RESEARCH ARTICLE

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Chemotherapy-Induced Peripheral Neuropathy in Egyptian Patients: Single Institution Retrospective Analysis

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a major toxicity that requires treatment modification or cessation and worsens patients' quality of life. Its incidence is 30–40%. Occurrence and severity depend on treatment- and patient-related factors. The symptoms are self-limiting with recovery rate about 50%. **Methods:** This retrospective analysis took place in our chemotherapy unit. We included patients treated between January 2014 and December 2015. **Results:** 250 patients were eligible. 53 received paclitaxel, 78 received docetaxel, 64 received cisplatin and 55 received oxaliplatin. Mean age was 50.11 years. Frequency of CIPN was 46.8% (Grade I 70.9%, GII 24.7%, GIII 4.4%). It was 74% with oxaliplatin, 73.5% with paclitaxel, 35.9% with cisplatin and 17.9% with docetaxel. After median of 6 months 24% of patients recovered completely. No significant correlation between occurrence of CIPN and age ($p = 0.781$), while was significant with cisplatin ($p = 0.043$). Diabetic patients had higher incidence ($p = 0.007$). With cisplatin, median cumulative dose of 450 mg/m^2 and ≥ 6 cycles had higher incidence of CIPN (p 0.006 and 0.010; respectively). With oxaliplatin, none was correlated with CIPN frequence. With paclitaxel, CIPN was more frequent if ≥ 4 cycles were received ($p = 0.005$). With docetaxel, > 4 cycles or cumulative dose ≥ 360 mg/m^2 had higher occurrence of GII CIPN ($p < 0.001$ for both). **Conclusion:** CIPN is common problem that affects patients' quality of life and leads to treatment interruption. There are many factors affecting its incidence and severity.

Keywords: CIPN- Neuropathy- Egypt

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a type of neuropathic pain that is a major disabling side effect of several commonly used chemotherapeutic agents. Its development may require chemotherapy dose reduction or cessation, which may increase cancer-related morbidity and mortality (Gutierrez-Gutierrez et al., 2010).

It is predominantly sensory, but may also occur as a motor dysfunction and occasionally it can be accompanied by dysfunction of the autonomic nervous system. Typically, it presents in patients with a "glove and stock" distribution (Boland et al., 2017).

The influencing factors to develop CIPN include: type of chemotherapy, treatment schedule, combinations of different neurotoxic agents, patients' characteristics (age, pre-existing causes of peripheral neuropathy as diabetes mellitus, Renal or hepatic dysfunction and vitamin B12 deficiency (Balayssac et al., 2011).

It is generally estimated that 30-40% of all patients treated with chemotherapeutic agents develop peripheral neurotoxicity (Wolf et al., 2008). However; incidences of up to 60% have been reported with cisplatin, paclitaxel, docetaxel and oxaliplatin (Velasco and Bruna, 2010).

It is assumed that platinum compounds, which bind irreversibly to the DNA, induce apoptosis of sensory neurons, (Von Schilippe et al., 2001), while anti-tubulins (as paclitaxel and docetaxel) bind to microtubules, interrupt axonal transport, target the sensory cell bodies and nerve axons, to induce neuronal cell death (Bennett, 2010).

The persistent cumulative injury caused by antineoplastic agents mostly affect sensory nerve cell bodies in the Dorsal root ganglia (mostly occurs with cisplatin) and/or the afferent and efferent axons of the peripheral nervous system (e.g., paclitaxel, oxaliplatin) (Quasthoff and Hartung, 2002).

The diagnosis of CIPN is mainly clinical. The most commonly used scale of CIPN grading is NCI-CTCAE (Common Terminology Criteria for Adverse Events). Other grading scales used in clinical practice are the WHO, Eastern Cooperative Oncology Group (ECOG) scales and the oxaliplatin grading scale of Levi, Patient Neurotoxicity Questionnaire (PNQ) and The Total Neuropathy Score (TNS) (Griffith et al., 2014).

Until now, there is no well-known effective preventive

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agent or treatment of established chronic neurotoxicity (Rao et al., 2007).

Materials and Methods

Patients and methods

This is a retrospective study that was conducted at the Department of Clinical Oncology, Ain Shams University.

After obtaining the approval of the ethical committee of Faculty of Medicine, Ain Shams University, we retrospectively collected the data of 250 patients who received regimens containing paclitaxel (53 patients), docetaxel (78 patients), oxaliplatin (55 patients) or cisplatin (64 patients) in the period from January 2014 to December 2015.

Data collection

Two hundred and fifty patients were included in this analysis. Their medical data were extracted from the medical records. These data included, patients' characteristics (Age, pre-existing causes of neuropathy as Diabetes Mellitus, Hepatic and Renal diseases), drug-related factors (type of chemotherapeutic agent, total number of cycles received, treatment schedule, cumulative dose). The incidence and grading of CIPN was done according to the NCI-CTCAE (Common Terminology Criteria for Adverse Events) v4.03. Recovery of CIPN symptoms in a median follow-up period of 6 months was recorded.

All statistical analyses were carried out using Statistical package for Social Science (SPSS V 20.0 for windows; SPSS Inc, Chicago, IL, 2001). The results obtained were interpreted and descriptive statistics (mean, median, standard deviation, range and percentages) were applied whenever feasible. The chi-square test and one way ANOVA test were used for interpretation of qualitative data. P-value of 0.05 or less was taken as significant value and < 0.01 as highly significant, whereas p -value > 0.05 was taken as non-significant.

Results

Patients' characteristics

From the 250 patients included in the analysis, 53 (21.2%) received paclitaxel-containing regimen, 78 (31.2%) received docetaxel-containing regimens, 55 (22%) received oxaliplatin-containing regimen and 64 (25.6%) received cisplatin-containing regimens (Table 1).

The mean age of the population was 50.11 years (SD ± 11.54). 66 patients had co-morbidities; 54 patients (21.6%) had diabetes-mellitus (DM), 10 (4%) had hepatic dysfunction and 2 patients (0.8%) had renal impairment.

The frequency of CIPN was 46.8%; most of them (83 patients, 33%) were grade I.

The Frequency of neuropathy was 35.9% with cisplatin, 74% with oxaliplatin, 73.5% with paclitaxel and 17.9% with docetaxel (Table 1).

The rate of grade III or higher neuropathy was reported in 3.6% and 5% of patients with oxaliplatin and paclitaxel respectively, versus 1.3% with docetaxel and none with cisplatin.

Table 1. Incidence of Chemotherapy-Induced Peripheral Neuropathy among Different Chemotherapeutics

Drug	Total	Frequency of CIPN (%)
Cisplatin	64	35.90%
Oxaliplatin	55	74%
Paclitaxel	53	73.50%
Docetaxel	78	17.90%
Total	250	46.80%

Table 2. Influence of Presence of DM on Chemotherapy-Induced Peripheral Neuropathy

Diabetes Mellitus (DM)	Frequency of CIPN of any grade		p-value
	No.	%	0.007
Diabetic	34	63%	
Non-diabetic	83	42.30%	

Table 3. Correlation of Cisplatin Administration and Chemotherapy-Induced Peripheral Neuropathy

Cisplatin		No CIPN	CIPN of any grade	P-value
Cumulative dose	Median (IQR)	240 (180 – 280)	450 (225 – 480)	0.006
	Range	100 – 480	100 – 480	
No of cycles	Median (IQR)	3 (3 – 4)	6 (3 – 6)	0.01
	Range	2 – 7	2 – 6	

IQR, Interquartile range.

Table 4. Correlation of Cisplatin Parameters and Grade of Chemotherapy-Induced Peripheral Neuropathy

Cisplatin		Grade 1 neuropathy	Grade 2 neuropathy	P-value
Cumulative dose	Median (IQR)	360 (225 – 480)	480 (450 – 480)	0.008
	Range	100 – 480	450 – 480	
no of cycles	Median (IQR)	4 (3 – 6)	6 (6 – 6)	0.01
	Range	2 – 6	6 – 6	

IQR, Interquartile range

Table 5. Correlation of Paclitaxel Administration and Chemotherapy-Induced Peripheral Neuropathy

Paclitaxel		No CIPN	CIPN of any grade	P-value
Frequency (weeks)	1	8 (57.1%)	15 (46.2%)	0.832
	3	6 (42.9%)	24 (53.8%)	
Cumulative dose	Median (IQR)	320 (240 – 525)	480 (240 – 1050)	0.074
	Range	160 – 1400	240 – 1400	
Total no of cycles	Median (IQR)	3 (3 – 3)	4 (3 – 6)	0.005
	Range	2 – 8	3 – 8	

IQR, Interquartile range

Table 6. Correlation of Paclitaxel and Grades of Chemotherapy-Induced Peripheral Neuropathy

Paclitaxel		Grade 1	Grade 2	Grade 3	P-value
Frequency (weeks)	1	13 (31.14%)	2 (11.11%)	0 (0.0%)	0.008
	3	17 (67.86%)	5 (88.89%)	2 (100.0%)	
Cumulative dose	Median (IQR)	502.5 (270 – 1050)	480 (240 – 1200)	685 (320 – 1050)	0.338
	Range	240 – 1400	240 – 1400	320 – 1050	
Total no of cycles	Median (IQR)	4 (3 – 6)	3 (3 – 6)	5 (4 – 6)	0.04
	Range	3 – 8	3 – 8	4 – 6	

IQR, Interquartile range.

Table 7. Correlation of Docetaxel and Grade of Chemotherapy-Induced Peripheral Neuropathy

Docetaxel		Grade 1	Grade 2	P-value
Cumulative dose	Median (IQR)	320 (225 – 700)	360 (1300 – 225)	<0.0001
	Range	225 – 1400	225 – 1400	
Total no of cycles	Median (IQR)	3 (3 – 6)	4.5 (3 – 7)	<0.0001
	Range	3 – 8	3 – 8	

IQR, Interquartile range.

After a median follow-up period of 6 months, 24% of patients who developed CIPN recovered completely and 76% suffered from persistent CIPN.

Factors affecting incidence of CIPN

We stratified patients below and above 60 years and there was no difference in the incidence of CIPN in both groups; 46.6% in ≤60 years versus 48.8% for patients > 60 years (p = 0.781).

The only significant difference was found with cisplatin; where grade II or higher CIPN was more frequent among old patients (>60 years) (p = 0.043).

Considering patients' associated co-morbidities, the development of CIPN was higher in diabetic patients (p = 0.007) while presence of DM was not associated with higher grade of CIPN (p = 0.064) (Table 2).

Sub-groups analysis

With cisplatin, a median cumulative dose of cisplatin 450 mg/m^2 was associated with higher rate of CIPN (p = 0.006). Also patients received cisplatin for 6 or more cycles had higher risk to develop CIPN (p = 0.010), while the frequency of cycles (weekly or Q3W) and average dose per cycle did not affect the rate of CIPN (Table 3).

Also, it was found that receiving 480mg/m^2 or more than 6 cycles of cisplatin increased grade II or higher CIPN; p values 0.008 and 0.010 respectively (Table 4).

With Oxaliplatin, there was no factor affecting the occurrence or grade of CIPN. Oxaliplatin-induced toxicity appeared in about 74% of the patients including both acute and cumulative toxicities and 29% of them developed grade II-III neuropathy with mean cumulative dose of 850 mg/m^2.

With paclitaxel, the only factor that significantly increased frequency of CIPN was the total number of cycles; 4 cycles or more increased CIPN occurrence (p = 0.005) and cumulative dose of 480 mg/m^2 had a trend to increase frequency of CIPN (p = 0.074) (Table 5).

Also, higher grades of CIPN (grade III-IV) was more frequent with every 3 weeks cycle compared to dose dense protocol (p = 0.008) and with 5 cycles or more (p = 0.04) (Table 6).

With docetaxel, no single factor increased the frequency of CIPN.

While, cumulative dose of 360 mg/m2 and 5 cycles or more of docetaxel were associated with grade II or higher CIPN with p values of <0.001 and <0.001 respectively (Table 7).

Discussion

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common complication of chemotherapy. The incidence of CIPN in our analysis reached 46.8%, where most of them (70%) were grade I, and only 4.4% developed grade III. This data was close to the data concluded in the meta-analysis of 31 studies of CIPN involving a total of 4,179 patients where the incidence of CIPN was 48% (Seretny et al., 2014).

Similarly in another study, about 30-40 % of patients treated with neurotoxic agents developed CIPN, with the highest incidence being reported with cisplatin, paclitaxel, docetaxel, vincristine, oxaliplatin and bortezomib (Velasco and Bruna, 2010).

The recovery of neuropathic symptoms after median period of 6 months was achieved in 24% of the patients in our analysis. However, in the meta-analysis recovery was 40% after 3 months of the last cycle of chemotherapy and 70% at 6 months or more this may be due to diversity of the population in the meta-analysis (Serenty et al., 2014).

Age (below and above 60 years) was found to be a non-significant risk factor for CIPN, exactly as that was found in a prospective study of 35 patients treated with paclitaxel or cisplatin-based regimens, where they were assessed for CIPN clinically and with electrophysiological tests (Argyriou et al., 2006).

There were not enough studies found for the relation between the presence of pre-existing causes of neuropathy or comorbidities related to peripheral neuropathy. However, our study revealed a significant correlation between the presence of DM and incidence of CIPN. About 63% of the patients who developed CIPN had positive history of diabetes (p=0.007). This is like the results of a study held in 2003, which showed significant worsening of a pre-existing neuropathy in patients who received non-toxic doses of neurotoxic agents including

paclitaxel, vincristine, cisplatin and thalidomide (Chaudhry et al., 2003).

The incidence of neuropathy with cisplatin varies between 30 % and 100 % (median 57 %) as described by Velasco and Bruna (2010), which supports our result where cisplatin-induced neurotoxicity reached about 35.9%.

The incidence and severity of cisplatin-induced neurotoxicity are mainly determined by the cumulative cisplatin dose. In our study, cumulative dose of 450 mg/m^2, reached after a median number of 6 cycles of cisplatin showed significantly higher incidence of CIPN (p=0.006). In other studies, patients developed cisplatin-induced neurotoxicity with cumulative dose of 300–400 mg/m^2 (Argyriou et al., 2011).

A significantly higher incidence of grade II neurotoxicity with cumulative dose of 480 mg/m2 and 6 cycles of cisplatin (p = 0.008 and p = 0.010 respectively), whereas none of the patients developed grade III toxicity. However, the results of other studies were somehow different, where the patients had grade III-IV neuropathy with cumulative cisplatin dose of 300–400 mg/m^2 (Valesco and Bruno, 2010; Argyriou et al., 2011).

Oxaliplatin induces both a reversible acute and partially irreversible cumulative neuropathy. Acute symptoms are very common, experienced by 60-90 % of the patients. Oxaliplatin also induces cumulative sensory neurotoxicity, which can be irreversible. Sensory neurotoxicity is generally seen in 10-15% of the patients after cumulative dose of 780–850 mg/m^2 and the risk of permanent neuropathy is significantly increasing at cumulative dose over 1,000 mg/m^2 (de Gramont et al., 2000). A similar result was obtained in our study where oxaliplatin-induced CIPN occurred in 74% of the patients including both acute and cumulative toxicities, and 29% of them developed grade II-III neuropathy with mean cumulative dose of 850 mg/m^2.

Cumulative neurotoxicity of oxaliplatin was observed in our study after median of 8 cycles. Similar results were obtained in other studies, where dose limiting neuropathy was observed in 20% of the patients after 6 cycles, in 38 % after 9 and in 63 % after 12 cycles (Valesco and Bruno, 2010; Mitchell et al., 2006; Pasetto et al., 2006; Kiernan, 2007).

Regarding paclitaxel-induced CIPN, the incidence reached 73.5%, which goes in line with the report of Kautio (2017), who reported neurotoxicity with paclitaxel in 70% of their study population.

A significantly higher incidence was found with a median of 4 cycles of paclitaxel (p = 0.005), also it was observed after cumulative dose of 1000-1400 mg and this is like the result of the study of Carlson and Ocean (Carlson and Ocean, 2011).

Neuropathy is less common with weekly paclitaxel regimen as described in many studies (Argyriou et al., 2011; Carlson and Ocean, 2011). Similar results were also noticed in our study, where the incidence of neurotoxicity was 46.2% and 53.8% in the weekly and every 3 weeks regimens respectively.

Also high grade CIPN (grade III) with paclitaxel was more frequent with every 3 weeks cycles (p=0.008) at a dose of 175 mg/m^2, and observed after 4-6 cycles. This result goes in line with that reported by Lee and Swain (2006), where severe neuropathy (WHO grade 3 or 4) was reported in the patients at a dose of 175 mg/m^2.

In monotherapy, Docetaxel-induced neurotoxicity is usually mild and transient, reaching about 10% with grade III toxicity about 0.4% (Baker at al., 2009). A slightly higher incidence was observed in our study, 17.9%, with grade III about 1%.

The mean cumulative dose to the onset of grade I-II CIPN with docetaxel was 371 mg/m^2 (Swain and Arezzo, 2008). Nearly a similar result regarding the cumulative dose was obtained in our study, where grade II neuropathy was significantly higher at mean cumulative dose of 360 mg/m2 reached after 4 cycles of docetaxel administered every 3 weeks.

In conclusion, peripheral neuropathy is the most common complication of chemotherapy, where the incidence of CIPN reached about half of the patients. The highest incidence was reported with oxaliplatin and Paclitaxel. Recovery of neuropathic symptoms in a median period of 6 months was achieved in quarter of the patients.

Disclosure

This study was conducted in the clinical oncology department, Ain Shams University and we did not receive any funding and all the authors declare no conflict of interest.

References

Argyriou AA, Polychronopoulos P, Koutras A, et al (2009). Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy?. *Support Care Cancer*, **14**, 223-9.

Argyriou AA, Bruna J, Marmiroli P, Cavaletti G (2011). Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. *Crit Rev Oncol Hematol*, **82**, 51-7.

Baker J, Ajani J, Scotté F, et al (2009). Docetaxel related side effects and their management. *Eur J Oncol Nurs*, **13**, 49-9.

Balayssac D, Ferrier J, Descoeur J, et al (2011). Chemotherapy-induced peripheral neuropathies: from clinical relevance to preclinical evidence. *Expert Opin Drug Saf*, **10**, 407-7.

Bennett GJ (2010). Pathophysiology and animal models of cancer-related painful peripheral neuropathy. *Oncologist*, **15**, 9-12.

Boland BA, Sherry V, Polomano RC (2017). Chemotherapy-induced peripheral neuropathy in cancer survivors. http://www.cancernetwork.com/oncology-nursing/chemotherapy-induced-peripheral-neuropathy-cancer-survivors. Accessed November 22, 2017.

Carlson K, Ocean AJ (2011). Peripheral neuropathy with microtubule-targeting agents: occurrence and management approach. *Clin Breast Cancer*, **11**, 73-1.

Chaudhry V, Chaudhry M, Crawford TO, Simmons-O'Brien E, Griffin JW (2003). Toxic neuropathy in patients with pre-existing neuropathy. *Neurology*, **60**, 337-0.

de Gramont A, Figer A, Seymour M, et al (2000). Leucovorin and fluorouracil with or without oxaliplatin as first line treatment in advanced colorectal cancer. *J Clin Oncol*, **18**, 2938-7.

Griffith KA, Dorsey SG, Renn CL, et al (2014). Correspondence

between neurophysiological and clinical measurements of chemotherapy-induced peripheral neuropathy: secondary analysis of data from the CI-PeriNoms study. *J Peripher Nerv Syst*, **19**, 127–5.
Gutiérrez-Gutiérrez G, Sereno M, Miralles A, Casado-Sáenz E, Gutiérrez-Rivas E (2010). Chemotherapy-induced peripheral neuropathy: clinical features, diagnosis, prevention and treatment strategies. *Clin Transl Oncol*, **12**, 81-1.
Kautio A-L (2017). Chemotherapy-induced neuropathy: prevention and treatment. Academic dissertation, Department of Oncology, Helsinki University Central Hospital, University of Helsinki, Finland. https://helda.helsinki.fi/bitstream/handle/10138/32955/chemothe.pdf?sequence=1 Accessed November 22, 2017.
Kiernan MC (2007). The pain with platinum: oxaliplatin and neuropathy. *Eur J Cancer*, **43**, 2631-3.
Lee JJ, Swain SM (2006). Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol*, **24**, 1633-2.
Mitchell PL, Goldstein D, Michael M, et al (2006). Addition of gabapentin to a modified FOLFOX regimen does not reduce oxaliplatin-induced neurotoxicity. *Clin Colorectal Cancer*, **6**, 146-1.
Pasetto LM, D'Andrea MR, Rossi E, Monfardini S (2006). Oxaliplatin-related neurotoxicity: how and why?. *Crit Rev Oncol Hematol*, **59**, 159-8.
Quasthoff S, Hartung HP (2002). Chemotherapy-induced peripheral neuropathy. *J Neurol*, **249**, 9-7.
Rao RD, Michalak JC, Sloan JA, et al (2007). Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer*, **110**, 2110-8.
Seretny M, Currie GL, Sena ES, et al (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*, **155**, 2461-0.
Swain SM, Arezzo JC (2008). Neuropathy associated with microtubule inhibitors: diagnosis, incidence and management. *Clin Adv Hematol Oncol*, **6**, 455-7.
Velasco R, Bruna J (2010). Chemotherapy-induced peripheral neuropathy: an unresolved issue. *Neurologia*, **25**, 116-1.
Von Schlippe M, Fowler CJ, Harland SJ (2001). Cisplatin neurotoxicity in the treatment of metastatic germ cell tumour: time, course and prognosis. *Br J Cancer*, **85**, 823-6.
Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C (2008). Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer*, **44**, 1507-5.