

erythema, plaque or irregularities, lesions or ulcers), humidity (texture and brightness of saliva, changes in the flow, quality and tenacity of secretions), cleaning (accumulation of fragments, bad breath and changes in staining of teeth), integrity (cuts, cracks, ulcers, vesicles and isolated or grouped lesions, in plaques, confluent or generalized) and the individual's perception (taste, hoarseness, timbre and voice strength, swallowing, pain, burning).⁵

There are also the scales of the *Nursing Outcome Classification* (NOC), composed of expected results indicators arranged in five-point Likert scale, ranging from the injury's distinct maximum degree to the maximum degree of normality for direct patient care. It can be highlighted the evaluation of oral hygiene (1100) and tissue integrity: skin and mucous membranes (1101), and Self-care: Oral hygiene (0308) and pain level (2102).²³

In caring for people with mucositis, the nursing professionals can make use of different treatments. Their actions may be guided by the interventions proposed in the *Nursing Intervention Classification* (NIC)²⁴, for example, Promotion of Oral Health (1720), Maintenance of Oral Health (1710) and Restoration of Oral Health (1730), in addition to Nutritional Monitoring (1160) and Nutrition Control (1100) and Electrolyte Control (2080).

Several studies reinforce the activities of these interventions or complement them. With regard to the oral care segment, the individual's behavior in relation to oral hygiene should be known. The results of a recent survey have shown that the use of a video as an educational strategy can promote changes in the immediate behavior of subjects in cancer treatment, and represents an important tool to be used by the multidisciplinary team; it can also help minimize complications in the oral and systemic cavities.²⁵ Moreover, given the close relationship between the changes of the oral mucosa and local and systemic infections, support measures and prophylactic should also be implemented.²⁶

A systematic review by Manzi,²⁷ on the prevention of mucositis induced by chemotherapy, have shown the use of palifermin, allopurinol, chlorhexidine, zinc sulfate, laser, amifostine, chewing gum, sulcrafato, recombinant human intestinal trefoil factor, kefir and vitamin E. The results have shown the use of cryotherapy as an intervention with strong evidence levels for the prevention of oral mucositis that result from chemotherapy treatment with 5-fluorouracil. Other interventions, despite

Kameo SY, Sawada NO, Zamarioli CM et al.

Mucositis, peripheral neuropathy and hand-foot...

presenting positive results for the prevention of oral mucositis, require tests that show its effect.

With regard to peripheral neuropathy, this reaction has specific aspects for each drug class. It may be noted, in this study, that it was induced by different classes of chemotherapies, where the most significant was the one with antimetabolites such as 5-fluorouracil (5-FU) and taxanes.

Lesions may occur by changes in tubulin polymerization and by mitochondrial dysfunction²⁸, and may also have different phases depending on the drug. It calls for attention the use of oxaliplatin,²⁹ that despite not having been related in this study, it may also hasten sharply in 80% to 100% of the patients, with manifestations in the early hours of infusion, that are triggered or exacerbated by exposure to cold, reversible only within hours or days and little related to the discontinuation of the treatment.³⁰ The late toxicity (15% to 20% of patients), however, when associated with the cumulative dose of 750 to 850 mg / m², presents the most serious form and it often causes treatment discontinuation.³¹

Ways to assess this phenomenon (peripheral neuropathy) consider electromyography and other nerve conduction studies, the use of quantitative methods and goals, not always accessible, and require a specialist for their execution.³² The diagnosis is established by anamnesis and physical examination, using scales based on subjective data reported by the patient. The most used are the ones from the CTC of the American National Institute of Cancer and the World Health Organization. In this study, periodic exams such as history and physical examination were used and it was also considered the graduation according to the Common Terminology for the Criteria of Adverse Events (CTCAE, v.4.0)³³ from NCI.

Peripheral neuropathy is a concept under construction in the field of nursing, as the latest issue of NANDA-I¹⁹ didn't present a nursing diagnosis that portrayed this concept, although it could be included in Area 5 that addresses the Perception /Cognition and more specifically in the Class 3, Sensation/Perception. This shows a gap that needs to be filled, as this is a common phenomenon in oncology.

The characterization of this phenomenon can be made by the scales contained in the nursing results expected for the peripheral neuropathy situation, such as, Neurological status: peripheral (0917), which evaluates skin color, pain in extremities and paresthesia; and

in a lower scale, by the result of Tissue Integrity: skin and mucosa (1101), which evaluates the function and structures of the skin²³.

In the field of nursing practice, the interventions identified by the NIC²⁴ guide the neurological monitoring (2620), with activities aimed at paresthesia and proprioception, in addition to Pain Management (1400) and Prevention of falls (6490).

Recent clinical studies have shown that the temporary interruption of neurotoxic chemotherapy can be established, besides changes in time of infusion of the medication³⁴ and the dose reduction. It is used also the infusion of calcium and magnesium before and after certain chemotherapy agents.³⁵

In the hand-foot syndrome, the literature indicates capecitabine, 5-fluorouracil, cytarabine and doxorubicin as the most responsible for its development.³⁶ It was observed that 60% of the patients received capecitabine, a fact that corroborates the literature.

The presentation of this reaction requires the reduction of the therapeutic dose of antineoplasms, cycle retardation, and in many cases, abandonment of treatment. The interference in the quality of life reported by patients makes us think of the quality of overall survival that is offered to them.⁹

In nursing, such occurrence is usually considered inserted into the concept of Impaired Tissue Integrity (00044)⁽¹⁹⁾, as there is the presence of an injury and even destruction of the tissue, in the most severe cases. Among the patients with this syndrome, 60% made use of capecitabine, one of the chemotherapeutic identified as a likely related factor.

To evaluate this phenomenon, the results of the NOC²³ indicated are Tissue Integrity: skin and mucous membranes (1101) and as an additional associated result, the Sensory Function: cutaneous and tissue perfusion: peripheral (0407). Nevertheless, they do not address the phenomenon in its entirety.

As part of actions for the management of this complication nurses can make use of nursing interventions:²⁴ Skin Care: Topical Treatments (3584) and Chemotherapy Handling (2240), with actions aimed at minimizing the effects of anticancer agents, in addition to Pain Control (1400) and Preparatory Sensory Information (5580).

When considering intervention with topical treatments, new strategies for hand-foot syndrome treatment include topical products based on urea, lanolin; hyaluronic acid;

Kameo SY, Sawada NO, Zamarioli CM et al.

allantoin and Aloe vera (aloe). It is also recommended the use of analgesics for pain control, non-steroidal and steroidal anti-inflammatories, anti-oxidants such as Vitamin E, Dimetilsulfoxide (DMSO), henna and pyridoxine (B6 vitamin).⁹

CONCLUSION

The phenomena analyzed in this study (mucositis, peripheral neuropathy, and hand-foot syndrome) are common in oncology, in spite of being presented in the medical files studied in a lower frequency than described in the literature.

Both mucositis as hand-foot syndrome can be considered phenomena studied by nursing and contemplated, even partially, by the aforementioned diagnosis. However, peripheral neuropathy still needs a closer look, since it does not portray a real diagnosis or risk that is contemplated in the present days.

Oral mucositis is the most investigated, both in medicine and in nursing, where traditional, alternative and / or complementary interventions are applied. It is one of the presentation of the damage caused by the integument antineoplastic agents, and it evidences only part of a larger range of the toxicities to the mucous membranes. However, comparative and multi-center clinical studies, with a larger number of participants have yet to be designed, as there are still a wide variety of interventions and lack of guidelines for treatment. Data from this study corroborate the literature regarding treatment where different approaches to the same degree of toxicity are presented.

Peripheral neuropathy may have risk factors and/or related factors similar to those of hand-foot syndrome, even though it has a different etiology. The use of NIC and the available evidences should guide future studies, because we still perceive as slight the actions of nursing in the presence or the imminent risk of such reactions. This fact points to the need to stimulate these areas of intervention, guided both by the knowledge of these reactions, as well as by the prevention and care differentiation.

With regard to the strategies used and proposed by NIC, these are also partial. And such fact leads us to reflect that there is still a vast field for incorporating these practices in care activities and in nursing research. A field to be highlighted for the research is the complementary and alternative therapies, recommended by the National Agenda of Priorities in Health Research (NAPHR), in

Mucositis, peripheral neuropathy and hand-foot...

order to seek new measures to prevent and treat these phenomena that directly affect the quality of life of cancer patients.

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