https://doi.org/10.31925/farmacia.2019.3.14 **ORIGINAL ARTICLE**

INCIDENCE OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN CANCER PATIENTS IN CLINICAL PRACTICE

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is major neurologic toxic event, with a negative impact on patient's quality of life (QoL), and frequently requires dose modification or treatment discontinuation. The prevalence of CIPN is expecting to increase as cancer survival continue to improve. The study was conducted on 163 eligible patients with neurotoxic chemotherapy, from the Oncology Department of Clinical Emergency Hospital of Constanța, Romania between January 2017 and June 2018. Patients received a taxane - paclitaxel or docetaxel, platinum-based agents - cisplatin, carboplatin or oxaliplatin, either as single agent or combination. The incidence of CIPN was 68.09%. The highest incidence of CIPN was associated with paclitaxel (73.14%), and with oxaliplatin (72.22%), followed by cisplatin (30%), and with docetaxel (23.07%). Cumulative dose, regimen schedule, and treatment duration are important risk factors for the development of chemotherapy-induced peripheral neuropathy. Advanced age does not seem to be a significant risk factor of CIPN in our analysis in patients without significant comorbidity.

Rezumat

Neuropatia periferică indusă de chimioterapie (CIPN) are un impact negativ major asupra calității vieții pacientului (QoL) și necesită frecvent modificarea dozelor sau întreruperea tratamentului citostatic. În plus se așteaptă ca prevalența CIPN să crească, pe măsură ce rata de supraviețuire crește. Studiul nostru a fost realizat în cadrul Clinicii de Oncologie a Spitalului Clinic Județean de Urgență Constanța, România și a inclus pacienții tratați cu citostatice cu potențial neurotoxic în intervalul ianuarie 2017 - iunie 2018; 163 de pacienți au fost eligibili pentru studiul nostru. Pacienții au primit un taxan - paclitaxel sau docetaxel, agenți pe bază de platină - cisplatin, carboplatin sau oxaliplatin, în monochimioterapie sau în combinație. Incidența cea mai mare a neuropatiei periferice induse de chimioterapie a fost asociată cu paclitaxel (73,14%), și cu oxaliplatin (72,22%), urmată de cisplatin (30%) și docetaxel (23,07%). Doza cumulativă, protocolul terapeutic și durata tratamentului reprezintă factori de risc importanți în apariția neuropatiei periferice induse de chimioterapie. Vârsta, în cadrul studiului efectuat, nu a reprezentat un factor de risc suplimentar în absența asocierii cu alte comorbidități.

Keywords: chemotherapy-induced neuropathy, cancer, quality of life, taxanes, platinum-based agents

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a major neurologic toxicity of many chemotherapeutic agents, has a negative impact on patient's quality of life (QoL) and frequently requires dose modification or treatment discontinuation. The incidence of CIPN ranges between 30% and 55% in patients receiving neurotoxic drugs, and approximately 68% of patients develop CIPN in the first month of treatment [1-3]. The prevalence of CIPN is expecting to increase as cancer survival continue to improve. Six main groups of chemotherapeutic drugs can cause peripheral sensory and motor neuropathy: platinum-based antineoplastic agents, in particular cisplatin and oxaliplatin, taxanes - paclitaxel and docetaxel, *Vinca* alkaloids, in particular, vincristine and vinblastine, proteasome inhibitors - bortezomib, and immunomodulatory agents - thalidomide.

On the other hand, even if the mechanism of action of these drugs is different, the physiopathology of CIPN have common features. Diagnosis of CIPN is a clinical one, and the most common scale used for grading CIPN are NCI-CTCAE (National Cancer Institute - Common Terminology Criteria for Adverse Events), TNS (Total Neuropathy Score), and PNQ (Patients Neurotoxicity Questionnaire) [4]. CIPN it is predominant sensory peripheral neuropathy and has a "stoking and glove" distribution [5-9].

Risk factor influencing the development of CIPN include the type of chemotherapeutic agent used,

treatment schedule, the combination of drugs, age, pre-existing diabetes, vitamin B12 deficiency, renal and hepatic diseases [10-13].

Materials and Methods

This retrospective observational study was conducted in Oncology Department of Clinical Emergency Hospital of Constanța, Romania and reviewed 163 patients who received chemotherapy regimens containing taxanes and platinum-based agents, between 01 January 2017 and 01 June 2018. Patients characteristics were obtained from medical records. Main including criteria was oncologic disease under potential neurotoxic chemo-therapy, and main excluding criteria was oncologic disease under chemotherapy without potential neurotoxic chemotherapy. All patients signed informed consent prior to chemotherapy.

We noted the demographic data (age, gender, body mass index and provenience), type of cancer, comorbidities, the type of drug used, the duration of treatment, median cumulative dose, and if chemotherapy-induced peripheral neuropathy was diagnosed, we also noted the grading of CIPN.

Grading of CIPN was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All chemotherapeutic agents analysed in this study have mechanisms of action responsible for sensory neuropathy. Statistical analyses was performed using the Statistical Package for the Social Sciences version 20.0 software (SPSS).

Results and Discussion

163 patients were included in this study, 75 males and 88 females. The median age of the study population was 58.3 ± 15.63 years. Patients general characteristics are described in Table I. When evaluating the patients according with age (over 60 years old and under 60 years old), we did not find a difference in the incidence of CIPN between these two groups; 44.8% in patients under 60 years old, and 45.7% in older patients developed CIPN. Regarding the type of cancer, most of the patients included are patients with lung cancer, followed by breast cancer and colon cancer.

98 patients had comorbidities - 22.08% had arterial hypertension, 20.24% diabetes, 12.88% osteoarthritis, 3.68% hepatic disorders, and 1.22% renal disease. No comorbidity was statistically significantly associated with a higher risk of CIPN in our study (Table I).

Table I

Clinical characteristics of patients with/without CIPN

Characteristics	CIPN (-) (n = 52)	CIPN (+) (n = 111)
Age	57.36 ± 13.21	60.8 ± 12.68
Sex		
Male	23	52
Female	29	59
Type of Cancer		
Lung	28 (53.84%)	46 (41.44%)
Breast	8 (15.84%)	28 (25.22%)
Colon	9 (17.3%)	23 (20.72%)
Ovarian	3 (5.76%)	7 (6.30%)
Pancreas	1 (1.92%)	3 (2.70%)
Gastric	2 (3.84%)	2 (1.80%)
Prostate	1 (1.92%)	2 (1.80%)
Comorbidities		
Arterial hypertension	9 (17.3%)	27 (24.32%), p = 0.4182
Diabetes	13 (25.0%)	20 (18.01%), p = 0.3041
Hepatic disease	1 (1.92%)	5 (4.50%), p = 0.6654
Renal disease	0	2 (1.80%)
Osteoarthritis	8 (15.84%)	13 (11.71%), p = 0.6166
Alcohol	2 (3.84%)	5 (4.50%), p = 1.0000
Chemotherapy regimen		
Platinum and fluoropyrimidines	14 (26.92%)	26 (23.42%)
Taxane only	9 (17.3%)	30 (27.02%)
Combination chemotherapy	29 (55.76%)	55 (49.54%)

The general incidence of CIPN was 68.09% (111 patients).

Patients received taxane-containing regimens (paclitaxel, docetaxel) or platinum-based regimens (cisplatin, carboplatin, oxaliplatin). from the total number of patients, 39 received only taxanes, 40 patients received combinations of platinum and fluoro-pyrimidines, and 84 patients received combination regimens of taxane and platinum.

Combination chemotherapy of taxane and platinum agents in this study were combination of Paclitaxel and Carboplatin used in most of the patients with

lung and ovarian cancer and in patients with gastric cancer that received combination of oxaliplatin and docetaxel.

The highest incidence of CIPN was associated with paclitaxel (73.14%), and with oxaliplatin (72.22%), followed by cisplatin (30%), and with docetaxel (23.07%) (Table II). Carboplatin is less neurotoxic comparing with cisplatin or oxaliplatin, 4 - 6% of patients receiving carboplatin may develop neuropathy. In this study all patients receiving carboplatin received this agent in combination with taxane. No clinical significant difference was found in our study regarding the patients receiving single agent regimen or combination of chemotherapeutic drugs, regarding the severity of CIPN.

Table II

The incidence of CIPN among chemotherapeutic drugs

Drug	Patients	CIPN (%)
Paclitaxel	108	79 patients (73.14%)
Docetaxel	13	3 patients (23.07%)
Cisplatin	10	3 patients (30%)
Oxaliplatin	36	26 patients (72.22%)

Classification of CIPN was done according to CTCAE 4.03, and most of the patients reported grade I or II CIPN (Table III).

Table III

The Common Terminology Criteria for Adverse Events (CTCAE)- version 4.03 – Nervous system disorders [14]

Adverse Event	1	2	3	4	5
The peripheral motor neuropathy	Asymptomatic; clinical/diagnostic observations only; the intervention is not indicated yet.	Moderate symptoms; limiting the instrumental ADL.	Severe symptoms; limiting self-care ADL; the assistive device is indicated.	Life-threatening consequences; urgent intervention is indicated.	Death
Definition: A disorder characterized by the process of inflammation or degeneration of the peripheral motor nerves					
Peripheral sensory neuropathy	Asymptomatic; the presence of deep tendon reflexes or paresthesia loss	Moderate symptoms; the instrumental ADL is limited	Severe symptoms; limiting self-care ADL	Life-threatening consequences; indicate the urgent intervention	Death
Definition: The disorder is characterized by inflammation or degeneration process of the peripheral sensory nerves					

Activities of Daily Living (ADL). *The Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money. ** Self-care ADL refers to bathing, dressing/undressing, feeding self, using the toilet, taking medications, and not bedridden.

The incidence of grade III peripheral neuropathy was high in patients receiving paclitaxel (6 patients) and oxaliplatin (4 patients), and we found no cases of grade III neuropathy for patients that received docetaxel or cisplatin regimens (Table IV).

Table IV

Correlation of chemotherapeutic agents and CIPN grading

Drug	Grade I	Grade II	Grade III
Paclitaxel	47	26	6
Oxaliplatin	13	9	4
Docetaxel	1	2	0
Cisplatin	7	3	0

When evaluating the patients according to median cumulative dose, we observed that for paclitaxel a median cumulative dose of 550 mg/m^2 was associated with a higher incidence of CIPN (Table V). Regarding the frequency of administration, a higher incidence and a more severe CIPN was found in patients receiving Paclitaxel every 3 weeks (doses of 75 mg/m^2), compared with those receiving Paclitaxel weekly (doses of 45 - 80, 65.95% *vs* 34.05% for grade I CIPN, 76.92% *vs* 23.08% for grade II CIPN, and 100% for grade III CIPN ($p = 0.01$), and also a higher number of cycles of chemo-therapy was associated with an increased risk for developing CIPN. Patients receiving more than 4 cycles of paclitaxel had a higher incidence of CIPN.

For cisplatin, patients received regimens containing cisplatin in dose ranging from 75 mg/m^2 to 100 mg/m^2 , a median cumulative dose of 380 mg/m^2 and a higher number of cycles, in medium after 3 - 4, cycles was associated with a higher incidence of CIPN (Table V).

For docetaxel, patients received chemotherapeutic regimens containing doses from 75 mg/m^2 to 100 mg/m^2, a higher number of cycles and a median dose of 385 mg/m^2 was associated with a higher grade of CIPN (Table V).

Table V

The median cumulative dose of chemotherapeutic agents associated with a higher risk of CIPN

Drug	Median cumulative dose
Paclitaxel	550 mg/m^2
Docetaxel	385 mg/m^2
Cisplatin	380 mg/m^2
Oxaliplatin	565 mg/m^2

For oxaliplatin the development and grade of CIPN appear to be influenced by the cumulative dose, time of infusion, treatment duration and pre-existing neuropathy. In our study, no patients had pre-existing neuropathy. Patients received oxaliplatin with doses ranging from 85 mg/m^2 every 2 weeks to 130 mg/m^2

every 3 weeks, depending on the treatment regimen used. Median cumulative dose was 565 mg/m^2. Acute neurotoxicity was observed in some patients after first administration of oxaliplatin and duration of the effect was for 3 - 4 days after chemotherapy. Chronic neurotoxicity was observed after 4 - 5 cycles of chemotherapy.

CIPN it is one of the most frequent adverse events of chemotherapy, with a negative impact on patient's QoL and survival, frequently associated with dose reduction or discontinuation of chemotherapy [15].

Advanced age does not seem to be a significant risk factor of CIPN for any of the drugs included in our analysis in patients without significant comorbidity [16].

In our study, the incidence of CIPN was 68.09% similar to other studies, for example, a meta-analysis conducted by Serenity *et al*. in 2014 reported an incidence of 68% [2].

Most patients (70.27%) presented grade I CIPN, 36.03% grade II, and only 10 patients (9.0%) developed grade III CIPN.

Paclitaxel was found to be more neurotoxic than docetaxel, in our study 73.14% of patients receiving paclitaxel *versus* 23.07% of patients receiving docetaxel, developed CIPN. The incidence in this study is higher than that reported in the literature, 60% for paclitaxel and 15% for docetaxel [12, 17]. We also we found that grade III CIPN is more common for paclitaxel comparing with docetaxel [18]. Similar to other studies, our analysis showed that weekly paclitaxel regimen is associated with a decreased risk of developing CIPN [19, 20].

docetaxel-related CIPN is usually mild and not so frequent, in our study 13.92% of patients had grade I CIPN, and there were no cases of grade III CIPN. These data are similar with those reported in the literature, approximately 10% of patients are developing docetaxel-related neuropathy, and 0.4% of patients developed grade III CIPN [21]. Median cumulative dose-related to the development of CIPN was 358 mg/m^2, similar to data from literature [22].

In our study the incidence of cisplatin-related CIPN was 30%, comparing to other studies that reported an incidence ranging between 30% and 100% [23]. For cisplatin a median cumulative dose of 380 mg/m^2, and a higher number of cycles was associated with a higher incidence of CIPN, and these data are comparable with those from other studies that reported a cumulative dose of 300 - 400 mg/m^2 [17].

Oxaliplatin-related CIPN is frequent, it can appear in 60 - 75% of patients, and has two clinical forms of manifestation, acute and chronic. In the acute form, CIPN emerges rapidly, may reappear in subsequent infusions, and requires prolongation of infusion duration or even discontinuation of treatment. The chronic form that follows the acute form is a progressive neuropathy induced by the morphologic and functional modifications in the dorsal root ganglion cells secondary to local accumulation of oxaliplatin [24-27]. In our study, the incidence of oxaliplatin-related neuropathy was 72.22%. Median cumulative dose for development of oxaliplatin-induced peripheral neuropathy was 565 mg/m^2. Pre-existing neuropathy and time of infusion are other important risk factors for the development of oxaliplatin-related neuropathy [28].

Conclusions

CIPN is one of the most frequent and severe adverse events of chemotherapy, affecting more than half of the patients receiving neurotoxic chemotherapy, with a significant negative impact on QoL of the patients, due to the persistence of symptoms for long periods that are very difficult to estimate.

It is essential to grade the severity of CIPN correctly and to estimate the long-term effects. Other important factor is to determine if there are biomarkers that will permit the identification of patients at risk for development of CIPN.

Conflict of interests

The authors report no conflict of interest in this work.

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