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ASSOCIATION OF VARIABLES (DEMOGRAPHIC AND CLINICAL) WITH PLATINUM BASED CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY AMONG CANCER PATIENTS

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is customarily observed, dose-related, nerve damaging side effect of chemotherapy that affects quality of life among cancer patients. There is 60–70% incidence rate of CIPN with platinum-based drugs; because these agents frequently used as first and second-line treatment for several common malignancies in cancer. Sixty (60) % of patient's reports 2nd degree peripheral nerve damage whose had received total cumulative platinum-based drug dose ranges from 225–500mg. However, 30-40% of them experience treatment-emergent grade 3–4 neurotoxicity. Incidence rate of neurosensory symptoms related to oxaliplatin-induced neurotoxicity (OXAIPN) was 60%–75% among patients treated with platinum-based regimens. With the use of platinum-based chemotherapy sensation may continue to deteriorate even after end of treatment. Recent research data enumerated predisposing factors such as low pre-treatment hemoglobin and higher BMI, that leads to development of chemotherapy induced peripheral neuropathy very speedy irrespective of chemotherapeutic agent. So, based on this recent data, researcher has interest to compile a study based on association of variables with platinum-based chemotherapy induced peripheral neuropathy among cancer patients. The present study was carried out to fulfill the following objectives1To find out the association of demographic variables with platinum based CIPN among cancer patients. 2. To find out the association of clinical profile variables with platinum based CIPN among cancer patients.

Key *words:* *Variables, Platinum, Chemotherapy Induced Peripheral Neuropathy, Cancer, Patients.*

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is customarily observed, dose-related, nerve damaging side effect of chemotherapy that affects quality of life among cancer patients. [1] CIPN prevalence was 68.1% (57.7-78.4) when measured in the first month after chemotherapy, 60.0% (36.4-81.6) at 3months and 30.0% (6.4-53.5) at 6months or more. Although CIPN prevalence decreases with time, at 6months after treatment 30% of patients continue to suffer from CIPN.[2] Development of CIPN can increase cancer-related morbidity and mortality.[3] Incidence rate of CIPN varies according to use of chemotherapeutic agents such as platinum, taxanes, plant alkaloids, and treatment schedule and assessment method.[4] The platinum based chemotherapeutic agents such as carboplatin and oxaliplatin, works by forming platinum-DNA adducts that damage neuronal apoptosis, programmed cell death, which leads to neuropathy.[5] The dorsal root ganglion is not protected by the blood-brain barrier, making the DNA lies within the cell body of the dorsal root ganglion preferentially susceptible to toxic agents, such as the platinum agents.[6] There is 60–70% incidence rate of CIPN with platinum based drugs; because these agents frequently used as first and

second-line treatment for several common malignancies in cancer.[7] Sixty (60) % of patient's reports 2nd degree peripheral nerve damage whose had received total cumulative platinum based drug dose ranges from 225–500mg. However, 30-40% of them experience treatment-emergent grade 3–4 neurotoxicity.[8] Incidence rate of neurosensory symptoms related to oxaliplatin-induced neurotoxicity (OXAIPN) was 60%–75% among patients treated with platinum-based regimens.[9] With the use of platinum based chemotherapy sensation may continue to deteriorate even after end of treatment.[10]At every visit of patient, nurse measure's the level of chemotherapy induced peripheral neuropathy by assessing numbness & tingling sensation in extremities, weakness, joint pain, muscle cramps, trouble hearing, ringing or buzzing in ears, trouble buttoning buttons, trouble walking caused by use of chemotherapeutic agents. Recently a research study by Nalley (2021) et al; concluded there are some predisposing factors such as low pre-treatment hemoglobin, higher BMI, age that leads to development of chemotherapy induced peripheral neuropathy very speedy. So, based on this recent data, researcher has interest to compile a study based on association of variables with platinum-based chemotherapy induced peripheral neuropathy among cancer patients.

The present study was carried out to fulfill the following objective

1. To find out the association of demographic variables with platinum based CIPN among cancer patients.
2. To find out the association of clinical profile variables with platinum based CIPN among cancer patients.

MATERIAL AND METHODS

Quantitative research approach with descriptive research design was used in the present study to fulfill the objectives. By using convenience sampling technique, 60 cancer patients who are receiving platinum based chemotherapy at Oncology ward of Sri Guru Ram Das Rotary Cancer Hospital, Vallah, and Sri Amritsar enrolled in the study to collect data. For collection of data, the tool was prepared and validated by 20 experts related to oncology field. The tool consists of two sections.

Section 1

Socio demographic variables of study subjects

It constitutes 11 items of socio demographic variables such as age, gender, monthly income, marital status, education, occupation, dietary habits, life style pattern, habitat, care giver at home and personal habits.

Section 2

Clinical profile variables of study subjects

It constitutes 14 items of clinical profile variables such as cycle of chemotherapy, TNM classification, duration of illness, BMI, site of cancer diagnosis, type of chemotherapy received, name of chemotherapeutic drug, dose of chemotherapeutic drug, tumor type, metastatic disease, tumor differentiation grade, number of co-morbid conditions, received neurotoxic drug along with platinum based chemotherapy, previous knowledge regarding CIPN. The data was collected during the time period from 16th December 2020 to 28th May 2021.

Ethical Consideration

The Institutional Review Board at SGRDUHS (Sri Guru Ram Das University of Health Sciences), Vallah

Sri Amritsar (IEC no: 1655/trust/org) approved the study. Written permission was obtained from Head of Sri Guru Ram Das Rotary Cancer Hospital regarding conduction of research study. Informed written consent was also taken from each study subject. Anonymity and confidentiality of each study subject were assured during research study.

RESULTS

The analysis and interpretation of data for this study were based on the data collected through socio demographic and clinical profile variables questionnaire for cancer patients (60) receiving platinum based chemotherapy. The results were computed by using descriptive and inferential statistics based on the objectives of the study as given below:-

Presentation of data

To begin with, data was entered in a master sheet, by using SPSS version 16.0 data was analyzed and interpreted.

Section A

Analysis of socio demographic variables with Platinum Based Chemotherapy Induced Peripheral Neuropathy among Cancer Patients

Section B

Analysis of clinical profile variables with Platinum Based Chemotherapy Induced Peripheral Neuropathy among Cancer Patients

Table 1: Association of Demographic Variables with Platinum Based CIPN among Cancer Patients

N=60

S. No	Demographic Variable (Number)	Mean	SD	F/t value	P value
1.	Age in years				
	a. 31-40 years (18)	17.94	4.69	0.310	0.818^{NS}
	b. 41-50 years (14)	16.86	5.27		
	c. 51-60 years (12)	17.17	3.58		
	d. 61-70 years (16)	16.44	4.93		
2	Gender				
	a. Male (27)	18.57	4.40	2.334	0.023*
	b. Female (33)	15.88	4.51		
3	Monthly family income (Rs)				
	a. < 10,000 (21)	17.62	5.16	0.644	0.590^{NS}
	b. 10,001-20,000 (21)	17.24	4.26		
	c. 20,001-30,000 (12)	17.33	3.96		
	d. > 30,000 (6)	14.67	5.53		
4	Marital status				
	a. Married (47)	17.28	4.80	0.494	0.688^{NS}
	b. Unmarried (01)	21.0	0		
	c. Widower (10)	16.60	4.35		
	d. Separated (06)	14.50	0.707		
5	Education				

	a. Primary education (15)	14.80	4.52	3.527	0.036*
	b. Middle education (36)	17.50	4.51		
	c. Secondary education (09)	19.56	3.97		
6	Occupation				
	a. Professional (05)	18.0	4.00	1.687	0.166^{NS}
	b. Business (07)	17.0	4.04		
	c. Agriculture (08)	18.25	4.71		
	d. Labor (15)	19.07	4.41		
	e. Housewife (25)	15.48	4.72		
7	Dietary habits				
	a. Vegetarian (12)	15.80	4.39	0.974	0.384^{NS}
	b. Non vegetarian (43)	17.64	4.56		
	c. Eggetarian (05)	15.67	5.31		
8	Life style pattern				
	Restricted but ambulatory (22)	16.0	9.89	0.311	0.817^{NS}
	Ambulatory/capable of self-care (16)	17.81	4.07		
	Capable of only limited self-care (38)	17.08	4.75		
	Completely disabled (04)	15.50	4.50		
9	Habitat				
	Urban (22)	17.12	4.61	0.011	0.991^{NS}
	Rural (38)	17.14	4.70		
10	Care giver at home				
	Spouse (21)	17.86	4.48	1.985	0.127^{NS}
	Children (18)	15.61	5.11		
	Family member (19)	17.16	4.04		
	Relative (02)	23.0	1.41		
11	Personal habits				
	Taking alcohol (10)	17.20	5.61	0.978	0.427^{NS}
	Smoking (03)	16.33	3.05		
	Alcohol and smoking (08)	19.25	2.81		
	Any other substance abuse (04)	19.75	7.18		
	None (35)	16.40	4.34		

***P<0.05 level of significance** **NS-Non significant**

Table 1: depicts that most of the study subjects were in the age group of 31 to 40 years of life. According to above table, most study subjects were females, married, non-vegetarian and having house wife as their occupation. The study subjects are capable of only limited self-care and residing at rural areas. P value is significant at <0.05 with Gender, Education according to socio demographic profile sheet of patients.

Figure1: Distribution of mean score among cancer patients (as per gender) related to Chemotherapy Induced Peripheral Neuropathy

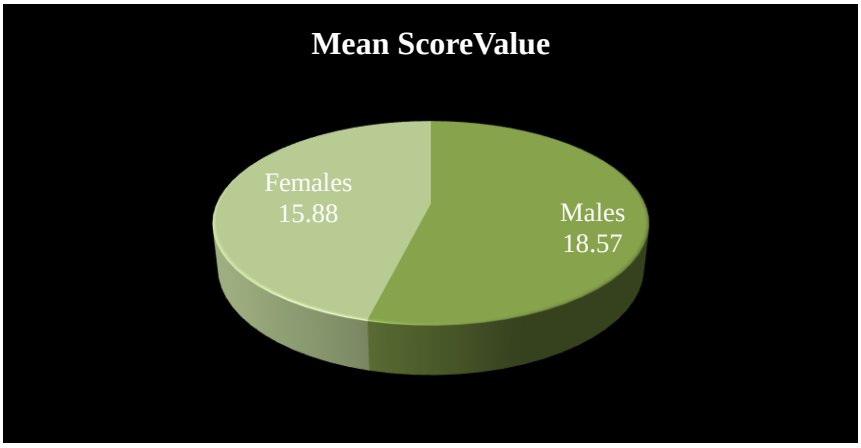

Figure 1: reveals that mean score value of males were 18.57 and females 15.88 respectively; this shows that males having more severity of platinum based chemotherapy induced peripheral neuropathy as compared to females

Table 2: Association of Clinical Profile Variables with Platinum Based CIPN among Cancer Patients

N=60

S. No	Clinical Variable (Number)	Mean	SD	F/t value	P value
1.	Cycle of chemotherapy				
	C3 (35)	17.08	4.54	0.119	0.906^{NS}
	C4 (25)	17.23	4.88		
2	TNM classification				
	$T_1 N_0 M_0$ (02)	17.50	4.95	1.338	0.227^{NS}
	$T_1 N_1 M_0$ (02)	23.50	0.707		
	$T_1 N_2 M_0$ (02)	15.0	2.82		
	$T_2 N_0 M_0$ (03)	16.67	6.65		
	$T_2 N_1 M_0$ (15)	18.07	4.20		
	$T_2 N_2 M_0$ (04)	18.75	2.98		
	$T_3 N_1 M_1$ (02)	22.0	0		
	$T_3 N_2 M_0$ (02)	19.0	4.24		
	$T_3 N_2 M_1$ (20)	15.79	4.77		
	$T_3 N_3 M_1$ (03)	16.67	4.04		
	$T_4 N_1 M_0$ (02)	20.0	0		
	$T_4 N_3 M_1$ (03)	15.33	5.50		
3	Duration of illness				
	< 2 months (03)	17.50	4.95	0.809	0.648^{NS}
	2-5 months (11)	13.0	2.82		
	6-10 months (28)	17.38	5.55		
	11-15 months (13)	19.20	3.07		
	> 15 months (05)	18.12	5.46		
4	BMI				
	Underweight (27)	15.04	4.30	5.995	0.004*
	Normal (24)	18.67	4.37		
	Overweight (09)	19.33	3.93		
5	Site of cancer diagnosis				
	Blood (4)	13.0	4.14	1.346	0.210^{NS}

	G.I system (17)	18.0	8.28		
	Respiratory system (11)	15.0	5.65		
	Reproductive system (16)	17.50	4.95		
	Bone (02)	18.50	0		
6	Type of chemotherapy received				
	Adjuvant chemotherapy (20)	16.60	4.58	0.905	0.444^{NS}
	Neo- adjuvant chemotherapy (24)	18.25	4.94		
	Combined of both (10)	15.60	4.24		
	Palliative therapy (06)	16.67	3.98		
7	Name of chemotherapeutic drug				
	Oxaliplatin (18)	18.44	4.80	1.103	0.339^{NS}
	Carboplatin (10)	16.10	4.30		
	Cisplatin (32)	16.72	4.60		
8	Dose of chemotherapeutic drug				
	50-100 mg (32)	17.0	4.76	0.942	0.447^{NS}
	101-150 mg (15)	17.73	4.52		
	151-200 mg (04)	13.50	3.31		
	201-250 mg (01)	15.0	0		
	251-300 mg (08)	18.62	4.77		
9	Tumor type				
	In situ (07)	15.12	5.93	1.211	0.305^{NS}
	Benign (31)	17.93	4.49		
	Malignant (22)	16.88	4.27		
10	Metastatic disease				
	Yes (35)	17.83	4.17	0.876	0.385^{NS}
	No (25)	16.74	5.03		
11	Tumor differentiation grade				
	Grade II (20)	17.95	4.71	0.658	0.522^{NS}
	Grade III (30)	16.86	4.74		
	Grade IV (10)	16.0	4.18		
12	Number of co-morbid conditions				
	1 (04)	17.75	5.50	0.425	0.656^{NS}
	2 (38)	16.71	4.43		
	3+ (18)	17.89	5.01		
13	Received neurotoxicity drug along with platinum based chemotherapy		5.11	0.837	0.438^{NS}
	None (41)	17.15	2.49		
	Bortezomib (05)	14.80	3.49		
	Vincristine (14)	17.93			
14	Previous knowledge regarding CIPN				
	No (48)	17.14	4.79	0.025	0.980^{NS}
	Yes (12)	17.10	3.90		

Table 2**:** concluded that majority of study subjects were receiving cycle 3 of chemotherapy and having 6 to 10 months of duration with cancer. Mostly study subjects were underweight, having cancer related to reproductive system, receiving cisplatin based neo-adjuvant chemotherapy. For the most part, study subjects are having tumor differentiation grade III with metastatic condition.

Figure 2: Distribution of mean score among cancer patients (as per BMI) related to Chemotherapy

Induced Peripheral Neuropathy

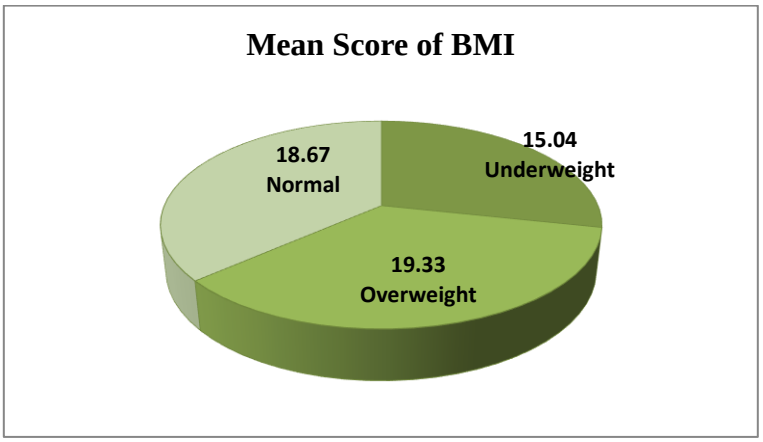

Figure 2: enumerated that mean score of cancer patients having normal BMI was 18.67, mean score of underweight cancer patients is 15.04 followed by mean score of overweight cancer patients 19.33. The data showed that high mean score of BMI is 19.33 which are related to overweight cancer patients. So, it is concluded that, over weight cancer patients having more severity of platinum based chemotherapy induced peripheral neuropathy as compared to normal and then to underweight cancer patients.

DISCUSSION

The present study data included that level of CIPN is more severe in males as compared to females and same findings are also supported by David Mizrahi **et al[12],** done a cohort study to identify the association of pretreatment blood-based and clinical factors with CIPN persistence in patients who received paclitaxel or oxaliplatin chemotherapy at urban multicenter cancer clinics between September 2015 and February 2020. Comprehensive neuropathy assessments were undertaken 3 to 12 months post treatment. Post treatment CIPN severity was compared with blood-based factors within 30 days prior to commencing chemotherapy. Data were analyzed between March and December 2020. The study included 333 participants (median [interquartile range] age, 58 [18] years) who were consecutively recruited and referred (228 treated with paclitaxel, 105 treated with oxaliplatin; 138 [41.4%] with breast cancer, 83 [24.9%] with colorectal cancer). Study result showed that level of CIPN is worse in males as compared to females at (β = −1.08; 95% CI, −1.76 to −0.16; *P* = .01).

The present study concluded that, advancing age have no significant relation to platinum based chemotherapy induced peripheral neuropathy at p value <0.05. The similar research findings were also presented by **Argyriou AA et al[13]**, who completed a *post hoc* analysis of data extracted from a prospective, multicenter study is to test whether advanced age increases the risk of developing OXA-induced peripheral neuropathy (OXAIPN). One-hundred and forty-five patients with CRC, without other significant co-morbidities predisposing to peripheral neuropathy, were divided according to their age into two groups: patients aged between 50 and 68 years (group I, *n* = 75); and patients aged ≥ 69 years (group II, *n* = 70). Patients were prospectively monitored at baseline and followed-up during chemotherapy using the motor and neurosensory National Cancer Institute Common Toxicity criteria, the clinical version of the Total Neuropathy Score and neurophysiology. No statistically significant difference was observed in the incidence of both the acute (*n* = 64/75 vs. 56/70; *P* = 0.510) and cumulative OXAIPN (*n* = 51/75 vs. 49/70; *P* = 0.858) between age groups. These research

findings are also similar to present study as above research study concluded that, age as a demographic variable is non-significant to CIPN.

Result of above study citied included that, Body Mass Index is directly associated with severity of chemotherapy induced peripheral neuropathy. Overweight cancer patients receiving platinum based chemotherapy have more severity of CIPN as compared to cancer patients have normal BMI level. **Ottaiano A et al'**[14] conducted a study to note association of CIPN with body mass index and prognosis in colon cancer patients treated with capecitabine and oxaliplatin receiving adjuvant chemotherapy. 102 colorectal cancer patients treated for 6 months with adjuvant CAPOX are followed up for CIPN. Associations between clinical variables, metabolic syndrome components, smoking and neurotoxicity were evaluated by the χ^2 test. The Kaplan-Meier product limit method was applied to graph disease-free survival (DFS). Result showed that significant associations were found between diabetes ($p < 0.001$), BMI ($p = 0.01$) and the occurrence of chronic neurotoxicity. After a median follow-up of 46 months, 14 patients (13.7%) had suffered recurrence. An analysis of the prognostic factors for DFS showed that prognosis is unfavorable for patients with high lymph-nodal involvement (HR: 5.23, $p = 0.0007$), diabetes (HR: 4.86; $p = 0.03$) and a BMI ≥25 (HR: 3.69, $p = 0.002$).

RECOMMENDATIONS

1. The same study can be done on large sample size to generalize findings.
2. The same study can be done on different chemotherapeutic agents to determine the severity of chemotherapy induced peripheral neuropathy.

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