Cisplatin-Induced Peripheral Neuropathy: An Observational Descriptive Study

Anjol Kurian¹, Bittu Babu¹, Benson Punnoose¹, Chinju Susan Chacko², Mallikarjuna Rao³, Sharad Chand¹, Vinay B C¹, Nandakumar U P*¹

¹Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Paneer, Deralakatte, Mangaluru, Karnataka, India-575018
²Department of Pharmacy Practice, College of Pharmaceutical Sciences, Dayananda Sagar University, Bangalore, India
³Department of Oncology, Justice K.S. Hegde Charitable Hospital, Nitte (Deemed to be University), Mangaluru, Karnataka, India-575018

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ABSTRACT
Peripheral neurotoxicity is a major adverse effect of cisplatin chemotherapy. A prospective observational study was conducted among 200 cancer patients who received cisplatin between October 2017 and March 2018 to evaluate the occurrence, causality and severity of cisplatin induced peripheral neuropathy. A suitable data collection form was used to record patient information required for the study. Peripheral neuropathy was assessed using the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE). As per the results, 19 (9.5%) patients developed peripheral neuropathy after receiving cisplatin therapy. Peripheral neuropathy was reported higher in males (84.2%) compared to females (15.7%) and more within the age group of 58-65 years (38.6%). Most of the patients developed Grade I neuropathy (84.2%), followed by Grade II neuropathy (15.7%). The study concluded that the severity of peripheral neuropathy increases with higher cumulative doses of cisplatin.

*Corresponding Author
Name: Nandakumar U P
Phone: 
Email: nandakumarvtkv@gmail.com

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INTRODUCTION
Chemotherapy-induced peripheral neuropathy (CIPN) is a main complication related to cancer treatment (Miltenburg and Boogerd, 2014). Adverse drug reactions are unwanted and noxious effects due to therapy which complicates the disease burden (Rachana et al., 2019; Anusha et al., 2018). Adverse drug reactions may range from mild to severe and may increase the length of hospital stay (Chand et al., 2019; Voora et al., 2019). Peripheral neuropathy is outlined as a condition where the peripheral nerves such as motor, sensory and involuntary nerves get damaged (Kannarkat et al., 2008). Almost 50% of patients treated with cisplatin develop neurotoxicity. CIPN is significantly painful and it causes immense loss of functional status as well as reduces the quality of life of patients (Quasthoff and Hartung, 2002). Cisplatin causes neurotoxicity by building up in the dorsal root ganglia and thereby destroying them. This results in deoxyribonucleic acid damage, oxidative stress and noxious effect on mitochondria that finally accelerate the nerve cell death (McWhinney et al., 2009). This has a significant impact on the quality of life of cancer patients receiving cisplatin
therapy. Hence, this study aims to find the occurrence, causality and severity of cisplatin-induced peripheral neuropathy.

**MATERIALS AND METHODS**

A prospective observational study was carried out among inpatients and outpatients of the oncology department of a tertiary care teaching hospital for six months (October 2017-March 2018). This study was approved by the Institutional Ethics Committee, NGSM Institute of Pharmaceutical Sciences, Mangaluru. Ref No: NGSMIPS/IEC/20/2017-18.

**Study Criteria**

All cancer patients between the age group of 18-65 years receiving a cumulative amount of at least 100mg/m² of cisplatin chemotherapy were enrolled in study. Cancer patients receiving chemotherapy drugs other than cisplatin and diabetic patients were excluded from the study.

**Sample size**

\[ N = \frac{Z^2 (1-\alpha/2)P (1-P)}{d^2} \]

N= No. of patients  
Z=1.96  
\(\alpha\) = Confidence level (5%)  
d = Population proportion (10%)  
P= anticipated proportion (30%)

The minimum sample size required for this study was 165 patients. Two hundred patients were included during the study period.

**Study Procedure**

The socio-demographic details of the study population including age, gender and social habits were recorded in a suitably designed patient data collection form. Other information regarding diagnosis, stage of cancer, cycles of chemotherapy, site of malignancy was also obtained. Peripheral neuropathy was diagnosed by the physician by evaluating the signs and symptoms.

**Analysis of cisplatin-induced peripheral neuropathy**

**Causality**

The causality assessment of ADRs reported was done by using Naranjo’s scale and WHO causality assessment scale (Shareef et al., 2018).

**Severity**

Depending upon the severity, cisplatin-induced peripheral neuropathy was classified into grade 1, grade 2, grade 3, grade 4 and grade 5 using the criteria developed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).

**Statistical analysis and software used**

Frequency and percentage were used to summarize the categorical variables. Descriptive statistics like mean and standard deviation were calculated for continuous variables. The statistical analysis was performed using SPSS version 20.0.

**RESULTS AND DISCUSSION**

**Socio-demographic variables**

Among 200 cancer patients, majority 133 (66.5%) were males and the rest 67 (33.5%) were females. In this study, 80 (40%) patients belonged to the age group of 58 – 65 years. The distribution of patients based on the age group is given in Table 1.

72 (36%) patients were found to have no social habits followed by 37 (18.5%) with habit of both alcohol consumption and cigarette smoking. Distribution of patients according to their social habits, is shown in Table 2.

Out of 200 patients, 31 (15.5%) were found to have a family history of cancer, and the remaining 169 (84.5%) patients had no history of cancer in their family. Out of the total patients enrolled, 149 (74.5%) had head and neck cancer; 37 (18.5%) had gynecological cancer; 12 (6%) patients had lung cancer and 1 (0.5%) had testicular cancer. Among head and neck cancer, carcinoma of buccal mucosa was found to be the highest, 52 (26.0%). Different types of head and neck cancer diagnosed are given in Table 3.

**Dosing pattern of cisplatin among the study population**

Different cumulative doses of cisplatin ranging from 120 -540 mg were given to the patients. A majority of patients, 72 (36%) received a cumulative dose of 150 mg. Table 4 summarizes the different cumulative doses of cisplatin given to patients.

**Occurrence and severity of peripheral neuropathy**

Among 200 cancer patients who received cisplatin, 19 (9.5%) patients were reported with peripheral neuropathy. NCI-CTCAE scale was used to evaluate peripheral neuropathy induced by cisplatin. Among 19 patients, 16 (84.21%) were reported with grade 1 neuropathy, and 3 (15.7%) developed grade 2 neuropathy.

**Demographics of patients with peripheral neuropathy**
Table 1: Age-wise distribution

| Age group | Frequency (n) | Percentage (%) |
|-----------|---------------|----------------|
| 18-27     | 1             | 0.5            |
| 28-37     | 17            | 8.5            |
| 38-47     | 42            | 21.0           |
| 48-57     | 60            | 30.0           |
| 58-65     | 80            | 40.0           |

Table 2: Distribution based on social habits

| Social habits                  | Frequency (n) | Percentage (%) |
|--------------------------------|---------------|----------------|
| No habits                      | 72            | 36.0           |
| Alcohol + smoking              | 37            | 18.5           |
| Smoking                        | 26            | 13.0           |
| Substance use                  | 20            | 10.0           |
| Alcohol                        | 18            | 9.0            |
| Smoking + substance use        | 13            | 6.5            |
| Alcohol + smoking + substance use | 11        | 5.5            |
| Alcohol + substance use        | 3             | 1.5            |

Table 3: Distribution of patients diagnosed with head and neck cancer

| Head and neck cancer diagnosed | Frequency (n) | Percentage (%) |
|--------------------------------|---------------|----------------|
| Buccal mucosa                  | 52            | 26.0           |
| Tongue                         | 37            | 18.5           |
| Esophagus                      | 11            | 5.5            |
| GB complex                     | 10            | 5.0            |
| Tonsils                        | 6             | 3.0            |
| Oropharynx                     | 5             | 2.5            |
| Supraglottis                   | 5             | 2.5            |
| Pyriform fossa                 | 4             | 2.0            |
| Cricoid                        | 3             | 1.5            |
| Hypopharynx                    | 3             | 1.5            |
| Retromolar trigon              | 3             | 1.5            |
| Submandibular gland            | 3             | 1.5            |
| Floor of mouth                 | 2             | 1.0            |
| Larynx                         | 2             | 1.0            |
| Lip                            | 2             | 1.0            |
| Soft plate                     | 1             | 0.5            |

The occurrence of peripheral neuropathy was found more among the males 16 (84.2%) than females 3 (15.8%). Peripheral neuropathy was reported more among the patients within the age group of 58-65 years, followed by 48-57.

**Distribution of dose of cisplatin and severity of neuropathy**

The results showed that 12 patients presented grade 1, and no patients had grade 2 peripheral neuropathy at a cumulative dose range of 100-199 mg, whereas four patients presented grade 1 and three patients had grade 2 peripheral neuropathy at a dose above >200mg.

**Causality assessment of cisplatin-induced peripheral neuropathy**

On assessing the causality using the WHO probability scale and Naranjo’s scale, it was found that all the suspected neuropathy cases were possible adverse drug reactions.

The study showed a higher occurrence of cancer...
among males than females. These results are supported by the study conducted by (Pace et al., 2003; Hill et al., 2010). In contradiction, a study conducted by (Postma et al., 1998) found that females were more than males. In the study population, more cancer patients were present in the age group of 58-65 years which was similar to the study conducted by (Hill et al., 2010). Among the study population, 15% showed a strong positive family history of cancer which was found to be similar to the study conducted by (Tracy et al., 2008).

Different types of cancers were diagnosed in the study population. Head and neck (74.5%) were found as the major type of cancer diagnosed, followed by gynecological cancer. This resembles the results of the study conducted by (Siegal and Haim, 1990). The results obtained from the study carried out by (Postma et al., 1998) showed ovarian cancer as the major type of cancer which is contradictory to the present study.

A total of 72 (36%) patients received cisplatin at a cumulative dose of 150 mg followed by 49 (24.5%) patients with 180 mg, 42 (21%) patients received 120mg, 10(5%) patients received 160 mg, 7(3.5%) patients received 240 mg and 6 (3%) patients received 200 mg. Similar results were found in the study conducted by (Thompson et al., 1984). Peripheral neuropathy is a major dose-dependent adverse effect of cisplatin chemotherapy. In the present study out of 200 patients who received chemotherapy with cisplatin, 19 (9.5%) patients developed peripheral neuropathy. A study conducted by (Kannarkat et al., 2008) showed that the occurrence of chemotherapy-induced peripheral neuropathy was almost 30-40 %. Different factors influence the occurrence of CIPN including age, dose, dosing frequency and cumulative dose. Peripheral neuropathy was observed at different doses ranging from 150 mg to 540 mg. Gender wise distribution of patients with peripheral neuropathy was found similar to the study conducted by (Cavalletti et al., 2007).

Peripheral neuropathy was assessed using the NCI-CTCAE scale, which revealed that a higher number of patients had grade 1 peripheral neuropathy at a lower cumulative dose and fewer patients had grade 2 peripheral neuropathy at higher cumulative dose. Higher the cumulative dose, higher is the occurrence of grade 2 neuropathy. This result has a resemblance to the study conducted by (Siegal and Haim, 1990). The results of the study conducted by (Pace et al., 2003) showed that peripheral neurotoxicity occurs only after a cumulative dose of 250 mg which was found contradictory to the present study.

**CONCLUSIONS**

The occurrence of peripheral neuropathy was found to be 9.5% among total cancer patients receiving cisplatin. On causality assessment, peripheral neuropathy was found as a possible adverse drug reaction of cisplatin. The study also concluded that higher the cumulative dose of cisplatin greater is the severity of peripheral neuropathy.

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**Conflict of Interest**

Authors declare no conflict of interest.
REFERENCES

Anusha, R., Chand, S., Lal, V., Sushmitha, D. M., Reddy, D. S., Tejaswini, S., Chitrahasini, S. 2018. Isoniazid Induced Liver Injury: a Case Series and Review. Journal of Pharmacy Practice and Community Medicine, 4(2):128–130.

Cavaletti, G., Frigeni, B., Lanzani, F., Piatti, M., Rota, S., Briani, C., Zara, G., Plasmati, R., Pastorelli, F., Caraceni, A., Pace, A., Manicone, M., Lissoni, A., Colombo, N., Bianchi, G., and, C. Z. 2007. The Total Neuropathy Score as an assessment tool for grading the course of chemotherapy-induced peripheral neurotoxicity: comparison with the National Cancer Institute-Common Toxicity Scale. Journal of the Peripheral Nervous System, 12(3):210–215.

Chand, S., Bhandari, R., Girish, H. N. 2019. Isoniazid induced psychosis. Journal of Global Pharmaceutical Technology, 11(05):11–14.

Hill, A., Bergin, P., Hanning, F., Thompson, P., Findlay, M., Damianovich, D., McKeage, M. J. 2010. Detecting acute neurotoxicity during platinum chemotherapy by neurophysiological assessment of motor nerve hyperexcitability. BMC Cancer, 10(1):451–451.

Kannarkat, G., Lasher, E. E., Schiff, D. 2008. Neurologic complications of chemotherapy agents. Current Opinion in Internal Medicine, 7(1):88–94.

McWhinney, S. R., Goldberg, R. M., McLeod, H. L. 2009. Platinum neurotoxicity pharmacogenetics. Molecular Cancer Therapeutics, 8(1):10–16.

Miltenburg, N. C., Boogerd, W. 2014. Chemotherapy-induced neuropathy: A comprehensive survey. Cancer Treatment Reviews, 40(7):872–882.

Pace, A., Savarese, A., Picardo, M., Maresca, V., Pacetti, U., Monte, G. D., Biroccio, A., Leonetti, C., Jandolo, B., Cognetti, F., Bove, L. 2003. Neuroprotective Effect of Vitamin E Supplementation in Patients Treated With Cisplatin Chemotherapy. Journal of Clinical Oncology, 21(5):927–931.

Postma, T. J., Heimans, J. J., Muller, M. J., Ossenkoppele, G. J., Vermorken, J. B., Aaronson, N. K. 1998. Pitfalls in grading severity of chemotherapy-induced peripheral neuropathy. Annals of Oncology, 9(7):739–744.

Quasthoff, S., Hartung, H. P. 2002. Chemotherapy-induced peripheral neuropathy. Journal of Neurology, 249(1):9–17.

Rachana, J., Shastry, C., Mateti, U. V., Sharma, R., Nandakumar, U. P., Chand, S. 2019. Incidence and Associated Factors of Adverse Drug Reactions in General Medicine Department of a Tertiary Care Teaching Hospital. International Journal of Pharmaceutical Research, 11(3):177–184.

Shareef, J., Nandakumar, U. P., Bhat, M. 2018. A study on assessment of adverse drug reactions in patients with tuberculosis in a tertiary care teaching hospital. Journal of Applied Pharmaceutical Sciences, 8(04):99–104.

Siegal, T., Haim, N. 1990. Cisplatin-induced peripheral neuropathy. Frequent off-therapy deterioration, demyelinating syndromes, and muscle cramps. Cancer, 66(6):1117–1123.

Thompson, S. W., Davis, L. E., Kornfeld, M., Hilgers, R. D., Standefer, J. C. 1984. Cisplatin neuropathy. Clinical, electrophysiologic, morphologic, and toxicologic studies. Cancer, 54(7):1269–1275.

Tracy, K. A., Quillin, J. M., Wilson, D. B., Borzelleca, J., Jones, R. M., McClish, D., Bowen, D., Bodurtha, J. 2008. The impact of family history of breast cancer and cancer death on women’s mammography practices and beliefs. Genetics in Medicine, 10(8):621–625.

Voora, L., Shastry, S. C., Bhandari, R., Sukeerthi, D., Rawal, K. B., Chand, S. 2019. Phenytoin-Induced Erythroderma. Journal of Young Pharmacists, 11(3):320–321.