

Characterization of Paclitaxel-associated hypersensitivity reactions in cancer patients

Caracterização de reações de hipersensibilidade associadas ao Paclitaxel em pacientes com câncer

Caracterización de reacciones de hipersensibilidad asociadas a Paclitaxel en pacientes con cáncer

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RESUMO

Objetivo: mapear a incidência de reações adversas por hipersensibilidade ao Paclitaxel em pacientes oncológicos. **Método:** estudo exploratório-descritivo, retrospectivo, realizado em uma central de quimioterapia de uma instituição de referência em oncologia. A amostra compôs-se de 240 pacientes, sendo 23 acometidos por reações adversas por hipersensibilidade à infusão de Paclitaxel com dose igual ou superior a 135mg/m². A coleta de dados ocorreu por análise dos prontuários. **Resultados:** prevalência de homens idosos e portadores de câncer pulmonar. Houve reações de hipersensibilidade ao Paclitaxel em 9,58%. A maioria ocorreu no primeiro e segundo ciclos de infusão e, em média, após 66 minutos, com uma duração média de 40 minutos. **Conclusão:** devem-se monitorar as infusões de Paclitaxel ininterruptamente. Assim, ressalta-se a importância do dimensionamento de enfermagem para ambulatórios de quimioterapia. Infere-se também que times de resposta rápida e implementação da consulta de enfermagem contribuem para manejo seguro e controle eficaz das reações adversas.

DESCRITORES:

Antineoplásicos; Enfermagem oncológica; *Taxus brevifolia*.

ABSTRACT

Objective: This study aims to map the incidence of Paclitaxel-associated hypersensitivity reactions in cancer patients, as well as to analyze the time frame between the drug administration and the reaction onset, to describe the signs and symptoms presented by patients and to list the measures taken by nurses in the event. **Method:** retrospective exploratory/descriptive study carried out at a

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chemotherapy center regarding a reference institution in the control of cancer treatment. The sample was consisted of 240 patients, in which 23 patients suffering from infusion hypersensitivity for Paclitaxel chemotherapy at a dose of 135 mg/m² or higher. The operationalization for collecting data included document analysis in patients' records. **Results:** Elderly, male and lung cancer patients prevailed. Hypersensitivity reactions (HSR) to Paclitaxel occurred in 9.58% of patients. These reactions occurred in most of the patients during the first and second infusion cycles and, on average, with a reaction rate of 66 minutes and average time of 40 minutes.

Descriptors:

Antineoplastic agents; Oncology nursing; *Taxus*.

RESUMEN

Objetivo: Este estudio tiene como objetivo mapear la incidencia de reacciones adversas por hipersensibilidad relacionadas con Paclitaxel en pacientes oncológicos, así como analizar el tiempo transcurrido entre la instalación del fármaco y el inicio de la reacción, para describir los signos y síntomas presentados por los pacientes y enumerar las medidas adoptadas por los enfermeros frente a lo ocurrido. **Método:** se trata de un estudio exploratorio-descriptivo, de carácter retrospectivo, realizado en un centro de quimioterapia de una institución de referencia en el tratamiento del cáncer. La muestra estuvo conformada por 240 pacientes, de los cuales 23 presentaron reacciones adversas por hipersensibilidad a la infusión del fármaco quimioterápico Paclitaxel con dosis igual o superior a 135 mg/m². La operacionalización de la recolección de datos ocurrió a través del análisis documental de los prontuarios de los pacientes. **Resultados:** Prevalcieron los pacientes adultos mayores, del sexo masculino y con cáncer de pulmón. Hubo reacciones de hipersensibilidad al Paclitaxel en el 9,58% de los pacientes. Estos ocurrieron principalmente en el primer y segundo ciclo de infusión y, en promedio, tardaron 66 minutos en ocurrir, con una duración promedio de 40 minutos. **Conclusión:** El seguimiento de las infusiones de Paclitaxel debe ser ininterrumpido, y para eso, se destaca la importancia del dimensionamiento de enfermería para las consultas externas de quimioterapia. Además, se infiere que la creación de equipos de respuesta rápida y la implementación de la consulta son estrategias para el manejo seguro y control efectivo de las reacciones adversas al Paclitaxel.

DESCRIPTORES:

Antineoplásicos; Enfermería oncológica; *Taxus*.

INTRODUCTION

Paclitaxel is an antineoplastic drug obtained by means of a semisynthetic process of *Taxus brevifolia* (alkaloid plant), which stimulates the formation and stabilization of microtubules and inhibits their depolymerization, making them nonfunctional, blocking cell division in the metaphase ⁽¹⁾.

Currently, this drug is used to treat various types of cancer, including lung, ovary, breast and Kaposi sarcoma ⁽²⁾. Its medical indication and apprehension depend on the type of cancer and its administration is dose-dependent, with doses of 135mg/m² and 175mg/m² performed every three weeks for three hours, and doses of 80mg/m² - weekly, over an hour ⁽²⁾. The severity of hypersensitivity reactions (HSRs) to Paclitaxel can be a predictor of continuity of treatment with this drug, mobilizing the medical team to change chemotherapy protocol, even with the benefit of disease control, to the detriment of

potentially fatal hypersensitivity reactions.

In general, 5% to 15% of patients treated with any drug develop adverse reactions, being 2% to 3% of these skin reactions ⁽³⁾. In the case of chemotherapy treatment, the occurrence of various reactions to drugs is even more intense, requiring the development of actions for their identification and management. The main adverse reactions described in the literature involving chemotherapy are: alopecia, spinal depression, vomiting, diarrhea, mucositis and stomatitis. However, the occurrence of reactions varies in each patient ^(1,4-5). Within the taxane group, Paclitaxel is often associated with the occurrence of hematological, gastrointestinal, cutaneous, neurological, cardiovascular, allergic reactions, among others ⁽¹⁾.

Allergic or hypersensitivity reactions (HSRs) are the most frequent and occur due to mast cell degranulation, leading to the release of histamine and other mediators of inflammation responsible for symptoms such as urticaria, bronchospasm, angioedema and/or anaphylaxis ⁽³⁾. Although the exact mechanism of HSR is not specifically known, it is suggested that its solvent - polyoxylated castor oil (Cremophor EL), used to solubilize Paclitaxel - is responsible for hypersensitivity reactions.

Recent studies have brought the possibility that some reactions are mediated by IgE ⁽¹⁻³⁾. A retrospective study with 414 patients who received Paclitaxel for treatment of gynecological cancer reported an incidence of 6.3% of HSR ⁽⁶⁾. Its occurrence points to the need to know it, developing actions for its identification and management, because when the symptoms resulting from hypersensitivity reactions are not properly controlled, they can bring a negative impact on the patient, and, consequently, affect compliance with the proposed therapeutic regimen.

In general, to prevent HSR, the patient receives a regimen of pre-chemotherapy drugs, composed of steroids and antihistamines ⁽²⁾. The doses vary according to the protocol used: dexamethasone (varies from 5 to 20 mg), diphenhydramine of 50 mg, ranitidine (from 50 mg to 150 mg), intravenous, 30 to 60 minutes before the administration of Paclitaxel ^(2,6-8). In addition, patients can receive oral dexamethasone 20 mg, 12 and 6 hours before administration of Paclitaxel, although, even receiving these drugs before infusion, approximately 10% of patients develop HSR ⁽²⁾.

Thus, the continuous evaluation of events that occur with patients during treatment is necessary and is of paramount importance in establishing protocols of conduct, according to the reality of the services. By monitoring and measuring the complications, it is possible to select relevant interventions and analyze whether prevention and treatment strategies are being effective ⁽⁹⁾.

Therefore, the objectives of the study are to map the incidence of adverse reactions due to hypersensitivity to Paclitaxel in a Chemotherapy Center of the Federal Hospital of Rio de Janeiro; to analyze the time elapsed between the installation of the drug and the beginning of the reaction; to describe the signs and symptoms presented by the patients and to list the measures adopted by the nurses in

relation to what happened.

METHODOLOGY

Study design, place and period

An exploratory-descriptive, retrospective study was conducted at a Chemotherapy Center of a Federal Hospital of Rio de Janeiro, from March to June 2017. The institution is a High Complexity Reference Center in Oncology and is divided into five units. The present study was conducted in the chemotherapy center of unit I, which performs treatment of patients with hematological and solid cancer (except for gynecological and connective bone tissue cancer). STROBE was used as a methodological guide.

Population

Data were collected from 240 patients who underwent treatment with Paclitaxel dose \geq 135mg/m².

Inclusion and exclusion criteria

The inclusion criteria adopted were: patients older than 18 years, treated in the chemotherapy sector of the institution and who performed infusion of the Paclitaxel chemotherapy, in the period between 01/01/2016 and 12/31/2016, at a dose equal to or greater than 135mg/m², for being doses with higher reports of reaction ⁽¹⁰⁻¹¹⁾. Participants whose medical records did not clearly describe the characteristics of the adverse reaction and those not available in the hospital file were excluded.

Study protocol

The sociodemographic variables studied were age and sex and the epidemiological variables constituted: type of cancer, purpose of treatment, chemotherapy protocol used and stage of disease. Moreover, the variables describing the type of adverse reaction, when occurred, were: infusion cycle of the drug, time elapsed between installation of the drug and reaction, duration of the reaction, compromised organic systems, signs and symptoms presented, conducts adopted by the nursing team and outcomes after reaction control.

The dose of Paclitaxel was used with intervals of three weeks. The calculation of the dose of the drug is performed according to the body surface of each patient, which causes variation in the dose. Patients were pre-medicated with dexamethasone 20 mg, ondansetron 8 mg and ranitidine 50 mg intravenously, with an infusion time of up to 30 minutes, in order to reduce the risk of severe hypersensitivity reactions. However, until the conclusion of this study, in this institution, there was still no defined protocol for the management of the occurrence of HSR.

Results and statistical analysis

The data were obtained through a data collection instrument created by the research team and

subsequently recorded and analyzed in a spreadsheet of SAS software version 9.3.1. Initially, a descriptive analysis of the data was performed, using simple frequency. After the descriptive analysis, a non-parametric Fisher test was performed to verify the relationship of the variable “reaction” with the other variables studied. The test was performed with a confidence level of 95% and significance of 0.05.

Ethical aspects

Data were collected after a favorable opinion of the Institution’s Research Ethics Committee (José Alencar Gomes da Silva National Cancer Institute - INCA), n. 1,909,191, on February 06, 2017.

RESULTS

In the evaluated period, data were collected from 240 patients who underwent treatment with Paclitaxel at a dose $\geq 135\text{mg/m}^2$, which has higher reports of reaction ⁽¹⁰⁻¹¹⁾. As for the characteristics of the patients, the average age was 61 ± 10.92 years, with a predominance of males (57.09%). Regarding the type of cancer, it can be observed that lung cancer was the most prevalent both for the 19 patients who had a reaction (7.92%) and for the 157 who had no reaction (65.42%), as shown in Table 1.

The purpose of treatment was mostly palliative (226), representing 8.97% of patients with reaction and 87.61% of patients who had no reaction. The most used treatment protocol was carboplatin and Paclitaxel (Carbotaxol), and 9.58% of patients had a reaction and 89.17% of patients had no reaction. Regarding the stage of development of the disease, IV was the most identified in patients with reaction (6.17%) and without reaction (70.04%). In six cases, the purpose of treatment was not reported and 13 did not indicate the stage, as shown in Table 1.

Table 1. Sociodemographic and epidemiological characteristics of patients who had a reaction and those who did not. Rio de Janeiro, RJ, Brazil, 2016. (n=240)

Quantitative Variables	N	Reaction		
		No	Yes	
		%	N	%
Sex				
Male	133	55.42	4	1.67
Female	84	35	19	7.92
Type of Cancer				
Lung	157	65.42	19	7.92
Parotid	1	0.42	0	0
Esophagus	14	5.83	2	0.83
Oral cavity	3	1.25	0	0
Testicle	3	1.25	0	0
Cardiac	1	0.42	0	0
Head and neck	3	1.25	0	0
Kaposi sarcoma	0	0	1	0.42

Oropharynx	8	3.33	0	0
Nasopharynx	2	0.83	0	0
Cavun	1	0.42	0	0
Metastatic lung	9	3.75	0	0
1 st undetermined	1	0.42	1	0.42
Gastric	2	0.83	0	0
Cervical skin	1	0.42	0	0
Other	11	4.58	0	0
Treatment Purpose				
Neoadjuvant	2	0.85	0	0
Adjuvant	5	2.14	1	0.43
Palliative	205	87.61	21	8.97
Treatment Protocol				
Carbotaxol	214	89.17	23	9.58
TIP	3	1	0	0.00
Stage				
II	2	0.88	1	0.44
III	44	19.38	6	2.64
IV	159	70.04	14	6.17
X	1	0.44	0	0

X - Non-determined stage; Carbotaxol: Carboplatin and Paclitaxel; TIP - Paclitaxel, Ifosfamide and Cisplatin

HRS occurred in 9.58% of cases, with an average time between the initiation of Paclitaxel and HRS of 66.0±77.33 minutes (Min. 1 - Max. 230 minutes) and mean duration of 40±30.37 minutes (Min. 10 - Max. 120 minutes), and this information was not reported in 12 cases, as shown in Figure 1.

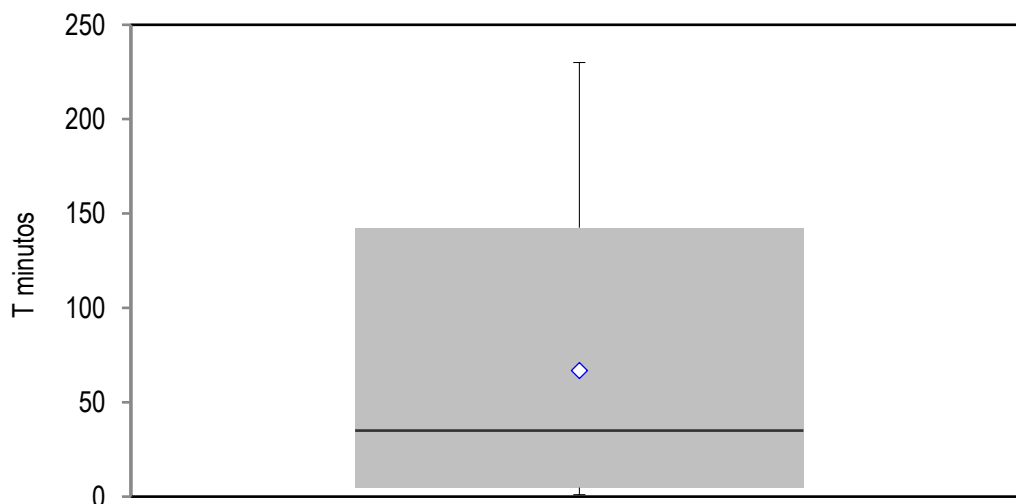


Figure 1. Time in minutes between Paclitaxel initiation and HRS. Rio de Janeiro, RJ, Brazil, 2016

When the characterization of patients who had adverse reactions due to Paclitaxel-related

hypersensitivity was evaluated (n=23), there was a greater representation of females (82.60%), 52.17% of the patients developed HRS in the first infusion cycle of Paclitaxel as shown in Table 2.

The pulmonary system was the most compromised organ (65.21%), followed by the cardiac one (47.82), recalling that some patients presented with impairment of more than one system. The most frequent signs and symptoms in patients were dyspnea (52.17%), hypertension (47.82%) and chest pain (26.08%). Significant variables ($p < 0.0001$) are shown in table 2.

Regarding the measures adopted by nurses in the presence of the reaction, it was observed that interrupting the infusion of Paclitaxel was the intervention adopted primarily in all cases (100.00%). However, some patients needed other measures, which included the administration of hydrocortisone in 65.21% of patients, as shown in Table 2.

After the stabilization of symptoms, 65.21% of the patients had the return of the infusion of Paclitaxel, 30.43% of the patients had the therapy interrupted, without the return of the infusion that day and 17.39% had severe reactions requiring referral to hospital emergency and change of protocol, as shown in Table 2.

Table 2. Characterization of adverse Paclitaxel-related hypersensitivity reactions. Rio de Janeiro, RJ, Brazil, 2016. (n=23)

Quantitative Variables	N	%	P value
Sex			
Male	4	17.39	< 0.001
Female	19	82.60	
Cycle			
1	12	52.17	< 0.0001
2	5	21.73	
4	3	13.04	
5	1	4.34	
Compromised System			
Pulmonary	15	65.21	< 0.0001
Integumentary	4	17.39	< 0.0001
Cardiac	11	47.82	< 0.0001
Other	2	8.69	0.0088
Signs and Symptoms			
Hyperemia	2	8.69	< 0.0001
Hypotension	0	0.00	*
Dyspnea	12	52.17	< 0.0001
Bronchospasm	2	8.69	0.0088
Tachycardia	2	8.69	0.0088
Urticaria	3	13.04	< 0.0001

Hypertension	11	47.82	< 0.0001
Abdominal pain	2	8.69	0.0088
Chest pain	6	26.08	< 0.0001
Pain in extremities	2	8.69	0.0088
Fever	1	4.32	0.0958
Headache	0	0.00	*
Measures Adopted			
Stop infusion	23	100.00	< 0.0001
Oxygen therapy	5	21.73	< 0.0001
Atrovent/Berotec	4	17.39	< 0.0001
Hydrocortisone	15	65.21	< 0.0001
Diphenhydramine	7	30.43	< 0.0001
Antihypertensive	6	26.08	< 0.0001
Conducts after controlling the Reaction			
Discontinued therapy	7	30.43	< 0.0001
Emergency	4	17.39	< 0.0001
Return of the infusion	15	65.21	< 0.0001

* No case; Fisher's non-parametric test

DISCUSSION

Studies related to HSR to Paclitaxel have been performed in gynecology services ^(7,13), but this study was conducted in a general oncology service, with men as the predominant population. This may be related to the most frequent type of cancer in this study - lung cancer -, because Paclitaxel is an antineoplastic drug used for the treatment of various types of cancer, such as ovary, breast, lung, head and neck and Kaposi sarcoma ^(1,3). The results show that the studied population had a mean age similar to that of other studies, 61 years ^(10,12).

The effectiveness of treatment with Paclitaxel can be compromised due to HSR during infusion, which represents an important impediment to the treatment of cancer patients ⁽¹²⁾. Paclitaxel HSRs occur in approximately 10% of treated patients ^(2,14) and are severe in 2% to 4% of cases ⁽¹²⁾. In this study, HRS reached 9.58% of patients undergoing treatment, that is, expected percentage in patients undergoing treatment with Paclitaxel. However, when compared to other studies ^(7,13), there was a higher frequency of reactions, which may be related to the severity of the patients, since most of the patients were in stage IV.

In this research, the presentation of HSR mostly happened in the first and second cycle. This fact is already reported in the literature, which points out that most HSRs to taxanes happen in the first or second infusion of the drug ^(2,12,14). A study conducted in Japan showed similar characteristics, with 85% of HSRs developed in the first administration of Paclitaxel and in a few minutes of infusion ⁽⁷⁾. However, some patients developed the reaction in the fourth and fifth infusion, which leads to infer that strict

vigilance in the administration of Paclitaxel needs to be performed in all infusion cycles of the drug. In a study conducted in Thailand, the HSRs to Paclitaxel occurred mostly between the third and seventh administration of the drug ⁽⁸⁾.

In the present study, the mean time between the initiation of Paclitaxel and HSR was 66 minutes with an average duration of 40 minutes, elapsed time from the identification of signs and symptoms of HSR to complete resolution, corroborating what the literature points out, that reactions usually occur in the first hour of infusion, 75% of cases in the first 10 minutes ⁽¹⁴⁾. Regarding the time for the reaction, it is believed that it is not related to the dose or time of infusion of Paclitaxel ⁽¹⁾ but to exposure to the drug. The individual may develop a reaction by activating the complement system induced by Cremophor, which generates anaphylatoxins, triggering basophils activation; histamine release by direct effect of Paclitaxel on basophils or the reaction may be mediated by IgE/IgG, caused by Paclitaxel or solvent (Cremophor EL) ⁽²⁾.

In the study population, patients who had Paclitaxel-related HSR presented statistically significant signs and symptoms, such as dyspnea (< 0.0001), hypertension (< 0.0001), chest pain (< 0.0001), urticaria (< 0.0001), hyperemia (< 0.0001), bronchospasm (0.0088), tachycardia (0.0088), abdominal pain (0.0088), extremity pain (0.0088). All these symptoms are described in the literature ^(1-2, 14), but the leaflet describes only angioedema, hypotension, shortness of breath and urticaria ⁽¹⁵⁾.

The symptoms caused by HSR somehow interfere with the treatment regimen proposed for the patient ⁽¹⁶⁾, since, from the moment it occurs, the medication is temporarily or definitively stopped. In addition, HSR is an unpleasant experience for the patient, since it affects their quality of life, contributing to decreased confidence in the health professionals involved, increases costs, delays treatments, which prolongs the patient's stay in hospital ⁽¹³⁾. In the context of the study, among the 23 reactions that occurred, as a procedure adopted, seven patients had the therapy canceled after the reaction; and four had severe reactions, requiring referral to hospital emergency and subsequent change of protocol. Thus, HSRs constitute an adverse reaction to medicines and are an important problem in professional health practice. Therefore, measures to prevent or reduce the harmful effects manifested by the patient need to be considered in order to improve the care provided ⁽¹⁷⁾.

Among the interventions indicated for the management of HSRs by the nurse are: stop the infusion immediately; maintain a patent airway; provide oxygen in a sufficient flow to maintain oxygen saturation; administer emergency medications; prepare the patient for intubation if necessary; monitor vital signs; infuse fluids to maintain blood pressure and initiate infusion of vasopressors if blood pressure control is not satisfactory with fluids ⁽¹⁷⁾. In this study, when patients had a reaction, the primary intervention adopted by nurses was to stop the infusion of Paclitaxel and, soon after, administer drugs according to the symptoms presented by the patient: hydrocortisone, diphenhydramine, antihypertensive,

oxygen therapy and or nebulization with ipratropium/phenoterol (Atrovent/Berotec).

In general, when a patient has an HSR, it is expected a treatment with corticosteroids and antihistamines and reassessment concerning the resolution of symptoms (within 30 minutes), for definition of conduct, which can culminate in: resumption of Paclitaxel infusion, suspension of the cycle for subsequent re-evaluation in medical consultation (with potentiation of oral desensitization by corticosteroids) or definitive suspension of treatment with Paclitaxel ⁽²⁾.

Nurses have performed these interventions, most of the time, achieving success with return of infusion. But the nurse also needs to exercise their role as an educator and perform the nursing consultation, a private activity of the nurse. At this time, they collect information, examine to know, understand and explain the patient's health/disease situation, which becomes an opportunity to create bonds and establish trust relationships, which may contribute to the patient's adherence to treatment ⁽²⁰⁾.

Nurses who administer chemotherapy should have knowledge about the agents most likely to trigger HSRs and, in addition, need to be skilled in recognizing and managing them, when they occur ⁽¹⁷⁾. Most HSRs identified in this study were moderate, that is, the patient presented with characteristics that involve respiratory, cardiovascular or gastrointestinal impairment ⁽¹⁸⁾. Therefore, a mandatory nursing care in the face of exposure to antineoplastic agents known to be hypersensitizing, such as Taxanes, is the evaluation of pre-infusional vital signs and mental state. These data will be evolutionary parameters of the degree of severity of the clinical presentation of HSR, since studies have demonstrated that dyspnea, the most frequent symptom in this situation, is a significant predictor of cyanosis and desaturation, classified as symptoms of severe HSR, which can lead to neurological symptoms of the patient before starting the administration of Paclitaxel, so that, if a reaction occurs, it can be quickly identified for its management ⁽¹⁹⁾.

When the nurse implements the nursing consultation in the context of chemotherapy and HSR, they provide guidance to the patient and their family about signs and symptoms that may appear during the infusion of the drug and about the interventions that will be performed in case of HSR ⁽²¹⁾. They can also review, together with the doctor, the premedication regimen, in order to reduce the anxiety of the patient and their family and improve the management of HSRs, if they occur.

Study Limitations

The study presents the limitation of the cross-sectional period of one year to evaluate the presentation of clinical manifestations presented by patients exposed to Paclitaxel. Longitudinal studies of observational characteristic may be required to assess whether there was permanent or prolonged injury, which are the determining factors for the occurrence of HSR and the impact on the cost of restoring homeostasis in patients.

Contributions for nursing, health and public policy

The study contributes to the knowledge of adverse events that occur during the infusion of chemotherapy drugs, demonstrating the complexity of this procedure and the importance of the performance of a trained and well-sized nursing team to meet the demands in a chemotherapy outpatient clinic. Furthermore, it presents reflections on strategies to assist a patient during an anaphylactic reaction with quality and safety.

CONCLUSION

The clinical profile of the study included mostly elderly male patients with lung cancer. It was evidenced that the prevalence of occurred HSRs is within the profile found in the literature, but there were insufficient data in the characterization of these reactions, especially regarding the time of initiation and its duration, limiting factor for the study.

The incipience of clinical records, in the face of complications with potential severity outcomes, compromises more robust clinical analyses, although it can be equally justified by its gravity and recruitment of material and human resources that mobilize and exhaust the teams.

The monitoring of Paclitaxel infusions should be uninterrupted, since the anaphylactic symptomatology ranged from moderate to severe, being triggered both immediately to the installation of the drug and near the end of the infusion, with a minimum of 1min and maximum of 230min, in 9.58% of patients with HSR, and in varied cycles. Thus, the importance of nursing dimensioning for chemotherapy outpatient services is emphasized, because, although HSRs have been managed, for the most part, successfully, these exhaust the health team, patient and family, requiring time to control the symptomatology and reestablishment of follow-up treatment, without desire for abandonment or implication in the self-confidence of patients and relatives, given the delicacy that all the circumstance of oncological illness imposes.

In addition, it is inferred that the formation of teams for rapid responses - with trained nurses skilled in recognizing patients more likely to develop adverse reactions - and the implementation of nursing consultation before and after infusion are strategies for safer management and possibility of effective control of adverse reactions to the drug.

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