Prevalence of peripheral neuropathy associated with chemotherapy in four oncology centers of Colombia

José W. Martínez, Julio C. Sánchez-Naranjo, Paula A. Londoño-De los Ríos, Carlos A. Isaza-Mejía, Juan D. Sosa-Urrea, Manuel A. Martínez-Muñoz, Juliet J. López-Osorio, Daniel S. Marín-Medina, Manuel E. Machado-Duque, Jorge E. Machado-Alba

Facultad de Ciencias de la Salud; Universidad Tecnológica de Pereira (Martínez JW, J.C. Sánchez-Naranjo, C.A. Isaza-Mejía, J.D. Sosa-Urrea, M.A. Martínez-Muñoz, J.J. López-Osorio, D.S. Marín-Medina, M.E. Machado-Duque, J.E. Machado-Alba). Oncólogos del Occidente (P.A. Londoño-De los Ríos). Fundación Universitaria Autónoma de las Américas (M.E. Machado-Duque). Pereira, Colombia.

Corresponding author:
Dr. Jorge E. Machado Alba. Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia. Facultad de Ciencias de la Salud. Universidad Tecnológica de Pereira. Audifarma S.A. Calle 105, n.º 14-140. CP 660003. Pereira, Risaralda, Colombia.

E-mail:
machado@utp.edu.co

Funding:
Oncólogos del Occidente, Audifarma S.A. and Universidad Tecnológica de Pereira.

Accepted:
12.04.19.

How to cite this paper:
Martínez JW, Sánchez-Naranjo JC, Londoño-De los Ríos PA, Isaza-Mejía CA, Sosa-Urrea JD, Martínez-Muñoz MA, et al. Prevalence of peripheral neuropathy associated with chemotherapy in four oncologic centers of Colombia. Rev Neurol 2019; 69: 94-8. doi: 10.33588/rn.6903.2019035.

Versión española disponible en www.neurologia.com

Introduction. Chemotherapy-induced peripheral neuropathy is a common adverse reaction in a variety of medications frequently used for a great number of cancer treatments. This condition consists of mainly sensory-type symptoms, motor components and autonomic changes. Reported prevalence ranges from 30-68%, after the completion of chemotherapy in non-Latin American people with different populations and socioeconomic levels.

Aim. To determine the prevalence of chemotherapy-induced peripheral neuropathy in a Colombian population.

Patients and methods. A real-world evidence cross-sectional retrospective study was performed in all patients from oncological clinical centers in Colombia, which received pharmacological therapy for any cancer between January 2015 and December 2016, with taxanes (paclitaxel, docetaxel), alkylators (oxaliplatin), proteasome inhibitors (bortezomib), and epothilone B analogs (ixabepilone).

Results. A total of 1,551 patients in four cities were included, and 11,280 doses were applied; predominantly females (*n* = 1,094; 70.5%), with a mean age of 57 ± 13 years old. Paclitaxel was the most commonly prescribed drug (*n* = 788; 50.8%). Chemotherapy-induced peripheral neuropathy was developed in 48.9% of paclitaxel, 58.5% of oxaliplatin, 50.5% of docetaxel, 43.7% of bortezomib and 95.2% of ixabepilone patients. Thirty-three patients were treated with two of these medications simultaneously.

Conclusions. Chemotherapy-induced peripheral neuropathy is a frequent adverse reaction to daily cancer therapy in Colombian patients managed with taxanes, alkylators, proteasome inhibitors, and epothilone B analogs. Hence, it is necessary to establish more successful diagnostic methods and incorporate validated scales in the routine evaluation of all patients receiving these medications in our environment

Key words. Antineoplastic agents. Docetaxel. Oxaliplatin. Paclitaxel. Pharmacovigilance.

Introduction

Cancer is the second leading cause of death worldwide, with health care systems carrying a heavy burden from the disease, including premature death, high costs, and complications derived from therapies. In Colombia, the burden of this disease has been on the rise in recent years, although secondary mortality has decreased mainly due to better, more timely diagnoses, along with more effective therapy. Still, adverse effects associated with chemotherapy are considerable in their implications for the management and effect on the quality of life of patients, both during and after pharmacological management [1-3].

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common adverse reactions associated with a variety of medications frequently used for cancer, including taxanes (paclitaxel, docetaxel), alkylators (oxaliplatin), proteasome inhibitors (bortezomib), and epothilone B analogs (ixabepilone) [4-11]. These medications are frequently used for their effectiveness in treating multiple types of cancer, such as breast, colon, lung, stomach, cervical, and ovarian cancers as well as myeloma, which represent some of the highest incidences of disease and mortality in the Colombian and global populations [1,2]. CIPN consists of mainly sensory-type symptoms, but it also has motor components and autonomic changes and may constitute a significant complication that limits the use of these medications, even when required in a therapeutic strategy. This situation is exacerbated when quality of life is compromised. Quality of life is considered part of the current vision for therapeutic planning, which emphasizes the need to take all necessary actions to preserve patient well-being to the highest extent possible.

The mechanisms of CIPN are not completely understood, but there is a clear association with alteration of calcium homeostasis in neurons, as shown in studies of paclitaxel and oxaliplatin treatment [12,13]. The cellular toxicity triggered by paclitaxel and other taxanes leads to injury of long myelinated fibers in peripheral pathways, characterized by axonal atrophy and demyelination [8,14].

With respect to the prevalence of CIPN, Seretny et al performed a meta-analysis that included 31 studies with 4,179 patients and reported that 48% of patients developed this adverse effect; the frequency was 68.1% in the first month after the completion of chemotherapy and 30% after six months or more, showing some differences depending on medication used, dosage, and route of administration [15]. Most of these patients received platinum derivatives, and nearly all the included studies were prospective in nature (following a single cohort or randomized clinical trials) and were conducted in latitudes other than Latin America, with different populations and socioeconomic levels. The objective of the present study was to determine the prevalence of CIPN in a Colombian population with cancer undergoing chemotherapeutic management between 2015 and 2016.

Patients and methods

A cross-sectional retrospective study was performed on all patients of any age and gender who initiated cycles of pharmacological therapy for any cancer between January 1, 2015 and December 31, 2016, with the medications paclitaxel, docetaxel, bortezomib, oxaliplatin, and ixabepilone, in one of the four clinical centers of Oncólogos del Occidente in the cities of Manizales, Pereira, Armenia, and Cartago, in Colombia. Patients were excluded who, prior to initiation of therapy, showed any symptoms that may be associated with CIPN, such as paresthesia, dysesthesia, myalgia, or a sensation of weakness.

All the patients in this study were initially evaluated by a chemo-pharmacist who asked about the presence of symptoms of neuropathy prior to chemotherapy. Subsequent evaluations were made by chemo-pharmacist and an oncologist. The research team reviewed all the clinical records and adverse events reports prior to beginning chemotherapy, in the second cycle and the following cycles until the end of the treatment. Patients who reported paresthesia, dysesthesia, sensation of weakness and other symptoms related to neuropathy were considered as having chemotherapy-induced peripheral neuropathy only if there was a temporal association between the administration of the drug and the occurrence of the symptoms and worsening or new occurrence of the symptoms in the following cycle of chemotherapy.

The following variables of interest for the study were collected from the patients' medical records:

- *Sociodemographics:* age, sex, area of residence (urban, rural), and city of treatment.
- *Clinical/pharmacological:* type of cancer diagnosis, TNM stage, and prescribed chemotherapy medication.
- *Neurotoxicity:* development of CIPN symptoms, including paresthesia, dysesthesia, myalgia, or sensation of weakness reported by the doctor or chemo-pharmacist in the controls and therapeutic follow-ups.

This study is considered to be in the no-risk research category, per law No. 8430 of 1993 of the Health Ministry of Colombia; confidentiality principles established by the Declaration of Helsinki were respected, and endorsement was obtained from the clinical institution to access the data.

To analyze the data obtained, a database was created in software R, duplicate patients were excluded, and the data for unique patients were established. Data analysis was performed in Stata v. 14; descriptive analyses were developed with measures of central tendency and dispersion for continuous variables and frequencies and proportions for the categorical data. The prevalence of CIPN was established by medication and the gender of patients.

Results

These drugs were dispensed in 11,280 doses, for a total of 1,596 patients, of whom 45 were excluded due to having symptoms that may have been associated with neuropathy prior to beginning chemotherapy. Finally, a total of 1,551 patients among the four cities included in the study were selected. There was a predominance of females, with 1,094 patients (70.5%) with an average age of 57.0 ± 13.0 years; the greatest number of patients was found in the city of Manizales (n = 511; 33.0%), followed by Pereira (n = 506; 32.6%), Armenia (n = 434; 28.0%), and Cartago (n = 100; 6.4%), with 95.6% of these patients coming from urban areas.

The primary diagnoses found in this population were tumors of the breast (n = 521; 33.6%), colon (n = 172; 11.1%), stomach (n = 120; 7.7%), ovary (n = 80; 5.2%), multiple myeloma (n = 77; 5.0%), rectum

Table. Frequency of presentation of peripheral neuropathy induced by chemotherapy according to medication and sex of the patient.

	Number of patients	Chemotherapy-induced peripheral neuropathy	Sex	Percentage by sex	Chemotherapy-induced peripheral neuropathy by sex
Paclitaxel	788 (50.8%)	48.9%	Female	85.9%	52%
			Male	14.1%	30.6%
Oxaliplatin	398 (18.1%)	54.5%	Female	50.2%	56%
			Male	49.8%	53%
Docetaxel	281 (18.1%)	50.5%	Female	61.5%	48.5%
			Male	38.5%	36.1%
Bortezomib	99 (6.4%)	43.7%	Female	49.4%	65.3%
			Male	50.6%	36%
Ixabepilone	21 (1.3%)	95.2%	Female	100%	95.2%
			Male	0%	0%

(*n* = 66, 4.2%), cervix (*n* = 54; 3.5%), lung (*n* = 36; 3.5%), prostate (*n* = 27; 1.7%), and endometrium (*n* = 23; 1.5%); the remaining 24.2% of cases was distributed among other types of neoplasms. At the initiation of therapy, 279 (18.0%) patients had stage IV cancer, and 265 patients were not categorized due to having hematological or unclassifiable neoplasms.

For the therapies used to treat the neoplasms included in the study, paclitaxel was the most commonly prescribed (*n* = 788; 50.8%), followed by oxaliplatin (*n* = 398; 25.6%), docetaxel (*n* = 281; 18.1%), bortezomib (*n* = 99; 6.4%), and ixabepilone (*n* = 21; 1.3%).

Regarding the symptomatology of neuropathy, a general prevalence of 49.9% was found in the patients managed with these drugs. Table shows the data on the prevalence of neuropathies by medication and gender. Finally, it was found that 33 patients were treated with two of these medications simultaneously, which raised the prevalence of CIPN to 60.6%.

Discussion

The studied chemotherapeutic medications are an important therapeutic resource in the management of various types of cancer and impact the morbidity and mortality of these diseases. At the same time, as seen in this study, the prevalence of CIPN is high in the Colombian cancer patient population, which clearly affects their quality of life as well as the treatment possibilities if these patients require more aggressive therapies [10].

In this study of real-world prevalence with data obtained from reports of adverse reactions in medical records, it was found that approximately half of all patients developed CIPN during the course of their anti-cancer therapy. These results are similar to those of multiple prospective studies included in a meta-analysis by Seretny et al [15].

The predominance of females undergoing therapy with these drugs in addition to their development of CIPN is notable, and this finding may be explained by the high frequency of patients with breast and ovarian cancer who require these medications. Oxaliplatin was the only medication for which similar proportions of CIPN were seen with respect to gender. This medication was prescribed for the management of gastrointestinal neoplasms, such as colon, rectal, and stomach tumors, and a similar proportion of CIPN was reported for both genders in other studies [11].

Nearly all patients treated with ixabepilone, an antineoplastic drug approved for localized, refractory metastatic, or resistant breast cancer, developed CIPN. This side effect limited the dose that could be used or ultimately required suspension of therapy, which affects the survival and management possibilities of patients with these advanced neoplasms [16]. In contrast, the medication with the lowest prevalence of CIPN was bortezomib, which is used for multiple myeloma and some lymphomas. In this case, the prevalence found is similar to that reported in a clinical trial performed by Dimopoulos et al (46.7% vs 43.7% in the present study), which also reported similar outcomes by gender [17]; in contrast, in the present study, CIPN prevalence in women versus men receiving this medication was nearly double.

The principal limitation of this study is the potential bias of information validating the presence of CIPN, which was determined based on reports of related symptomatology instead of on the application of standardized, validated scales or the Common Terminology Criteria for Adverse Events (NCI-CTCAE) because these are not routinely used in evaluating these patients. It is also possible that the incidence of CIPN may have been underestimated, given that patients do not report symptomatology in all cases, especially if not specifically questioned about it; health care providers do not

always initiate these conversations, as it is not part of standard routine during control visits. Still, the large sample of patients and the complete reports of adverse reactions experienced during the monitoring of therapies provide information of great interest, particularly as it applies to a population about which there have been no prior reports.

It can be concluded that CIPN is a frequent adverse reaction to daily cancer therapy in Colombian patients managed with paclitaxel, oxaliplatin, docetaxel, bortezomib, and ixabepilone. Hence, it is necessary to establish more successful diagnostic methods and incorporate validated scales in the routine evaluation of all patients receiving these medications in our environment, such that early diagnosis and intervention planning can positively impact the quality of life of these patients. The only path to begin this process involves designing studies that investigate the mechanisms of action of these medications at the cellular and molecular levels and to derive clinical trials from this information to evaluate the effectiveness of possible strategies to prevent or intervene in CIPN, using multidisciplinary teams who consider this problem a priority.

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Prevalencia de neuropatía periférica asociada a quimioterapia en cuatro centros oncológicos de Colombia

Introducción. La neuropatía periférica inducida por quimioterapia es una reacción común a una variedad de medicamentos usados en el tratamiento del cáncer, que consiste principalmente en síntomas sensitivos, con componentes motores y cambios autonómicos. La prevalencia es del 30-68% después de terminar la quimioterapia en países no latinoamericanos.

Objetivo. Determinar la prevalencia de la neuropatía periférica inducida por quimioterapia en la población colombiana.

Pacientes y métodos. Estudio retrospectivo con evidencia del mundo real en la totalidad de pacientes atendidos en cuatro centros oncológicos de Colombia, quienes recibieron terapia farmacológica para algún tipo de cáncer entre enero de 2015 y diciembre de 2016 con taxanos (paclitaxel, docetaxel), agentes alquilantes (oxaliplatino), inhibidores de proteasoma (bortezomib) y análogos de epotilona B (ixabepilona).

Resultados. Se siguió a un total de 1.551 pacientes en cuatro ciudades a quienes se les aplicaron 11.280 dosis, con predominio femenino (*n* = 1.094; 70,5%) y una edad media de 57 ± 13 años. El paclitaxel fue el fármaco más prescrito (*n* = 788; 50,8%). La neuropatía inducida por quimioterapia se presentó en el 48,9% de los pacientes con paclitaxel, el 58,5% de

los pacientes con oxaliplatino, el 50,5% de los pacientes con docetaxel, el 43,7% de los pacientes con bortezomib y el 95,2% de los pacientes con ixabepilona. Se trató a 33 pacientes con dos de estos medicamentos simultáneamente.

Conclusiones. La neuropatía periférica inducida por quimioterapia es una reacción adversa frecuente en pacientes con cáncer en Colombia tratados con taxanos, alquilantes, inhibidores de proteasoma e ixabepilona. Es necesario establecer métodos diagnósticos efectivos e incorporar escalas validadas en la evaluación rutinaria de los pacientes que reciben estas medicaciones.

Palabras clave. Agentes antineoplásicos. Docetaxel. Farmacoepidemiología. Oxaliplatino. Paclitaxel.